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ON THE COVER

The modern world is filled with network-connected sensors—gyroscopes, cameras, microphones, and so on. Generally, the data they produce are used for single applications. Once sensor data become freely available to all devices, however, we could enter an era of ubiquitous computing, in which sensors in the external world augment human perception. Image by André Kutscherauer.

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FEATURES

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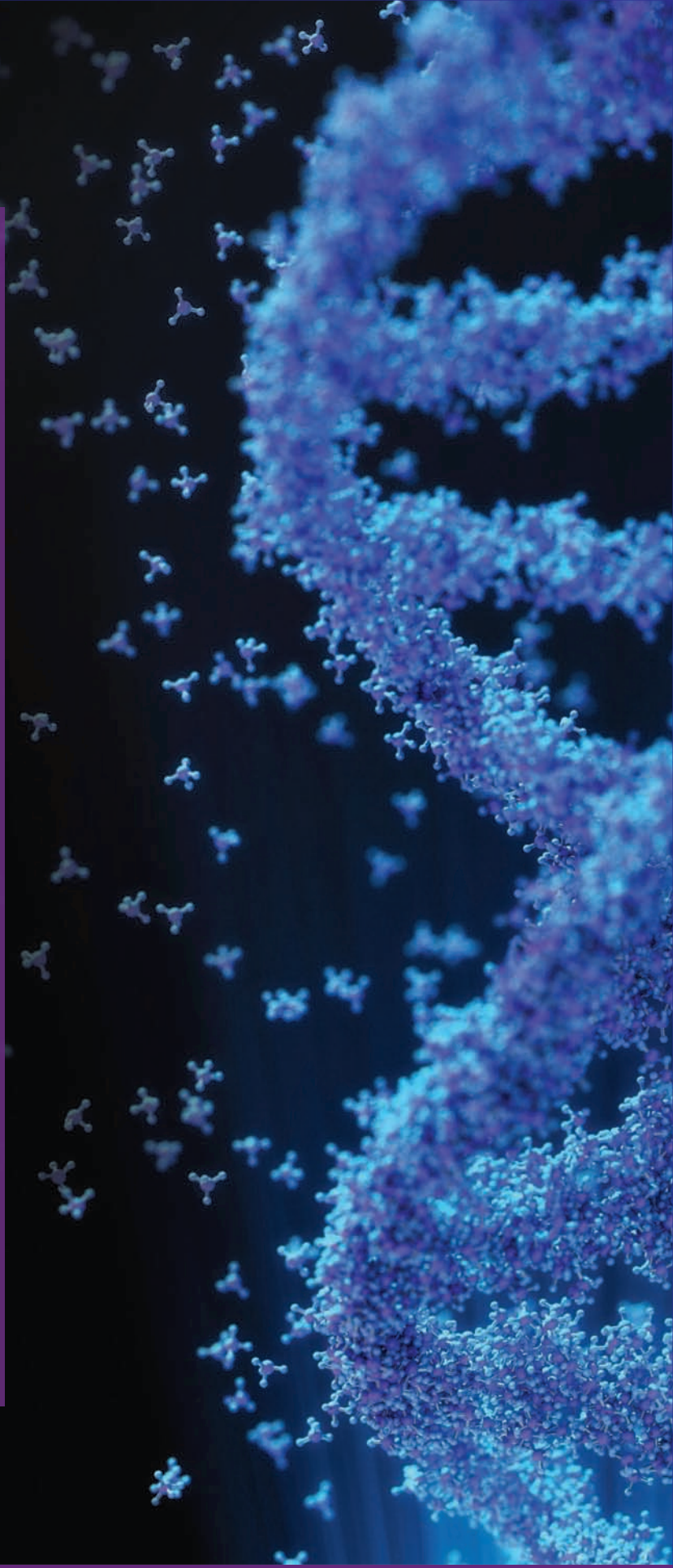

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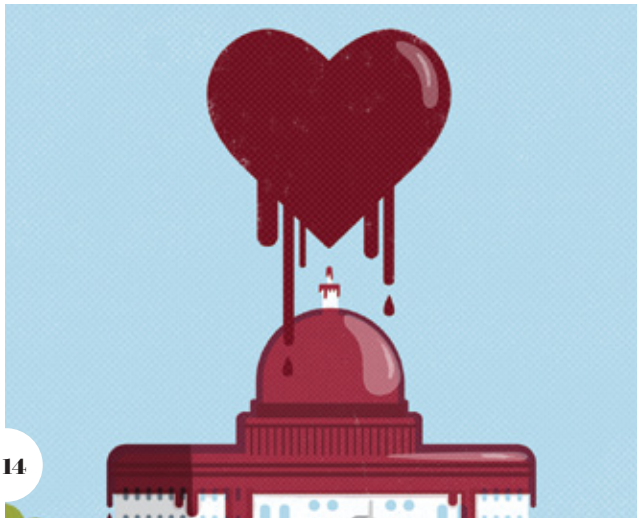

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SPECIAL REPORT

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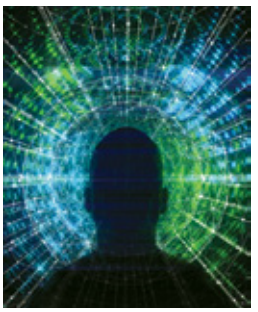
A Connected World

In *SCIENTIFIC AMERICAN*'S FIRST ISSUE, DATED AUGUST 28, 1845, the editors marveled at what we now know to be the rise of telecommunications. Samuel Morse's telegraph, "this wonder of the age," was sending messages between Baltimore and Washington, D.C., and they declared that "it appears likely to come into general use through the length and breadth of our land."

Of course, it was impossible to fully appreciate then how wired networks would one day connect so many facets of the world. Now, however, we have a better vantage point. The cover story, "Extra Sensory Perception," by Gershon Dublon and Joseph A. Paradiso, starting on page 36, outlines how ubiquitous sensors will expand our real-time knowledge of the world. Today such sensors largely exist in disconnected "silos," working only on specific applications. But if they were networked, such configurations would have profound implications for our current expectations surrounding privacy and physical presence.



Our most intimate networks are, of course, internal. In their feature article, "Add Neurons, Subtract Anxiety," Mazen A. Kheirbek and René Hen describe research about the role of new brain neurons in existing neural arrays. The work could lead to novel approaches to treating anxiety disorders. Turn to page 62.

While I'm talking about cooperative efforts, let me cite others in this issue, which were produced with our sister publication, the scientific journal *Nature*. (*Scientific American* is part of Nature Publishing Group.)

First, in "Body Works," beginning on page 76, we offer the fourth annual selection of excerpts by Nobel Prize–winning authors of past *Scientific American* articles, timed for the yearly Lindau meeting of Nobel laureates and young scientists in Germany; additional stories from both publications appear online. More than 150 Nobelists have written, collectively, 245 articles for the magazine, often long before they received that recognition.

In the realm of applied sciences, "Bottoms Up," by Olive Heffernan, details how treated sewage could provide an environmentally sound way to get crystal-clear refreshment from your tap; go to page 68. Online, a co-branded In-Depth Report at ScientificAmerican.com, offers more articles about water and the sustainability of this precious resource from both our editorial teams.

Last, we offer a 26-page special report: a *Nature* Outlook surveying advances in cancer. In it, you will find articles on tailoring therapies for personalized treatments, the use of nanoparticles for better drug delivery and the challenge of solving three fundamental mysteries that still exist about cancer.

As always, we welcome comments from you, our readers—and our most essential network contacts. SA

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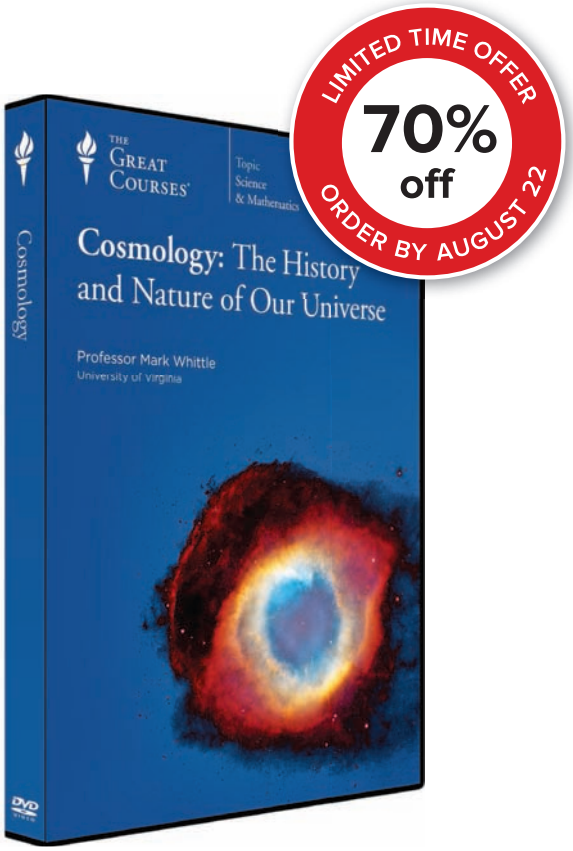

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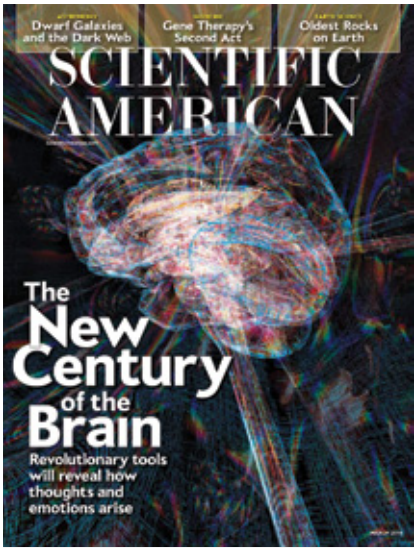

March 2014

ELEPHANTS IN CAPTIVITY

Your editorial, "Free Willy—And All His Pals" [Science Agenda], fails to accurately reflect the facts about elephants and orcas in human care and reaches the wrong conclusion in asserting elephants and orcas that "can be, should be" released.

The Association of Zoos and Aquariums (AZA) sets high and rising standards for animal care and welfare, which is especially important for elephants and orcas. AZA's science-based accreditation standards are the best way to make sure large and intelligent animals receive the higher level of care they need. Not surprisingly, the only specific example of poor care you note comes from a non-AZA-accredited facility.

There is no solid science to show that captive elephants and whales can or should be released into the wild. For whales and dolphins, the few attempted releases have resulted in suffering and death. A proved solution is to provide these animals with enriching habitats, appropriate social interaction, high-quality veterinary care and nutritious diets—all mandated by AZA standards.

AZA-accredited zoos and aquariums are also taking a leading role in fighting illegal elephant poaching and in promoting protection of our marine ecosystems. The animals at these facilities play a key role in educating and inspiring 180 million people to take conservation action. AZA-accredited institutions have spent more than $1 billion on field conservation projects over the past 10 years. AZA and its members have made considerable efforts to advance animal welfare and conserve wildlife, and we invite your readers to take a second look.

"There is no solid science to show that captive elephants and whales can or should be released into the wild."

KRISTIN L. VEHRS
ASSOCIATION OF ZOOS AND AQUARIUMS

KRISTIN L. VEHRS
Executive Director
Association of Zoos and Aquariums

THE EDITORS REPLY: There is considerable and increasing evidence that orcas and elephants suffer even in institutions accredited by AZA. Results announced last year from a three-year study on 255 of the roughly 300 elephants in North American AZA-approved zoos found that 74 percent of the elephants were overweight or obese; 25 percent had joint problems in 2012; 67 percent had foot problems in 2012; and nearly 80 percent displayed behavioral tics, such as pacing and head bobbing.

CHECKMATE

In "Why Good Thoughts Block Better Ones," Merim Bilalić and Peter McLeod present a chess scenario to illustrate how the brain has difficulty looking past a problem's familiar solution to find a better one. In the scenario, player A can win against player B with the well-known five-move "smothered mate" sequence but supposedly can also win more quickly with a three-move sequence. The latter sequence is contrived. B's response to A's second move would not be to move a rook into the path of A's bishop's but would logically be to capture A's queen with a pawn.

ANDY PREVELIG
Tallahassee, Fla.

THE AUTHORS REPLY: We've received several letters that come to the same conclusion about the shorter sequence. That sequence involves the critical move of putting player A's queen on a square (H6), where it seemingly can be captured by player B's pawn on G7. But B cannot capture the queen on H6, because that move would expose B's king to a check by the bishop on B2, at the other side of the board. In other words, B's king is pinned, and the queen cannot be taken on H6. In our article, we neglected to explicitly state why this move (queen to H6) is possible. As these letters suggest, it turns out that our omission worked perfectly to illustrate the main message of the article! Once you have an idea about how things work, it becomes increasingly difficult to see alternative ways of dealing with the problem no matter how obvious they seem to others.

PROFESSIONAL SKEPTICS

Ricki Lewis's article on gene therapy, "Gene Therapy's Second Act," cites the clinical trial that led to Jesse Gelsinger's death.

That is just one story of experiments with unfortunate results that I summarize in my book *Experimenting with the Consumer* (Praeger, 2008). I am pleased by Lewis's hopeful conclusion for the new promise of gene therapy. But I suggest that institutions pursuing it should name designated Cassandras, or critics, who might backstop institutional review boards in certain cases of frontier experiments. This would sometimes avoid the trap of "Good Thoughts Blocking Better Ones."

MARSHALL SHAPO
Northwestern University School of Law

COOKING AND TRANS FATS

"The Case for Banning Trans Fats," by Walter Willett [Forum], omits any mention of a source of trans fats besides partial hydrogenation: heating naturally occurring cis fats during cooking converts them to an equilibrium mixture of the cis and trans isomers, in which the trans isomer is usually favored. The extent of reaction depends on time, temperature and structure.

This process has been described for a long time, including in studies by Changmo Li et al. in the *Journal of Agricultural and Food Chemistry* last year and by Clayton A. Martin et al. in *Anais da Academia Brasileira de Ciências* in 2007.

EDWARD J. BEHRMAN
Professor Emeritus, Ohio State University

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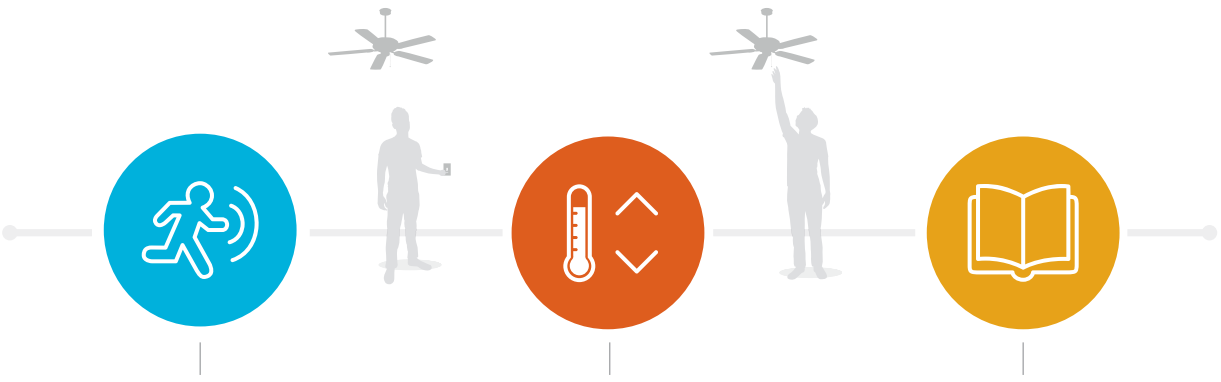

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WILLETT REPLIES: One should always be careful not to overheat oils. But under usual cooking conditions, trans fat formation is small. The Li et al. paper, for instance, found that under what the authors called "extreme conditions" (three hours of heating at 150 degrees Celsius), the amount of trans fat that formed was less than one tenth of 1 percent of each gram of oil.

SCI-FI FORECASTING

In discussing the difficulty of predicting future technology in "Future Imperfect" [TechnoFiles], David Pogue cites the Internet as among the "enormous zigs or zags" that "not even [science-fiction writer Isaac] Asimov saw coming." But Asimov did envision an Internet in the form of a planetwide communications network for robots in his 1957 novel *The Naked Sun*.

He used the terms "net" and "web" to denote a possible nefarious tinge to the network: "Perhaps robots listened to all that went on…, and if [a] particular robot was not designed for a particular job … the radio web that united all robots went into action…. [Elijah] Baley had the vision of Solaria as a robotic net with holes that were small and continually growing smaller."

ED SHAYA
via e-mail

HOW BOMBED WAS BOND?

In "007 and 7" [Anti Gravity], Steve Mirsky cites a *BMJ* paper as claiming that James Bond had 18 drinks over a single dinner in Ian Fleming's 1959 novel *Goldfinger*.

But I checked the book and counted the following drinks in that scene: one "large vodka and tonic with a slice of lemon peel," a "strong gin and tonic," "another drink," "some" wine "tasted" (no further mention of the wine bottle) and "a bottle of Mouton Rothschild 1947" (no mention as to how much of it he consumed). That's it.

DON SMITH
Indianapolis

MIRSKY REPLIES: Technically, the researchers spoke in terms of "units" of alcohol—10 milliliters or eight grams of pure ethanol. I roughly translated 18 units as 18 standard-sized drinks, but that was inaccurate. The paper specifies different numbers of units for different drinks, including three for Bond's famous vodka martini.

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Poisoned Well

Recent spills show that tougher rules are needed to protect water supplies

In January storage tanks owned by Freedom Industries spilled 10,000 gallons of industrial chemicals into the Elk River in West Virginia. The toxic liquids washed a short distance downstream into the region's largest drinking-water treatment plant. About 500 residents checked into local hospitals; 300,000 people could not use tap water for weeks on end; and businesses closed, leaving employees without a paycheck.

Similar stories abound. In February failed pipes at a Duke Energy dump sent tens of thousands of tons of hazardous coal ash into the Dan River in Eden, N.C., which supplies the drinking water for communities in both North Carolina and Virginia. Industrial and agricultural chemicals show up repeatedly in groundwater that serves millions of Californians. Nationwide, 19 million Americans become sick every year from viruses, bacteria and parasites that sneak through ineffective municipal drinking-water treatment plants, according to a *New York Times* investigation.

Contamination of water supplies occurs for many reasons. Chemical storage tanks, often poorly built and monitored, can leak and foul drinking water. Inspectors in many (if not most) states do not even know where all those states' chemical storage facilities are located. And the Environmental Protection Agency has placed significant restrictions on only five of the tens of thousands of chemicals used commercially.

It is time for state and federal legislators to strengthen regulations that protect U.S. drinking-water supplies and for government agencies to aggressively enforce the rules. Regulation-averse West Virginia passed its own bill after the Elk River spill. Congress should follow its lead and pass the Chemical Safety and Drinking Water Protection Act. The law would require states or the EPA to inventory chemical storage facilities and to examine them annually. Storage tanks would also have to meet minimum standards for construction and leak detection. The Senate Committee on Environment and Public Works approved the legislation in April, but as of early May, the bill had not been scheduled for a full Senate debate. Opposition to the bill is being led by energy, utility and industrial companies that would be forced to upgrade their infrastructure.

A thorny question is where states would get the money to enforce the rules. One place is the Drinking Water State Revolving Fund, which provides federal aid for such purposes. The Obama administration and some members of Congress, however, want to cut $100 million from the $900-million fund. Those cuts should not go through.

Wider measures should also be taken to safeguard drinking water. The Toxic Substances Control Act, last updated in 1976, allows industry to use new chemicals without first demonstrating that they are safe. Instead it places the burden of proof on the EPA. Yet of the more than 50,000 chemicals used commercially, the EPA has tested just 300.

The EPA can more effectively tackle those 50,000 chemicals by improving and expanding the experimental Tox21 and ToxCast systems it has developed with the National Institutes of Health. These systems rely on automated, robotic laboratories that can examine the effects of hundreds of chemicals at a time on human cells and proteins. Those that react should be put on a short list for thorough toxicity testing.

One welcome development is that municipal treatment plants have started to go beyond basic filtering and disinfecting, which can allow chemicals, bacteria and pharmaceuticals to remain in the water supply. Cincinnati and Louisville use activated carbon filters and ultraviolet light disinfection to make water cleaner. San Diego has built a pilot plant that can turn wastewater directly into superclean drinking water [see "Bottoms Up," on page 68]. Regulators should allow municipalities to bring such plants online.

Unfortunately, there is no single solution to our water woes. Clean water requires keeping water sources pristine and then scrubbing the water further at advanced treatment plants. It requires coordinated actions from federal, state and municipal governments—actions that may lead to increased costs for industries and perhaps even consumers as well. But as residents of West Virginia and North Carolina have recently learned, there is perhaps no more vital resource than the one we count on to flow out of our taps. SA

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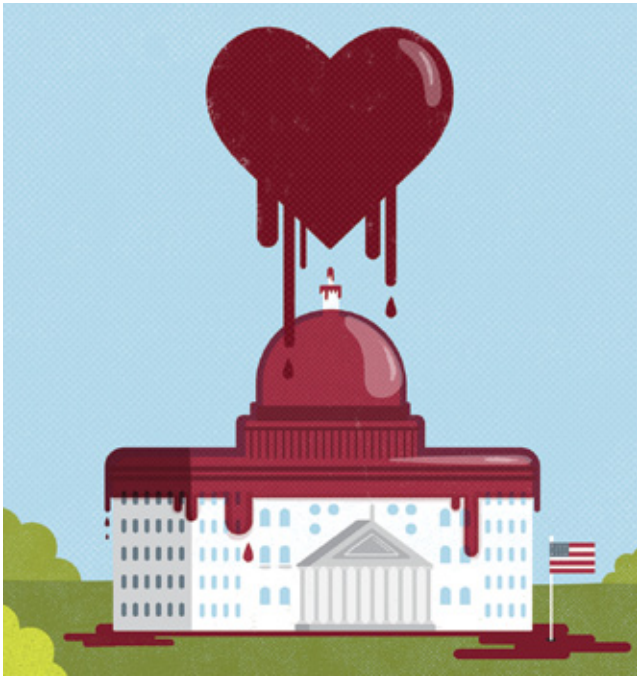
Commentary on science in the news from the experts

Edward W. Felten is Robert E. Kahn Professor of Computer Science and Public Affairs and director of the Center for Information Technology Policy at Princeton University. He serves on *Scientific American*'s board of advisers.

Joshua A. Kroll is a Ph.D. candidate in computer science at Princeton.



Help Wanted on Internet Security

The U.S. government must step in to fill the leadership vacuum

For much of the past two years, two thirds of all Web sites were susceptible to having their memory extracted by remote attackers—memory containing private information, passwords and encryption keys. The flaw, called Heartbleed, was the most serious Internet security flaw ever found. Heartbleed attacks would not have shown up in most sites' logs, so we cannot be sure how widely it was exploited or what might have been leaked.

When the flaw came to light earlier this year, the White House made an unusually clear and direct statement that no part of the U.S. government had known about Heartbleed before it was disclosed, heading off the outcry that would have ensued had the National Security Agency been withholding knowledge of so severe a vulnerability. But the federal government does not get off so easily in the incident. It is guilty of not providing leadership that could have averted the crisis in the first place—and that will be needed to avert the next one.

The leadership gap has arisen largely because more and more security software is "open source"—code that is made and shared widely by programmers for the common good. Heartbleed was caused back in 2011 by an error in code submitted by a German Ph.D. student to an encryption package called OpenSSL. It was a common type of error, but somehow nobody spotted it. The flawed code made it through OpenSSL's vetting process and was adopted into the official OpenSSL version, where it sat unnoticed for two years.

Open-source software such as OpenSSL is supposed to be good for security because everyone is free to read and analyze the code. Open code maximizes the odds that somebody, somewhere, will find a bug before it burns end users. Open-source advocate Eric S. Raymond famously called this Linus's law: "Given enough eyeballs, all bugs are shallow." That's good news, if you have enough eyeballs.

But OpenSSL suffers from a major eyeball shortage. The project's Web site lists a core team of three people, and its annual budget is less than $1 million. Another million or two spent on a security audit might well have prevented Heartbleed. OpenSSL security, however, is a public good with the attendant funding problems: once it exists, no one can be prevented from benefiting from it, so many hope for a free ride on someone else's dime.

Government often pays for public goods such as basic scientific research. But government did not invest in the security of OpenSSL. Despite spending billions a year on cybersecurity and declaring "cyber" a national priority, the feds did not offer even a few million dollars to bolster this core security infrastructure.

Government also failed to provide authoritative, concrete advice after Heartbleed was made public, when users and small-site operators across the Net were wondering what to do. Although it offers such advice to people faced with natural disasters or physical safety risks, government left users stranded when Heartbleed showed up. Most companies, meanwhile, did little more than warn users to change their passwords.

Somebody needs to take the lead in funding and coordinating audits of infrastructure, organizing useful disclosures of vulnerabilities to the public, and providing accessible advice and guidance for users and operators of small Web sites. Existing entities perform some of these functions—for example, in the aftermath of Heartbleed, the Linux Foundation and several tech companies pledged support, including funding, for open-source security—but a central organization should unify efforts, identify unaddressed issues and present clear information to the public. If neither government nor private companies step up, then we need an independent institution dedicated to serving the security needs of end users.

We will be fighting the security battle for a long time, and nothing can make us entirely safe. But better institutions can make these crises less frequent, less serious and less confusing to users. With some leadership, and a modest investment, we could have a champion for user security. SA

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Illustration by Shaw Nielsen

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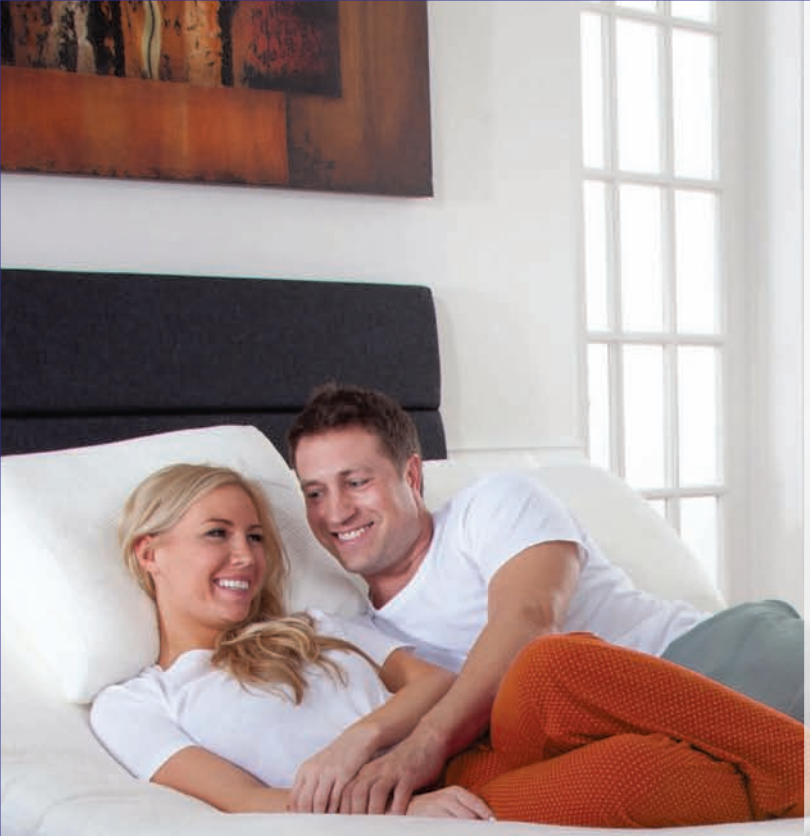

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The number of methane-producing single-celled organisms may have exploded because of prehistoric volcanoes.

EVOLUTION

Microscopic Mass Murderer

Microbes may be responsible for the largest extinction in Earth's history

At the end of the Permian period, about 252 million years ago, animals started dying at ferocious rates. In just 20,000 years 90 percent of all species on the planet had gone extinct. What triggered this die-off? Researchers have been trying to figure that out for decades.

Because the scale of the extinctions was so large, paleobiologists and geochemists started looking for an equally massive disaster as the root cause. Some proposed that an asteroid struck Earth, similar to what ended the reign of the dinosaurs. More recently, they have focused on volcanoes in what is now modern-day Siberia that were highly active at the time. They spewed out large amounts of carbon dioxide and methane, an event documented in the chemical signatures of rocks from Xiakou, China. Scientists think that the surge in these gases warmed the planet and made its oceans more acidic, which, together, ultimately snuffed out most life.

In those same rocks, though, Dan Rothman, a geochemist at the Massachusetts Institute of Technology, saw a discrepancy with the volcano story. The chemical signatures indicated that the concentrations of carbon dioxide and

EDU LEON *Getty Images (volcano)*; SCIENCE SOURCE *(microbes)*

FURTHER READINGS AND CITATIONS ScientificAmerican.com/jul2014/advances

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methane kept rising over time. If the gases were the result of volcanic eruptions, one would expect that their levels would rise and then fall back down again. To Rothman and his colleagues, the pattern looked more like a biological factor—not unlike the exponential growth of microbes.

In a study published in April in the *Proceedings of the National Academy of Sciences USA,* the group names a methane-producing single-celled organism, *Methanosarcina,* as one of the main culprits behind the Permian extinctions.

The new hypothesis does not disregard the influence of the volcanoes. Instead the M.I.T. researchers think that the vast quantities of nickel deposited by the eruptions allowed *Methanosarcina* to flourish. The microbe, which had acquired the ability to produce methane right around the time of the extinctions, is dependent on nickel to metabolize organic material into the gas. As ocean currents carried the nickel around the globe, the sudden influx allowed *Methanosarcina* numbers to skyrocket.

That release of large amounts of methane caused temperatures and ocean acidification to increase, and oxygen levels plummeted as O_2 was used in the natural conversion of methane to carbon dioxide. Species began to die off. Then *Methanosarcina* dined on the decomposition and released more methane, triggering a positive feedback loop.

The findings suggest that microbial evolution has important consequences for the evolution of the environment as a whole, Rothman says: "Microbes run this world. We just live in it."

Some scientists are skeptical that a single microbe played such a big role in the Permian extinctions. Pennsylvania State University geochemist Lee Kump says that Rothman and his colleagues have not proved for certain that this is what happened because they studied only one group of rocks from southern China. "If this phenomenon led to these extinctions, then you would expect to see this in rocks around the world," he says. "It's something the researchers still need to look for." —*Carrie Arnold*

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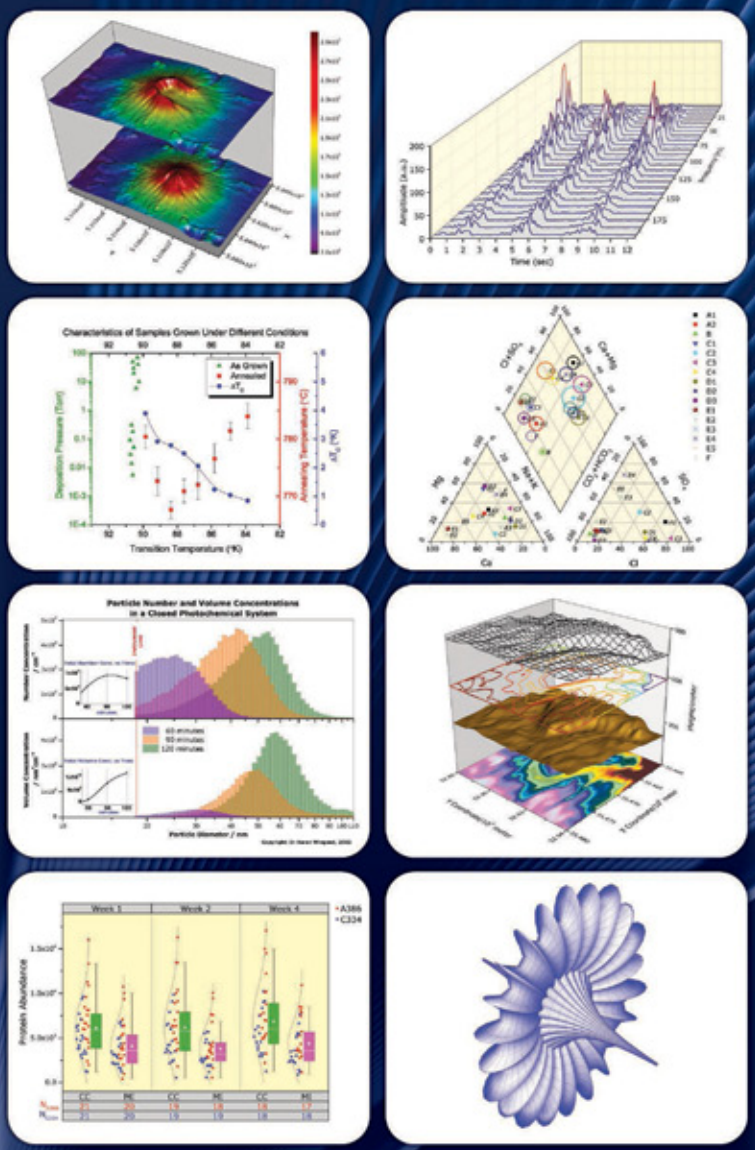

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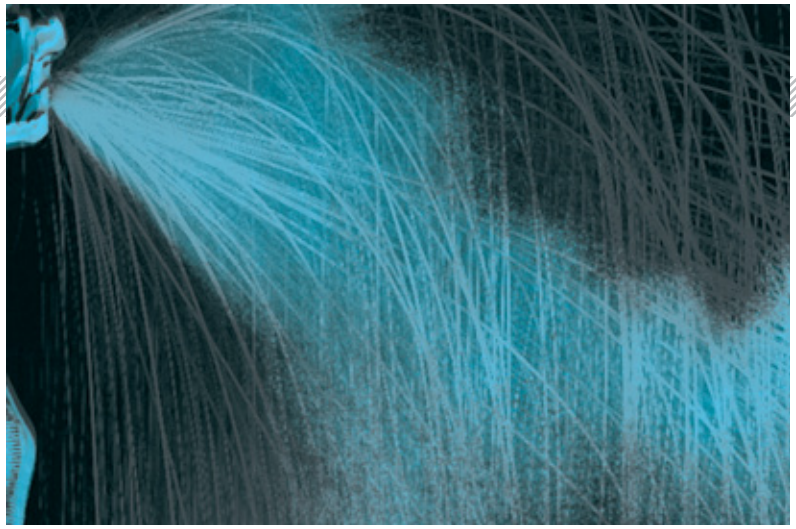

KNOW THE **JARGON**

Multiphase turbulent buoyant cloud:

(*n.*) A floating conglomeration of liquid droplets and small solid particles suspended in a gas that travels through space.

This cloud has nothing to do with the weather. It's a cloud of snot, and when propelled by a sneeze, it can carry droplets 200 times farther than experts previously thought, according to research published in the *Journal of Fluid Mechanics.*

After filming people coughing and sneezing at high speed, mathematicians and engineers at the Massachusetts Institute of Technology ran mathematical models and simulations to investigate the cloud's role. Approaching the violent respiratory event from a fluid mechanics perspective, the researchers found that some previous assumptions about sneezes were wrong. The largest mucus and spittle particles, for example, do not travel the farthest, even though that is what momentum would predict. Unexpectedly, the tiniest droplets all interact with the gas instead of operating individually. Caught up in the cloud, they behave more like a whiff of smoke than the spray of a garden house. As a result, whereas the large droplets travel up to four feet, the small droplets can reach eight feet.

This finding may be fundamental to our ability to control the spread of disease. A gaseous cloud of hitchhiking microbes could travel far enough to reach ventilation units, meaning its dispersal potential is much greater than had been assumed. The work could help researchers estimate the disease-spreading potential of various air conditioners and map how pathogens may ultimately float around an office, airplane or home. —*Rachel Nuwer*

SCALE

Fastest Animal on Land? A Mite

Paratarsotomus macropalpis, a sesame seed–size mite found in southern California, is the speediest terrestrial animal, according to body-length-per-second measurements reported in a new study.

What if Usain Bolt, the fastest known human, and a cheetah were each reduced to the size of a mite and engaged in a race with *P. macropalpis* around a 4.5-inch-diameter bagel (*shown at actual size*)? The race would be over by the time Bolt made it about a quarter-inch.

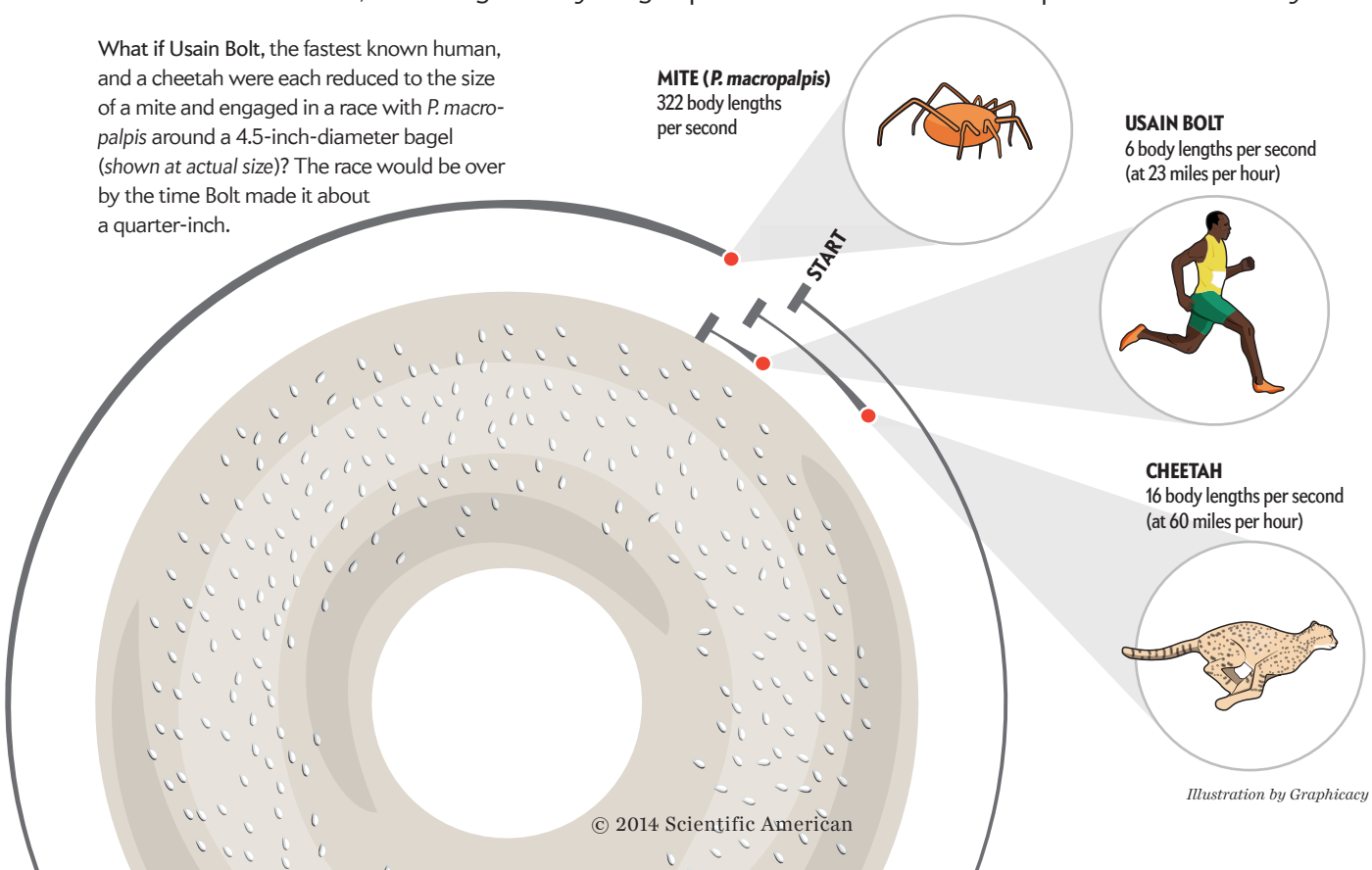

Illustration by Graphicacy

FROM "VIOLENT EXPIRATORY EVENTS: ON COUGHING AND SNEEZING," BY LYDIA BOUROUIBA, ELINE DEHANDSCHOEWERCKER AND JOHN W. M. BUSH, IN *JOURNAL OF FLUID MECHANICS,* VOL. 745; APRIL 2014 (*sneeze*)

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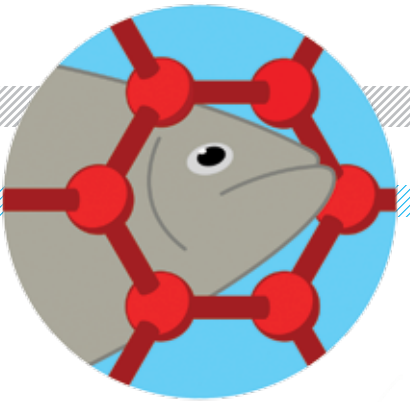


ENVIRONMENT

Graphene's Dark Side

The wonder material may pose risks if spilled

Graphene is one popular nanomaterial. Made from single-atom-thick sheets of carbon, it is the strongest material ever tested and boasts superlative electronic properties, too. After a decade of research, it is on the verge of moving from the laboratory into commercial technologies, perhaps appearing soon as lightweight airplane parts or batteries with incredible capacities.

So now might be a good time to anticipate potential risks posed by graphene, before workers are exposed to it or it gets into the water supply, says Sharon Walker, an environmental engineer at the University of California, Riverside. In research described in May in *Environmental Engineering Science*, Walker's group observed how one form of the material, graphene oxide, behaves in water.

Walker found that in a solution mimicking groundwater, graphene oxide clumped and sank, suggesting it is not a risk. That was not the case in a solution mimicking surface water, which includes lakes and storage tanks for drinking water. Instead of falling to the bottom, it stuck to the organic matter produced by decomposing plants and animals and floated around. Such mobility might increase the chances that animals and people could ingest graphene oxide, which has shown toxicity in some early studies in mice and human lung cells.

"This is a good first glimpse of how graphene might behave in the water supply," Walker says. If these materials do turn out to pose a risk to human health, their mobility in surface water could be a big problem. She hopes these studies are early enough in the conversation to inform how industry develops graphene and its derivatives and how agencies, such as the Environmental Protection Agency, regulate them.

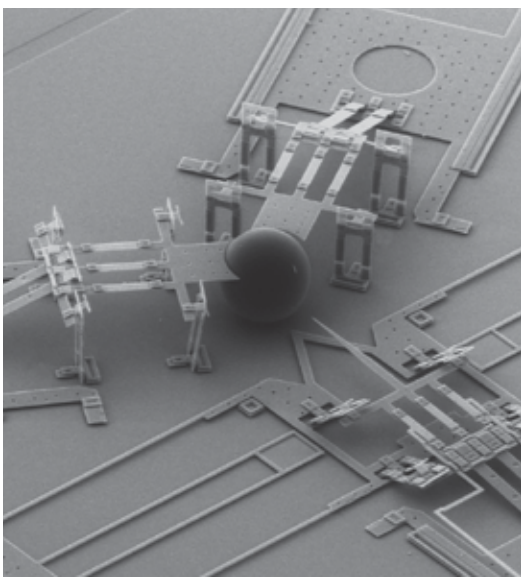
—Katherine Bourzac

NANOTECHNOLOGY

Hold Still

A teeny device for fundamental genetics

To insert genes into a cell, scientists often prick it with a tiny glass pipette and inject a solution with the new DNA. The extra liquid and the pipette itself, however, can destroy it: only half of cells that undergo this procedure survive. In place of a pipette, scientists at Brigham Young University have developed a silicon lance. They apply a positive charge to the lance so that the negative-charged DNA sticks. When the device enters a cell, the charge is reversed and the DNA is set free. In the study, 72 percent of nearly 3,000 mouse egg cells survived. *—Geoffrey Giller*



The nanoinjector is only about a millimeter across. Here a bead stands in for the egg cell of a mouse.

FROM "A SELF-RECONFIGURING METAMORPHIC NANOINJECTOR FOR INJECTION INTO MOUSE ZYGOTES," BY QUENTIN T. ATEN ET AL., IN *REVIEW OF SCIENTIFIC INSTRUMENTS*, VOL. 85, NO. 5, MAY 2014 (*nanoinjector*)

Illustrations by Thomas Fuchs

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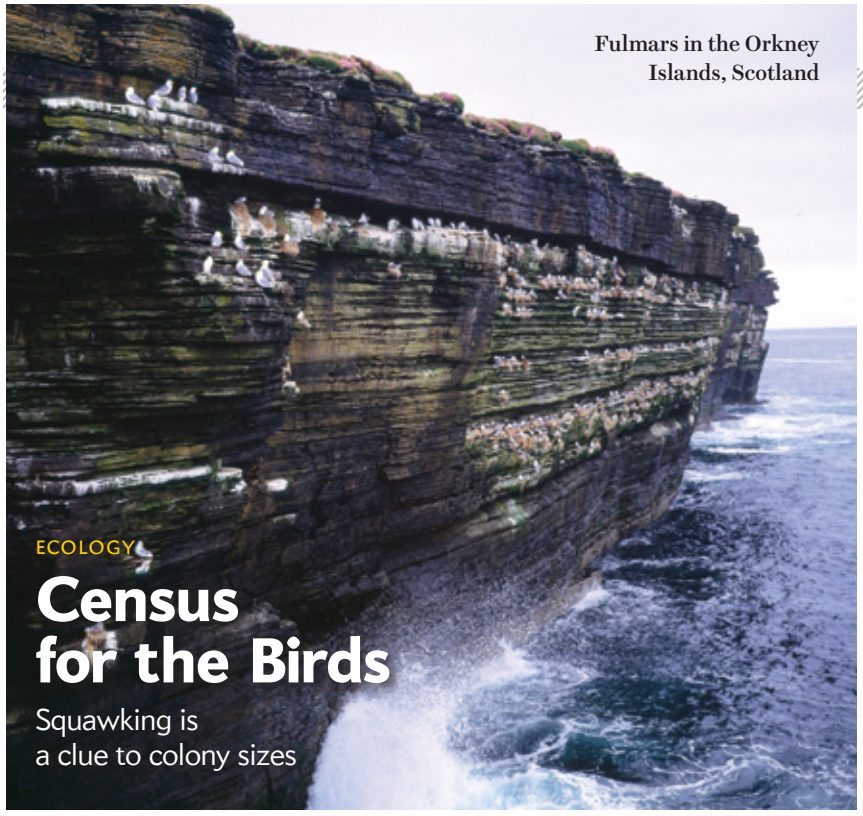

Fulmars in the Orkney Islands, Scotland

ECOLOGY

Census for the Birds

Squawking is a clue to colony sizes

One of the most basic field research techniques in bird conservation is counting birds and their nests. Tallying songbirds in a suburban garden is one thing; spotting seabirds is another. Seabirds, which reflect the health of their marine ecosystems, often build their nests in inaccessible areas—wedged into vertical cliffs or on remote islands battered by intense waves. Many lay their eggs in burrows more than a meter deep to protect them from weather. And on top of that, most are nocturnal, making them hard to see even in plain sight.

"There is a vast number of shearwater and petrel colonies for which we have absolutely no idea whether there are hundreds of pairs, or thousands, or tens of thousands," says Steffen Oppel of the Royal Society for the Protection of Birds. So Oppel and his colleagues have come up with a new method for monitoring the populations without being able to see them: they listen.

Oppel and his team found that they could use audio recordings to estimate a bird's population size after testing the method on a raucous colony of Cory's shearwaters that breeds on a small island in the Azores called Corvo. They describe their findings in the journal *Nature Conservation*. By combining acoustic data from nine microphones placed around Corvo with information about nest density, the researchers developed an algorithm that took terabytes of audio recordings and automatically counted the number of individual calls. They found, as expected, that more nests meant louder recordings and more calls. That correlation enabled them to extrapolate an estimate for the seabird population for the entire island—6,000 breeding pairs—something that in the past has been little more than a simple guess.

Even if the estimate is off somewhat, Oppel's method will be useful for detecting increases or decreases in populations over time. From that, scientists can infer the health of the seabirds' food chains as well as observe how rookeries are faring in the face of invasive predators and climate change. —*Jason G. Goldman*

BY THE NUMBERS

28

Percentage of seabird species that are threatened or endangered.

SOURCE: "Seabird Conservation Status, Threats and Priority Actions: A Global Assessment," by John P. Croxall et al., in *Bird Conservation International*, Vol. 22, No. 1; March 2012

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SPACE

A Moonlet Is Born

Saturn's rings appear to have spawned a small satellite

Best known for its stunning rings, Saturn also boasts a fleet of 62 moons—ranging from giant Titan, which is larger than the planet Mercury, to one as small as the ocean liner *Titanic*. Now astronomers may be witnessing something they have never seen before: the birth of a moon out of the same rings that make Saturn such a spectacle.

"The discovery was accidental," says Carl Murray, a planetary scientist at Queen Mary, University of London. In April 2013 he was examining fresh images of Saturn's moons taken by the Cassini spacecraft when he noticed a bright feature more than 1,000 kilometers long at the edge of the A ring, the outermost of Saturn's three main rings.

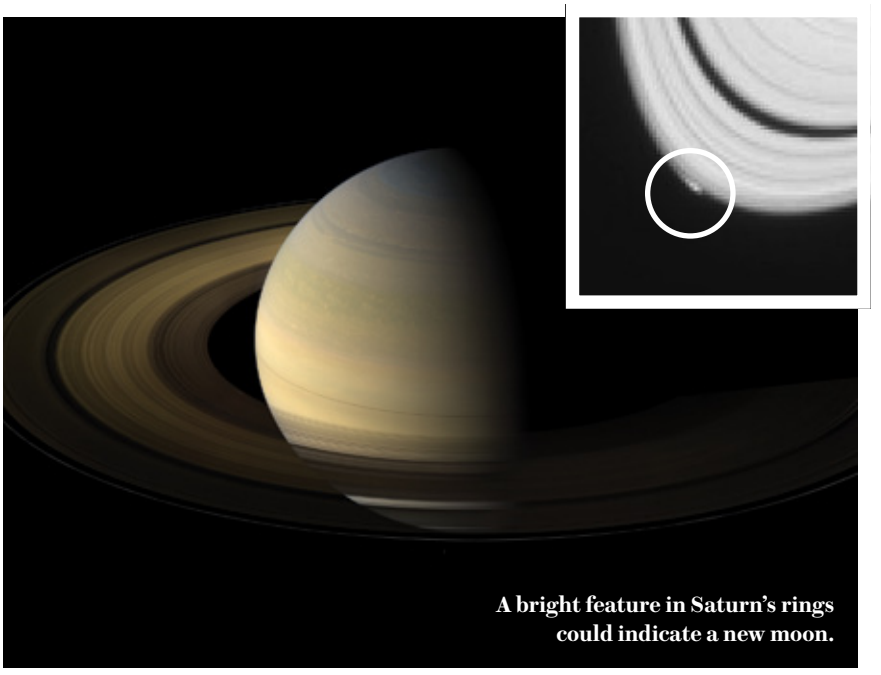
The bright spot may signal the presence of a new moon struggling to arise, Murray and his colleagues speculate in the July 1 issue of the journal *Icarus*. The new moon is less than a kilometer across, too small to be seen—until something hit the moon last year and produced the flare-up that attracted his attention. The A ring is ripe for spawning new moons because the gravitational influence of a larger satellite, Janus, located beyond the ring causes particles at the ring's outer edge to congregate. If the particles form a big enough clump, their own gravity should then attract more material, eventually creating a moon. Murray thinks this one formed recently but does not know whether it was born just a few years ago or millions of years earlier.

Jeff Cuzzi of the NASA Ames Research Center, who was not involved in the discovery, has little doubt that Murray has found a nascent moon. The more important question now, he says, regards the moon's fate: Will it successfully migrate out of the rings to take its place among the established moons, or will it disintegrate?

The fledgling moon still faces some challenges. Because it is presumably made of water ice, like Saturn's rings, impacts from meteoroids could pulverize it in the next few million years.

Murray hopes to catch a direct sighting in 2016, when Cassini skirts close enough to the A ring to capture a good image. Saturn's ring system resembles a young star's protoplanetary disk in that each is flat and revolves around a massive object. The moon's creation could yield insight into how planets are born. Saturn's rings may therefore offer a microcosm of newborn solar systems throughout the galaxy.

—Ken Croswell



A bright feature in Saturn's rings could indicate a new moon.

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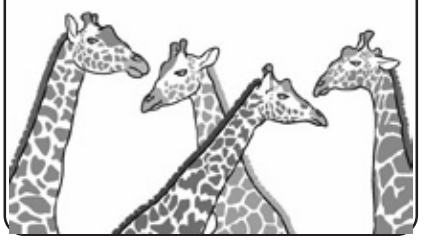

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Putting innovation on the front burner: NPAF's blueprint for action on cancer

If there was ever a time to accelerate cancer innovation, it is now. Already the nation's most costly disease[1] and the second most common cause of death in the United States[2], cancer kills nearly 1,600 Americans every day and costs the country more than US $200 billion yearly in health-care costs and lost productivity[3]. What is more, we face a future where the incidence of cancer will rise dramatically as the 'baby boom' population ages. As a result, cancer is predicted to soon become the number one disease-related killer of Americans.

Despite these projections, it is clear that we have the tools to reduce the burden of cancer. What can change this situation? The same kind of medical breakthroughs that eradicated polio in the United States in 1979, turned HIV/AIDS into a treatable, chronic condition and led to childhood leukaemia survival rates of 90%[4].

Already, innovative new cancer treatments have led to decreases in the incidence of many of the more than 200 types of cancer and are contributing to the rise in the number of people who are surviving longer and living fuller lives after receiving a cancer diagnosis. In fact, overall cancer deaths dropped 20% since 1991[3] while 5-year survival rates now average 68.5%, up from 48.7% in 1975[5] (Figure 1). As a result, there are now more than 13.7 million cancer survivors in the United States, almost 2 million more than in 2008[1].

At the same time, new cancer therapies are associated with 50 million life years saved over the last 15 years[6] as well as reduced spending on hospital and physician care, amounting to an economic gain of $1.2 million per person[7]. This translates into $3.2 trillion per year in national wealth added to the economy between 1970 and 2000, a value equal to about half the annual Gross Domestic Product (GDP) over this 30 year period[7]. Further breakthroughs will have similar results, with a substantial portion of health care savings to be realized within the federal Medicare and Medicaid programs.

CHALLENGES IN DEVELOPING CANCER TREATMENTS

Despite these major advances, continued progress in cancer innovation is not a certainty. Even as the science driving medical discovery is accelerating exponentially, venture capital investment in biotechnology has declined since 2007[8] and overall government spending on basic medical research has declined by close to 20% since 2010[9]. At the same time, the biopharmaceutical innovators and private research institutions now responsible for the majority of the nation's investment in cancer research and development are impeded by significant institutional and regulatory obstacles, especially in developing new drug therapies.

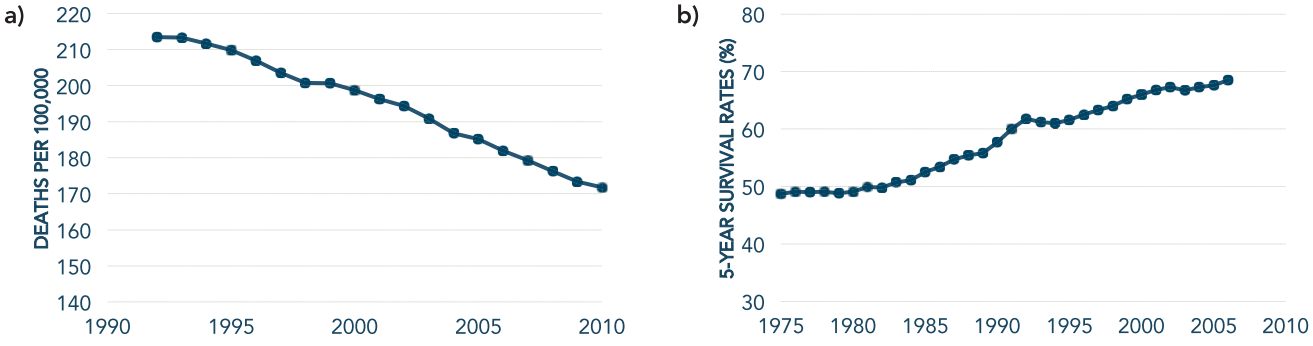

Figure 1. (a) US cancer-related death rates have declined over two decades. All cancer sites combined, all races/ethnicities, both sexes, age-adjusted. (b) 5-year US cancer survival rates, 1975–2006. All cancer sites, all races/ethnicities, both sexes and all ages combined. Source: Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats.

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Some of the major hurdles are the time and costs involved in developing a promising cancer drug and getting it approved. Compared to an average time of two years from discovery to approval for HIV drugs, it takes nine or more years to bring a new cancer therapy to patients[10]. Development is also an uncertain process in which an estimated 19 out of every 20 experimental drugs never make it to market[11]. Not surprisingly then, development costs for cancer treatments have reached new highs. According to a 2010 Tufts University study, the cost of developing one innovative cancer drug can be upwards of $1 billion[12].

Compounding the problem, there are also considerable deficiencies in how cancer clinical trials are conducted, from lack of public awareness and not covering patients' non-treatment costs to no singular repository of clinical trials listings. One potential solution is the use of smaller, more-targeted studies that target specific cancer patients and achieve results more quickly.

THE THREE PILLARS OF INNOVATION

The obstacles to accelerated cancer innovation affect everyone, which is why addressing these persistent and pervasive problems cannot wait. Accordingly, the National Patient Advocate Foundation (NPAF), in collaboration with the Cancer Innovation Coalition, conducted a thorough review of the impediments to cancer innovation and identified some readily achievable solutions. The result is a blueprint for action that involves three pillars of innovation.

Expand the science of innovation by reducing logistical obstacles

This will require moving to a more standardized regulatory-approval process, streamlining the many logistical hurdles to conducting clinical trials, allowing patients expedited access to innovative new therapies before they are approved for general use, and developing a centralized, nationwide hub from which data relating to cancer trials can be accessed and shared.

Improve the value of innovation by bolstering funding opportunities

To accelerate cancer innovation, NPAF encourages a new wave of experimentation in research funding. This could include new models that increase the incentives of research and eliminate uncertainty for innovators and investors, allowing them to pursue bold, high-risk investments that will ensure a sustainable pipeline of next-generation cancer therapies for decades to come. It is also imperative that all stakeholders align around the need for increased congressional appropriations for government-funded cancer research, especially for basic biomedical research, a key driver of late-stage research.

Enhance the delivery of innovation through improved communication and coordination between providers and patients

According to recent estimates, only 2–5% of adult patients enroll in cancer clinical trials[13]. This low uptake is the result of impediments, such as lack of awareness, the complexity of consent forms and other patient materials, and the costs for travel and other non-treatment expenses not reimbursed by payers. Addressing these problems will require improved communication and coordination between providers and patients, and regulatory policies that ensure that payers cover clinical trial costs as required by an Executive Order signed by President Clinton in 2000 and a National Coverage Decision (NCD) for Routine Costs in Clinical Trials issued by the Centers for Medicare and Medicaid Services on September 19, 2000 and reaffirmed in 2007[14].

LOOKING FORWARD

All Americans — from patients and health-care providers to research scientists, biomedical innovators, payers, venture capitalists and the business community — have a stake in accelerating the pace of progress against cancer. Thus, advancing realistic and achievable policy solutions is a crucial step towards saving lives, reducing health-care costs and achieving greater economic prosperity. The time for action is now.

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DISEASE

Two of a Kind

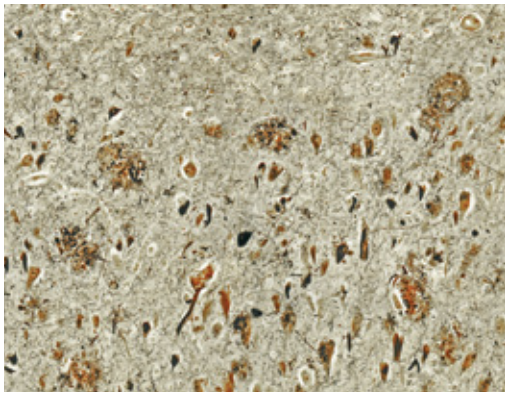
The similarities between Alzheimer's disease and Down syndrome draw attention

Is Alzheimer's disease an acquired form of Down syndrome? When neurobiologist Huntington Potter first posed the question in 1991, Alzheimer's researchers were skeptical. They were just beginning to explore the causes of the memory-robbing neurological disease. Scientists already knew that by age 40, nearly 100 percent of patients with Down syndrome, who have an extra copy of chromosome 21, had brains full of beta-amyloid peptide—the neuron-strangling plaque that is a hallmark of Alzheimer's. They also knew that the gene that codes for that protein lives on chromosome 21, suggesting that people acquire more plaque because they get an extra dose of the peptide. Potter, though, suggested that if people with Down syndrome develop Alzheimer's because of an extra chromosome 21, healthy people may develop Alzheimer's for the same reason. A quarter of a century later mounting evidence supports the idea.

"What we hypothesized in the 1990s and have begun to prove is that people with Alzheimer's begin to make molecular mistakes and generate cells with three copies of chromosome 21," says Potter, who was recently appointed director of Alzheimer's disease research at the University of Colorado School of Medicine, with the express purpose of studying Alzheimer's through the lens of Down syndrome.

He is no longer the only one exploring the link. In recent years dozens of studies have shown Alzheimer's patients possess an inordinate amount of Down syndrome–like cells. One 2009 study by Russian researchers found that up to 15 percent of the neurons in the brains of Alzheimer's patients contained an extra copy of chromosome 21. Others have shown Alzheimer's patients have 1.5 to two times as many skin and blood cells with the extra copy as healthy controls. Potter's own research in mice suggests a vicious cycle: when normal cells are exposed to the beta-amyloid peptide, they tend to make mistakes when dividing, producing more trisomy 21 cells, which, in turn, produce more plaque. In August, Potter and his team published a paper in the journal *Neurobiology of Aging* describing why those mistakes may occur: the inhibition of a specific enzyme.

Meanwhile University of Kentucky researchers have been collecting brain scans, blood tests and lifestyle surveys from dozens of adults with Down syndrome over the past five years. They aim to understand why—even though nearly all patients develop plaque—only 60 to 80 percent develop dementia.



THOMAS DEERINCK *Science Source*

Plaque buildup in the brain is a hallmark of Alzheimer's disease.

National Institutes of Health director Francis Collins recently told a Senate subcommittee that there is "intense interest" in studying the two conditions together. And in 2013 the Alzheimer's Association teamed up with the Linda Crnic Institute for Down Syndrome to fund work examining the link.

In general, by studying Alzheimer's in a smaller population guaranteed to develop the pathology, scientists can learn more, faster, says Dean Hartley, director of science initiatives for the Alzheimer's Association. He and others say it is too early to conclude that Alzheimer's is indeed a form of Down syndrome: "But we need new ideas like this in the field to help us better understand the underlying pathways of the disease." —*Lisa Marshall*

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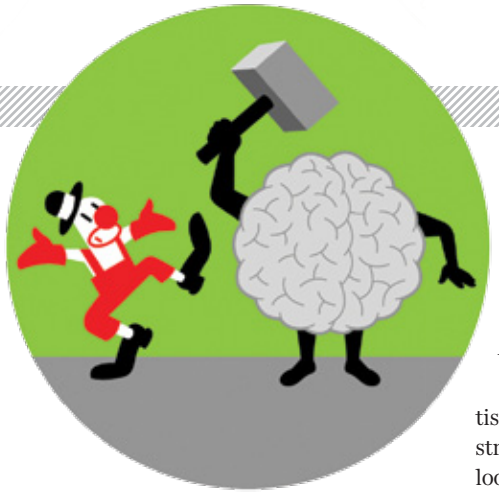

NEUROSCIENCE

The Brain's Power to Avoid Diversions

Paying attention requires more than focus

You know the exit is somewhere along this stretch of highway, but you have never taken it before and do not want to miss it. As you carefully scan the side of the road for the exit sign, numerous distractions intrude on your visual field: billboards, a snazzy convertible, a cell phone buzzing on the dashboard. How does your brain focus on the task at hand?

To answer this question, neuroscientists generally study the way the brain strengthens its response to what you are looking for—jolting itself with an especially large electrical pulse when you see it. Another mental trick may be just as important, according to a study published in April in the *Journal of Neuroscience:* the brain deliberately weakens its reaction to everything else so that the target seems more important in comparison.

Cognitive neuroscientists John Gaspar and John McDonald, both at Simon Fraser University in British Columbia, arrived at the conclusion after asking 48 college students to take attention tests on a computer. The volunteers had to quickly spot a lone yellow circle among an array of green circles without being distracted by an even more eye-catching red circle. All the while the researchers monitored electrical activity in the students' brains using a net of electrodes attached to their scalps. The recorded patterns revealed that their brains consistently suppressed reactions to all circles except the one they were looking for—the first direct evidence of this particular neural process in action.

"Neuroscientists have known about suppression for quite some time, but it's not given as much thought as mechanisms that boost attention," McDonald says. "We have nailed down how you can prevent distraction through suppression." Such research may eventually help scientists understand what is happening in the brains of people with attention problems, such as attention-deficit/hyperactivity disorder. And in a world increasingly permeated by distractions—a major contributor to traffic accidents—any insights into how the brain pays attention should get ours.

—Ferris Jabr

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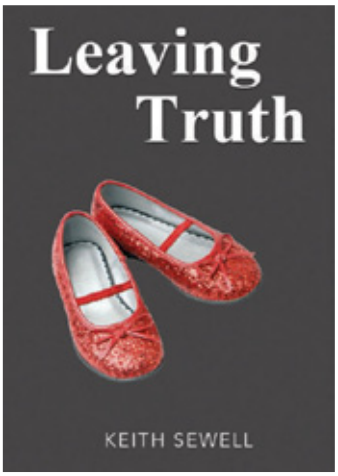

I think that our most functional criterion for identifying proposals as knowledge is physical observation, repeatable on demand.

* * * * * * * *

What I'd like to understand, at last, is the ostensibly more powerful basis upon which theists seek to deny this. They must have one, as their defining proposals are directly controverted by our entire body of on-demand-repeatable physical observation based knowledge. Reality cannot show us, more clearly than it already has, that the miracles upon which our theists base their initial beliefs in their Supernatural Beings never really happened.

To be explicit, I am not merely claiming that the theists are wrong. I'm claiming that they are wrong by any criterion through which right and wrong can be coherently distinguished. This claim is a lot stronger, and it's testable. For example, if Christians can show any functional basis for knowledge-selection that validates the existence of Yahweh over his logically exclusive alternatives (Allah, Vishnu, Wotan, etc.), or if Muslims can show any such basis that preferentially selects Allah, then my claim would be invalidated. We have never been able to win at the level of our 'truths' against the theists' 'truths,' but I think that we can now win at the level of on-demand-repeatable physical observation vs. our species' common-sense concept of 'truth' itself. I think that we have had all of the needed philosophical pieces in place, for about the 80 years since publication of Karl Popper's Logic of Scientific Discovery, to definitively call the theist's bluff at this deepest accessible epistemic level. My book's essays therefore argue and provide ammunition for such a bluff call, between ourselves and all who still proselytize for emotionally seductive irrational knowledge systems (systems that can only be propagated as 'truth'). If I can get enough of you in own my camp to understand and help me to spread this call, then – like Archimedes with his lever – we will start to move the world.

* * * * * * * *

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HIV kills immune system cells.

MEDICINE

How to Curb an Epidemic

The next generation of HIV prevention

Doctors now consider HIV infection to be a chronic disease rather than a death sentence because of the success of antiretroviral drugs (ARVs), which stop the infection's progression to AIDS. With that success in hand, the top priority is now prevention. The choices available to most of the world—abstinence, condoms and male circumcision—are not doing enough; more than 6,000 people contract HIV every day. And those methods are especially problematic for women, who, because of social and economic circumstances, often have less control over their options.

As an alternative for women, scientists are testing a new class of antiretroviral drugs, called ARV microbicides, that prevent HIV infection altogether. Researchers have fashioned the microbicides into an array of devices currently undergoing human trials. "These are extremely promising products," says Robert Grant, an AIDS expert at the University of California, San Francisco. "I'm optimistic we can end HIV, but for too long we've been looking for the holy grail, a single product to prevent HIV. It's not one size fits all." Here are three of the microbicide options in development today. —*Annie Sneed*

Stay-in-Place Ring

Placed in the vagina, this silicone ring releases the ARV drug dapivirine for one month. Dapivirine is a reverse transcriptase inhibitor: a drug that blocks HIV's replication from RNA to DNA, halting its takeover of human cells. More than 5,000 African women are testing the ring in two phase III clinical trials that will end in 2016. If safe and effective, it could become a two-in-one device: researchers are developing a dapivirine ring with birth control to prevent both HIV and pregnancy.

Gel for before Sex

Tenofovir gel, another reverse transcriptase inhibitor, comes in a tamponlike applicator that women use before sexual intercourse. The clear gel was the first microbicide to indicate significant reduction in HIV in humans in a large clinical trial; in the study, which had nearly 900 women participating, the gel reduced infection by 54 percent in women who used it consistently. Researchers are continuing to test its effectiveness at nine sites in South Africa. Those results are expected in late 2014.

Gel for after Sex

Raltegravir gel could someday offer what the others do not: protection against HIV when applied *after* sex. Raltegravir stops HIV late in its life cycle, just before the virus integrates into the human chromosome. The Centers for Disease Control and Prevention evaluated the gel in macaques in March and found it highly effective in preventing infection up to three hours after exposure. If it passes future trials and becomes an option, it could give women a backup, especially in cases of sexual assault.

SCIENCE SOURCE

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DARK MATTER

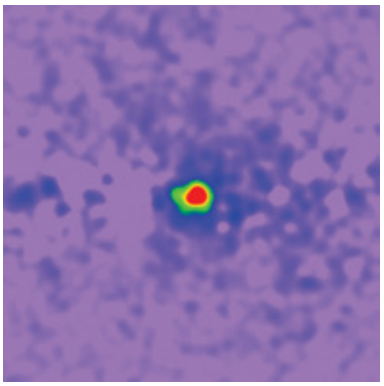
A Glimpse at the Unseen

Mysterious light from the center of the Milky Way may be our first look at dark particles

Dark matter is one of the universe's most befuddling, and elusive, components. It could make up roughly a quarter of the universe's total mass and energy, yet no one knows for sure because no one has actually seen it. Well, it may be showing itself at last. NASA's Fermi Gamma-ray Space Telescope has recorded high-energy gamma-ray light emanating from the center of the Milky Way that fits well with dark matter predictions. "I would consider it currently the most exciting signal that we have," said physicist Rafael Lang of Purdue University, who was not involved in the study, at the American Physical Society's meeting in April in Savannah, Ga. If the light were truly caused by dark matter, it would be the first indirect detection of the particles that make up this shadowy substance.

Dark matter is most likely made of so-called weakly interacting massive particles (WIMPs), particles that would be their own antimatter partners and therefore destroy one another on colliding. Such WIMP annihilations would produce normal matter particles that would in turn create gamma-ray photons. Because dark matter should be densest at the Milky Way's core, that is the best place to look for that light.

Scientists had previous hints that the Fermi telescope is seeing more light at the galactic center than expected. [For news of another unexplained Fermi signal, see page 42.] But where earlier analyses were inconclusive, the new study found a stark signal: an excess of gamma-ray photons extending at least



5,000 light-years from the Milky Way's center (*above*). "It looks exactly like we've always expected dark matter to look," says Dan Hooper of Fermi National Accelerator Laboratory in Batavia, Ill., an author of the study.

Of course, extraordinary claims require extraordinary evidence. Most scientists are reserving judgment until the signal is seen by other instruments or in other places. But dark matter may have gotten a little less elusive.

—Clara Moskowitz

FROM "THE CHARACTERIZATION OF THE GAMMA-RAY SIGNAL FROM THE CENTRAL MILKY WAY: A COMPELLING CASE FOR ANNIHILATING DARK MATTER" BY TANSU DAYLAN ET AL. PREPRINT PUBLISHED ONLINE FEBRUARY 26, 2014 *http://arxiv.org/abs/1402.6703*

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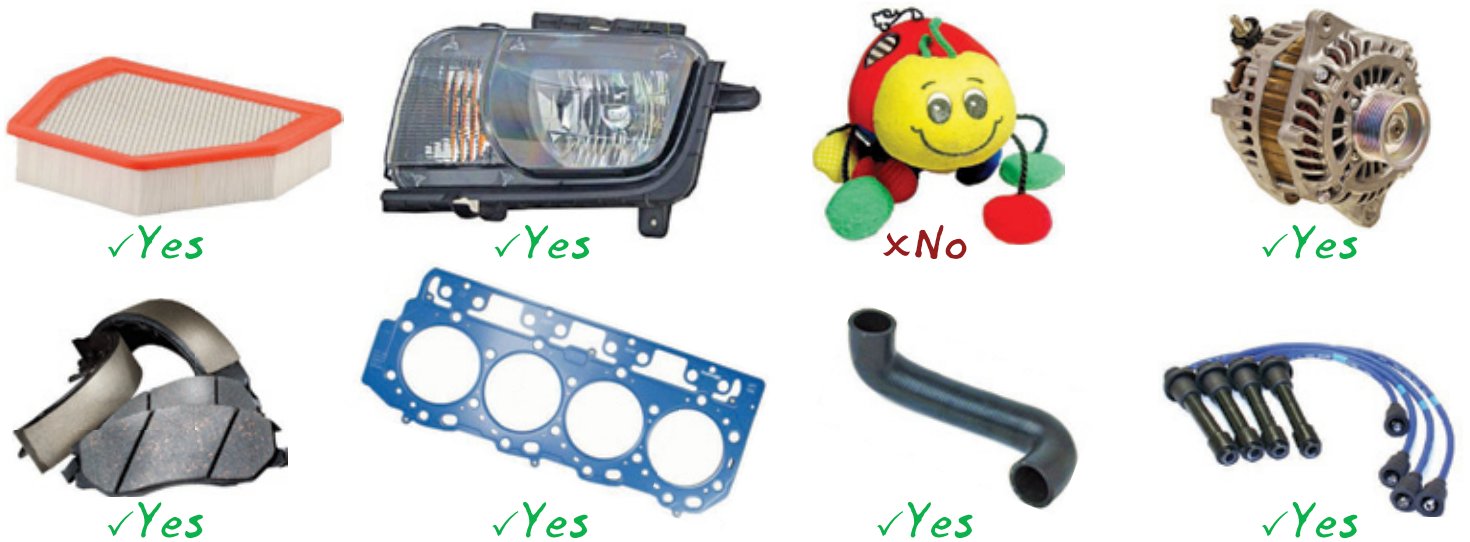

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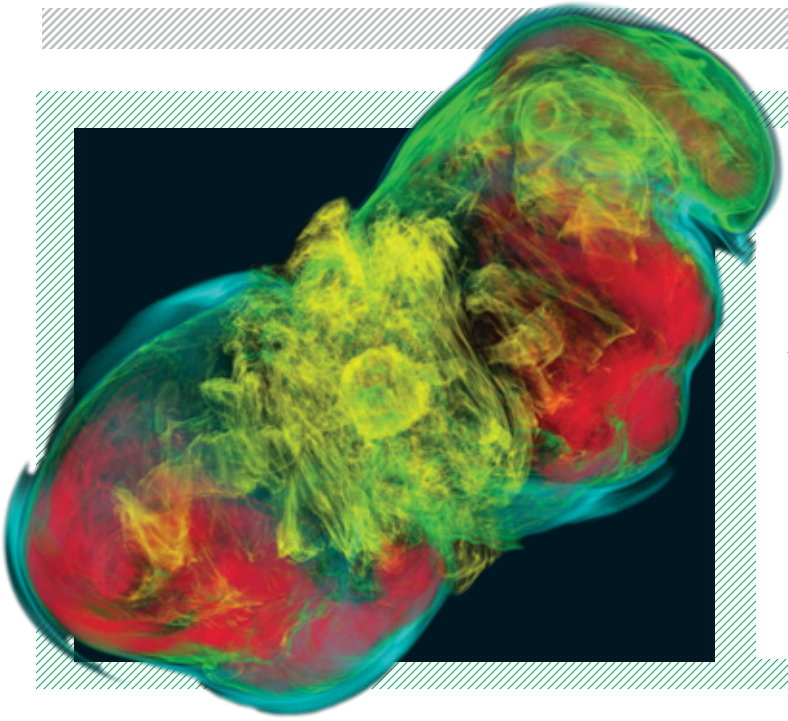


WHAT IS IT?

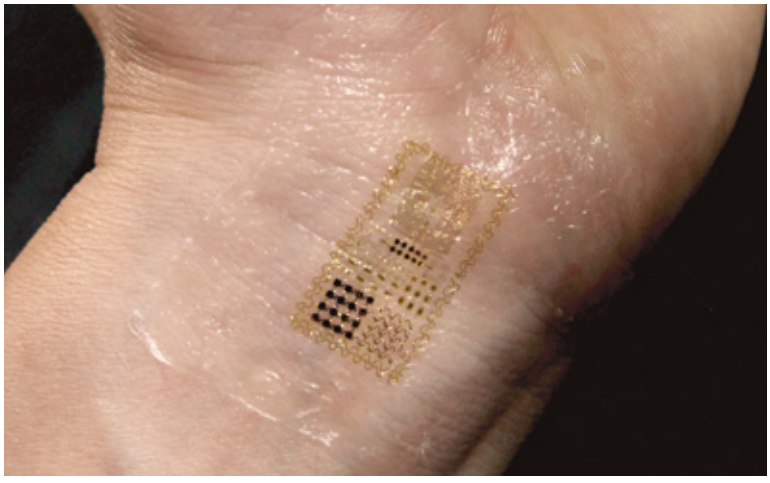
What looks like a soap bubble is actually a 3-D simulation of a supernova—or rather a failed attempt at a supernova. Cosmic explosions mark the death of massive stars and are some of the most energetic phenomena in the universe, but they are not all-or-nothing events: some supernovae halt before they ever take off, as a new supercomputer simulation detailed in the *Astrophysical Journal Letters* shows.

The simulation modeled a class of supernovae that start from fast-spinning, highly magnetized stars. To the researchers' surprise, the program showed that such supernovae easily stall. If the magnetic field around the star is less than perfectly symmetrical, tiny kinks can become major instabilities that cause matter from the star to push out in the lopsided bulbs seen here. The process prevents the star from blowing up in typical supernova fashion. To understand what ultimately becomes of these aborted explosions, the scientists, led by California Institute of Technology astrophysicists Philipp Mösta and Christian Ott, say they will need an extended simulation on a more powerful supercomputer. —*Clara Moskowitz*

MATERIALS SCIENCE

The Circuit Made for Your Arm

"Electronic skin" is blurring the lines between biological tissue and electronics. These filmlike patches, introduced in 2011, contain incredibly thin circuits, sensors and other electronic components and mount onto the skin with all the flexibility and stretchiness of a temporary tattoo. Within the past few months scientists have demonstrated numerous practical applications for the devices, setting the stage for a revolution in health care monitoring. —*Joseph Bennington-Castro*



ELECTRONIC SKIN CAN KEEP TABS ON:

The Brain	*Wounds*	*Motion*	*Medication Needs*	*The Heart*
When placed on the forehead, it can read the electrical activity of the brain and provide electroencephalographic data just as well as conventional wired devices while being far more comfortable and less motion-restrictive—a boon for neonatal intensive care units.	By measuring temperature changes near a surgical wound, it can spot early signs of inflammation and infection. It can also gauge how well a cut is healing by measuring hydration levels (proper recovery requires moisture).	When integrated with an accelerometer, it can collect body-motion data throughout the day. This information is vital to understanding how a patient with Parkinson's disease, for instance, responds to new treatments.	With memory, physiological sensors and onboard prescription drugs, it can store diagnostic information and then deliver the correct drug dosage when a patient needs it.	Applied surgically, large electronic-skin membranes can envelope the heart to fully oversee cardiac activity or possibly to function as low-energy pacemakers or implantable cardioverter defibrillators (devices that help to control irregular heartbeats) in the future.

COURTESY OF PHILIPP MÖSTA AND SHERWOOD RICHERS *California Institute of Technology (3-D simulation)*; JOHN ROGERS *University of Illinois at Urbana-Champaign (electronic skin)*

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BIOLOGY

Here to Stay

The male sex chromosome isn't shrinking

The Y chromosome is the runt of our 46-chromosome litter. Despite its well-known role—determining whether a mammal will be male—it pales in comparison to the other chromosomes, especially its partner, X. Indeed, 200 million to 300 million years ago Y shared roughly 600 genes with X. Today they share only 19. Those losses, some geneticists noted in 2002, indicated Y was actually rotting away. Give it another 10 million years, they said, and Y would be extinct. Others then wondered whether males would go with it.

But Y has stopped shedding those genes, according to recent research, and, in fact, has been stable for the past 25 million years, says David Page, a biologist at the Massachusetts Institute of Technology and an author of the study, which appeared in *Nature*. (*Scientific American* is part of Nature Publishing Group.) Page and his colleagues found that although Y was much skimpier in more recently evolved species, the attrition had stopped millions of years ago.

That stability may come from a core of about 12 genes that have nothing to do with sex and are instead responsible for vital cellular functions in the heart, blood, lungs and other tissues. "These are powerful players in the central command room of cells," and natural selection would favor their survival, Page says.

One proponent of the rotting Y idea is not convinced. The past several million years may simply be a lull, says Jennifer Graves, a geneticist at the Australian National University. She notes that at least two rodent groups have managed to dispense with it altogether. The new research suggests, however, that Y will remain at its current, if slight, size. —*Josh Fischman*

IN REASON WE TRUST

Steven Pinker
Johnstone Professor of Psychology, Harvard University, and author of *The Blank Slate* and *The Better Angels of Our Nature*
FFRF Honorary President

"The biology of consciousness offers a sounder basis for morality than the unprovable dogma of an immortal soul. Once we realize that our own consciousness is a product of our brains, and that other people have brains like ours, a denial of other people's pleasures and pains becomes ludicrous. 'Hath not a Jew eyes?' asked Shylock. Today the question is more pointed: Hath not a Jew—or an Arab, or an African, or a baby, or a dog—a cerebral cortex and a thalamus? The undeniable fact that we are all made of the same neural flesh makes it impossible to deny our common capacity to suffer."

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Black Holes

Speaker: Jenny Greene, Ph.D.

Black Holes: Galactic Gobblers

Lurking at the heart of every massive galaxy is a giant black hole. Learn what we know of these behemoths, thought to be nearly infinitely small and infinitely dense. Here the current laws of physics break down, but modern observatories can provide some hints of what lies inside.

Black Hole Origins

Which came first: giant black holes, or the massive galaxies that surround them? Black holes can form in multiple ways, and they influence the evolution of the galaxies they inhabit. Learn what we do and don't know about the birth of black holes, and how we stand to revolutionize our knowledge in the coming years.

Black Hole Evolution

Black holes feasting on matter are some of the most luminous objects in the universe. We know that many black holes grew up when most of the stars formed in the universe, yet the details of this process are mysterious. Learn how observations of gravity waves could help us understand black hole evolution.

Women in Astronomy & Physics

Women are underrepresented in many science fields, but especially astronomy and physics. We'll discuss the real numbers behind this problem, and the various factors that play into it, including sub-conscious bias in hiring and test-taking practices. We'll also examine ways to change this pattern in the future.

The Intelligent Brain

Speaker: Richard J. Haier, Ph.D.

Mysteries of Intelligence and the Brain

Yes, intelligence is something real and it can be defined and studied scientifically. We'll consider savants and geniuses, how to define intelligence, and discuss how intelligence tests work. We'll review the key research and discuss why a person's intelligence is both liberating and constraining. We'll also consider why smart people do dumb things.

The Origins of Intelligence

We know there is a strong genetic component of intelligence from studies of twins and investigations that combine genetic analyses and neuro-imaging. Surprisingly, research results showing the influence of specific environmental factors, including early childhood education, are rather weak. Learn why brain development, as revealed by neuro-imaging, may be a key.

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What Makes a Brain Smart?

Neuro-imaging research has identified brain features and specific areas distributed throughout the brain that are related to intelligence test scores. We'll review, in non-technical terms, how neuro-imaging works and we'll see some amazing dynamic views of intelligence at work in the brain during problem-solving, including some findings "hot off the press."

How Smart Do You Want To Be?

As we learn about the neural mechanisms of intelligence, prospects for enhancing intelligence become more likely. We'll discuss the ethical quandaries this raises. If there were an IQ pill, would you take it? What about enhancing intelligence in children? If we could enhance intelligence, do we have a moral obligation to do so?

Dinosaurs

Speaker: Darren Naish, Ph.D.

Predatory Dinosaurs and the Origins of "Birdiness"

Theropods, which included giants like Allosaurus and Tyrannosaurus, also had numerous lineages of smaller bird-like dinosaurs, and many theropods were feathered. Take a tour through theropod diversity, and examine the many controversial ideas of how they lived, how they hunted, and what they looked like when they were alive.

Sauropod Dinosaurs and the "Necks For Sex" Debate

Sauropod dinosaurs had immensely long necks, sometimes more than four times longer than their bodies. Some have suggested this evolved as a sexual signal, its length driven by sexual selection pressure. I'll discuss my work testing this hypothesis, and why the neck might actually have evolved for feeding and foraging.

Pterosaurs: Flying Reptiles of the Mesozoic

Ancient reptiles called pterosaurs flew on membranous wings supported by enormous fourth fingers. They had furry bodies, air-filled bones and many species possessed crested skulls. Little is known about pterosaur behavior and social life, but we can make some educated guesses. Learn about the diversity, anatomy and biology of this amazing group.

The Remarkable Azhdarchoid Pterosaurs

Among the most unusual of pterosaurs are the azhdarchoids—animals with huge wingspans that stood over 4 meters tall. They have been imagined as mud-probers, vulture-like scavengers, skim-feeders and heron-like waders. We'll discuss the newest data that has changed our view of these fascinating animals.

Eclectic Astronomy

Speaker: Donald Kurtz, Ph.D.

Planets and Pulsations: The New Keplerian Revolution

The Kepler space telescope has discovered more than 3,500 candidate exoplanets, and is closing in on finding another Earth—a rocky planet in the "Goldilocks zone" where life might exist. Kepler has also allowed us to see stars as never before. Learn how this mission is revolutionizing our knowledge of the galactic zoo we inhabit.

It's About Time!

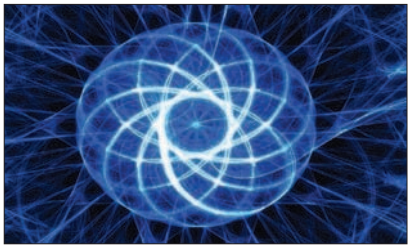
Days, weeks, months, years and more: Hear about Roman emperors, Zulu wars, Rider Haggard, Thomas Hardy, the English time riots, and how the days of the week got their names in an amusing and informative tour of the Western calendar.

The Stars are Ours!

"What good is astronomy?" Through colorful historical anecdotes and science, we'll answer that question. Hear stories of wealth and poverty, castles and dungeons, kings and princes, sailors and maidens, sea battles and Shakespeare, as we look back at the improbable, unpredictable path that gave us the Power of the Stars.

The Sun-Earth Connection

Learn how magnetic activity on the Sun affects Earth, from our planet's magnetosphere to the aurora lights. We'll see why the Sun is not the source of global warming, and we'll discuss weather on other stars. I'll also introduce you to a group of peculiar magnetic stars that I discovered.



Particle Physics

Speaker: Don Lincoln, Ph.D.

The Higgs Boson

Hear the saga of the Higgs boson particle, from its initial prediction in 1964 through its discovery to the 2013 Nobel Prize. As a member of one of the teams that discovered it, I will give an insider's perspective, including answering the very important question, "What's next?"

Accelerators and Particle Detectors

The Higgs boson, the top quark, dark matter—none of these particles are part of our everyday experiences. So how do scientists study these elusive particles? Learn about the complex technology we use to glimpse them, from 14,000-ton experiments with over a hundred million elements to particle observatories under the Antarctic ice.

History of Particle Physics

The search for the ultimate building blocks of matter has a long history. Hear the story, from the 1987 discovery of the electron to finding protons, neutrons and eventually particles that have no role in ordinary matter. Learn how we arrived at our current picture of quarks, leptons and a handful of force-carrying particles.

The Dark Side of the Universe

We understand the nature of the ordinary matter that makes up you and me, but ordinary matter is only 5% of the universe. Learn about the data that led us to conclude that a bizarre dark world must exist, and hear about current experimental efforts aimed at finding it.

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Maia Szalavitz is a neuroscience journalist based in New York City. Her work has been published in *Time* magazine, the *New York Times*, *Elle* and the *Washington Post*.

When Does Self-Help Actually Help?

Dangers lurk within the U.S.'s $12-billion self-help industry. Here is how to spot the warning signs

Kirby Brown was not afraid to take risks. The 38-year-old decorator learned to ride horses as a child and surfed giant waves in Mexico's Sea of Cortez as an adult. She was not reckless, though. "She loved adventure, but she was very safety-conscious," says her mother, Virginia Brown. So when Kirby decided in 2009 to take part in a spiritual retreat in the Arizona desert organized by well-known self-help guru James Arthur Ray, she probably did not think her life was in danger.

Intended as a "catalyst for personal transformation," the five-day retreat included 36 hours of meditation without food or water, followed by a ceremony in a makeshift sweat lodge. Kirby and one other participant did not survive the ritual; a third became comatose and died a week later. Eighteen others were hospitalized for injuries ranging from heat exhaustion to kidney failure. "Basically, these people were boiled," says Christine Whelan, a visiting sociologist at the University of Pittsburgh who studies the self-help industry.

The Arizona deaths, as well as suicides and psychotic episodes that have resulted during and after similar events, are extreme examples of the dangers that can lurk in the U.S.'s $12-billion or so self-help industry. The self-help philosophy stems from the commonsense assumption that many people are capable of coping with various problems—from the financial to the psychological—on their own; paid professional assistance is not always necessary. The broad umbrella of "self-help" approaches includes retreats such as Ray's, support groups that aim to improve mental health or change behavior, and more than 45,000 books and apps designed to help people live happier lives. Self-help books in particular are so popular that there is a separate best-seller list in the *New York Times* mainly devoted to them.

Although dozens of studies suggest that research-based self-help can provide real benefits—in particular, for anxiety, depression and drug addiction—more than 95 percent of self-help books and programs have never been subjected to scientific scrutiny, according to John C. Norcross, a professor of psychology at the University of Scranton and co-author of *Self-Help That Works* (Oxford University Press, 2013). People can, however, better protect themselves from potentially dangerous self-help rituals, Norcross and other investigators say, by learning to recognize warning signs of dubious experts and by understanding how peer pressure impairs judgment.

UNDER SCRUTINY

RESEARCHERS HAVE ASSESSED only an estimated 50 self-help programs for safety and efficacy, Norcross says. And the resulting evidence shows that some programs do work. The best-studied approaches for combating psychological problems, for example, emphasize the techniques of cognitive-behavior (CBT) therapy: learning to detect and deflect anxious, depressing or otherwise negative thoughts. A 2013 Cochrane review—considered a gold standard for large systematic reviews of health research—notes, for instance, that when it comes to anxiety disorders, seeing a therapist in person is most likely superior to self-help based on books and on apps but that "self-help is probably better than no treatment."

Aside from examining approaches based on CBT, researchers have also devoted a good deal of attention to "12-step" groups, such as Alcoholics Anonymous (AA), in which members urge one another to follow certain guidelines to cope with their addiction. Whereas a 2006 Cochrane review of AA concluded that "no

Illustration by Daniel Zalkus

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experimental studies unequivocally demonstrated" its effectiveness, many observational studies show that those who willingly participate are more likely to quit drinking than those who do not. (Unlike experimental studies, observational studies do not involve researchers changing the conditions that participants experience to determine if an intervention is effective.) One such study demonstrated that two thirds of people who stuck with the program for at least 27 weeks were still refraining from alcohol 16 years later. Yet according to AA's own surveys, the majority of people who come to the program for the first time are no longer attending after six months.

PEER PRESSURE

SITTING ON THE COUCH at home and reading a self-help manual might not seem like a dangerous activity. But anyone who blindly follows ill-advised instructions, such as eating a nutrient-poor diet, is asking for trouble over the long term—starting, at the very least, with gum disease in the case of the diet.

Self-help becomes particularly perilous whenever someone joins a group and peer pressure begins to counteract one's better judgment. Twelve-step programs, for example, typically remind participants not to "play doctor" because members have sometimes urged newcomers to stop taking psychiatric medications on the grounds that drugs of any kind could impede recovery. Not wanting to go against the group, vulnerable individuals have obliged and subsequently relapsed into depression, psychosis, anxiety or other disorders, in some cases resulting in suicide.

Add physical and emotional stress to peer pressure, and you have a potentially more dangerous brew. Seminars like the one Ray organized in the Arizona desert are known among psychologists as "large-group awareness trainings." During these kinds of retreats, which can include vague promises about self-improvement, a charismatic leader generally guides a group of people through several continuous days of meditation, self-hypnosis, fasting, sermons and discussions in which they share intimate details about their lives. All the while, the leader alternately rebukes and praises the participants—and denies them basic needs—to leave them psychologically vulnerable.

Before they even entered the sweat lodge, for example, Kirby and her fellow participants received limited amounts of food, water, bathroom breaks and sleep for several days. Hunger, thirst and sleep deprivation alone can profoundly stress the body and alter consciousness—but the ceremony was also emotionally taxing. Ray claimed at the time that the ordeal would bring them close to death, followed by a spiritual rebirth. (My repeated requests for an interview with Ray, made to his representative, were to no avail.)

Such stressful conditions frequently produce strong emotions ranging from despair to ecstasy and forge a sense of intimacy and affection between strangers. This sense of camaraderie makes people all the more susceptible to peer pressure and more obedient of authority figures. Stress also reduces blood flow to regions of the brain important for planning, self-control and reasoning. Even apparently minor stresses, such as being denied access to the bathroom, can wear down one's ability to resist social pressure, Whelan says.

The end result is that even highly intelligent and educated people can behave irrationally—say, staying in a tarp-covered hut so overheated that people begin to lose consciousness. The smartest individuals are, in fact, often at the highest risk because they tend to think they are immune to peer pressure. One of the participants who died carried a woman to safety before returning to the lodge. Apparently he did not realize he was in exactly the same kind of danger. "When people saw what happened in [Arizona], most of them said to themselves, 'Those people were idiots.'" Whelan says. "We like to think we are different, but we're not, and these are really powerful techniques. If you had been there, you might be dead, too."

Given how easily the brain succumbs to peer pressure, experts recommend avoiding group situations in which a leader deliberately induces stress—a technique that does not lead to helpful psychological changes according to the relevant studies. If you do wind up in such circumstances, be aware that they can profoundly alter your thinking and behavior; therefore, do not make life-changing decisions.

WHAT TO LOOK FOR

WHAT, THEN, ARE the critical elements of good self-help programs? First, overcoming depression, anxiety, addictions or other disorders typically requires learning new coping skills over many months or years, not in a matter of days or weeks. This is why successful forms of self-help prepare one for a long period of self-improvement and why groups like AA suggest long-term attendance. Intense, one-time experiences typically do not provide the ongoing support needed for lasting change.

Second, good programs have independent data showing their effectiveness, not just anecdotes, and they are generally adapted from techniques shown to work in more conventional therapy administered by professionals. If there is no published literature supporting a program—no matter how popular it may be—that is a red flag.

Whelan now serves on the advisory board of Seek Safely, an organization set up by the Brown family that offers tips to those who might be attracted to potentially dangerous programs. Seek Safely has also written a pledge that self-help gurus can sign as a way of promising to take the necessary safety precautions and to avoid using stress to make people more submissive.

Ray, who has rebooted his self-help business, has not signed. The biography on his Web site does not mention the deaths in the sweat lodge, his subsequent conviction for negligent homicide or his incarceration for 20 months—although he briefly alludes to them in old blog entries. In addition, a video prominently displayed on the home page features his prescandal 2007 appearance on *The Oprah Winfrey Show*.

Ultimately, of course, looking for a signature on a safety pledge is no substitute for doing your homework, checking out scientific claims and maintaining a healthy dose of skepticism. Realizing that anyone's instinct for self-preservation can, under the right conditions, simply be erased should go a long way toward keeping you from harm. SA

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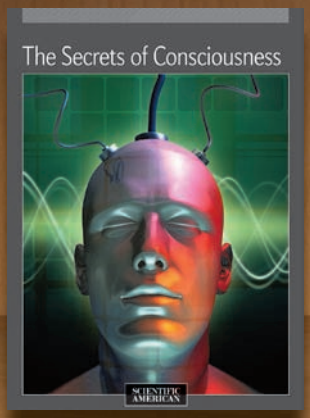

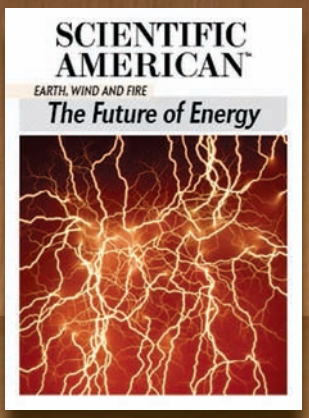

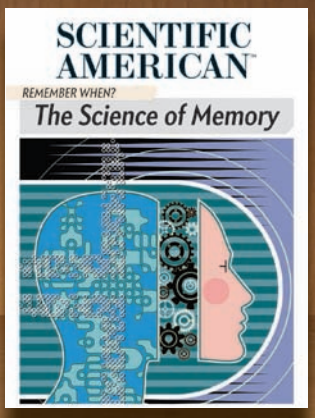

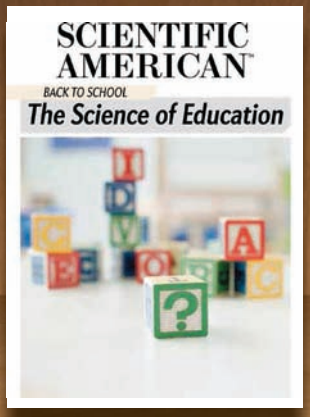

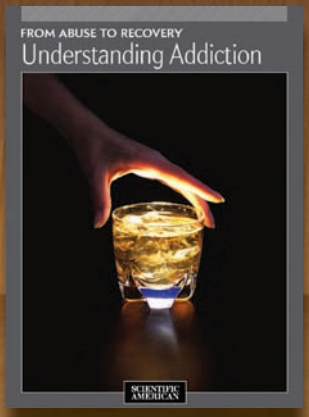

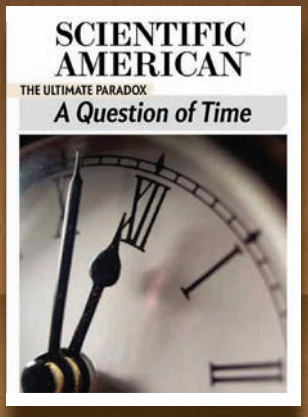

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David Pogue is the anchor columnist for Yahoo Tech and host of several *NOVA* miniseries on PBS.

Smart Sharing

Peer-to-peer transactions are spreading offline and into the real world. Are you riding with strangers yet?

The other day I needed a ride to the San Francisco airport. My driver was a cheerful soccer mom, 40 years old, in a spotless Honda CR-V. When I got in, she smiled and offered me bottled water. She saw that I had an iPhone and handed me a charging cable. The fare for that trip is usually $50, but this time I paid $32. And no tip was expected or given.

If that doesn't sound like a typical cab ride to you, it must be because you haven't tried UberX.

Maybe you've heard of UberX's parent app, Uber, which lets you summon a car service with a single tap on your phone's screen (now operating in 100 cities). A map shows the exact location of the car that's coming to pick you up, along with the driver's name, photo and phone number and ratings from previous passengers.

UberX, though, is something crazy different. Like its rival Lyft, UberX lets you summon *ordinary* people in their own cars. People who have some time and want to make a little money.

That was my first real exposure to the sharing economy.

We, the People, have always initiated our transactions by going to a Company. If we want to rent a car, we call Hertz or Avis. If we want to stay in a new city, we call Hilton or Sheraton.

But in the sharing economy, clever Web sites put us in touch with *each other*. UberX and Lyft are only the beginning.

Airbnb, for example, lets you rent someone's home instead of a hotel. After all, an actual home is often warmer, more relaxing and much less expensive than a hotel; the site has facilitated 11 million nights of lodging so far.

On TaskRabbit, you list grunt work you want done—do an errand, fix a computer, stand in line at the DMV—and fellow citizens bid to do your jobs. Then there's Parking Panda (rent out your garage or driveway). Rentoid (rent out stuff you own). DogVacay (take care of someone's dog).

Of course, Web sites such as eBay and Etsy have always facilitated peer-to-peer transactions. But those interactions have now moved into the real world. You actually meet other people. You enter their cars, their homes and their lives. It's joyous, it's cool—and, for many, it's scary.

Taxi and limo drivers are, of course, furious about Uber and Lyft, to the point of staging protests and slashing tires.

And Airbnb made unwanted headlines in 2011, when a host, on her return, found her apartment trashed. Earlier this year a Manhattanite discovered that his Airbnb renter was hosting a sex party in his apartment.

But clever safeguards can help. Ratings and reviews are essential components of these systems. (I asked my UberX driver, Heather, how she knows that I'm not a serial killer. She smiled and showed me: after I get out, *her* app also asks her to rate *me,* the passenger.)

Airbnb now offers $1 million in damage protection for your rented domicile. (The company rushed over to the Manhattanite's place with $24,000, a locksmith and a hotel room reservation during the cleanup.)

The sharing economy was born during the post-2008 financial meltdown, when money was tight; these services are a monetary win for both parties. But now they're coming on strong. They make sense not only financially but environmentally (does *everyone* need to own a power drill?) and psychologically (why should we pay all our money to The Man?).

There will be more questions to settle as the sharing economy spreads beyond big cities and younger clientele. Who's collecting taxes on all these peer-to-peer transactions? Who's insuring them? And do they comply with all the regulations in their respective industries?

But those obstacles won't last. The "sharing economy" has arrived. And as for me, I'm done hailing cabs. From now on, I'm hailing fellow citizens. SA

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What will we be sharing next? ScientificAmerican.com/jul2014/pogue

Illustration by Katie Carey

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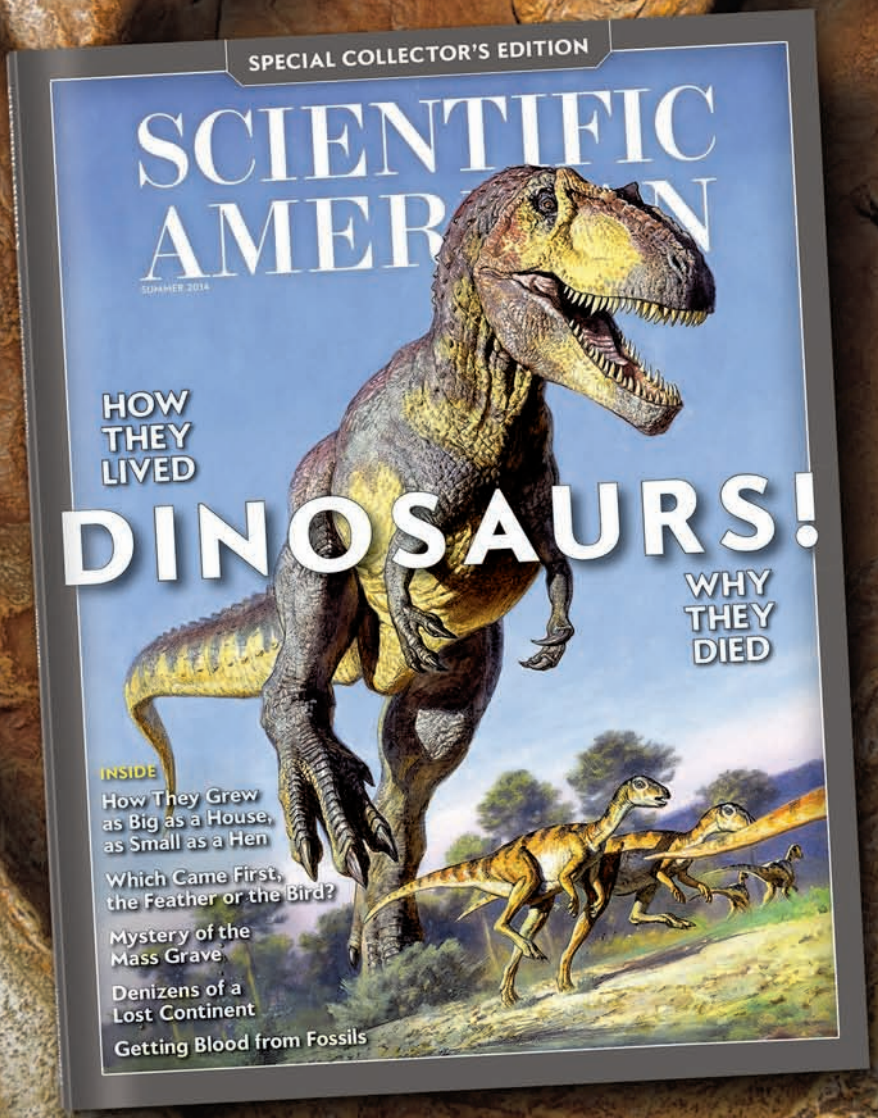

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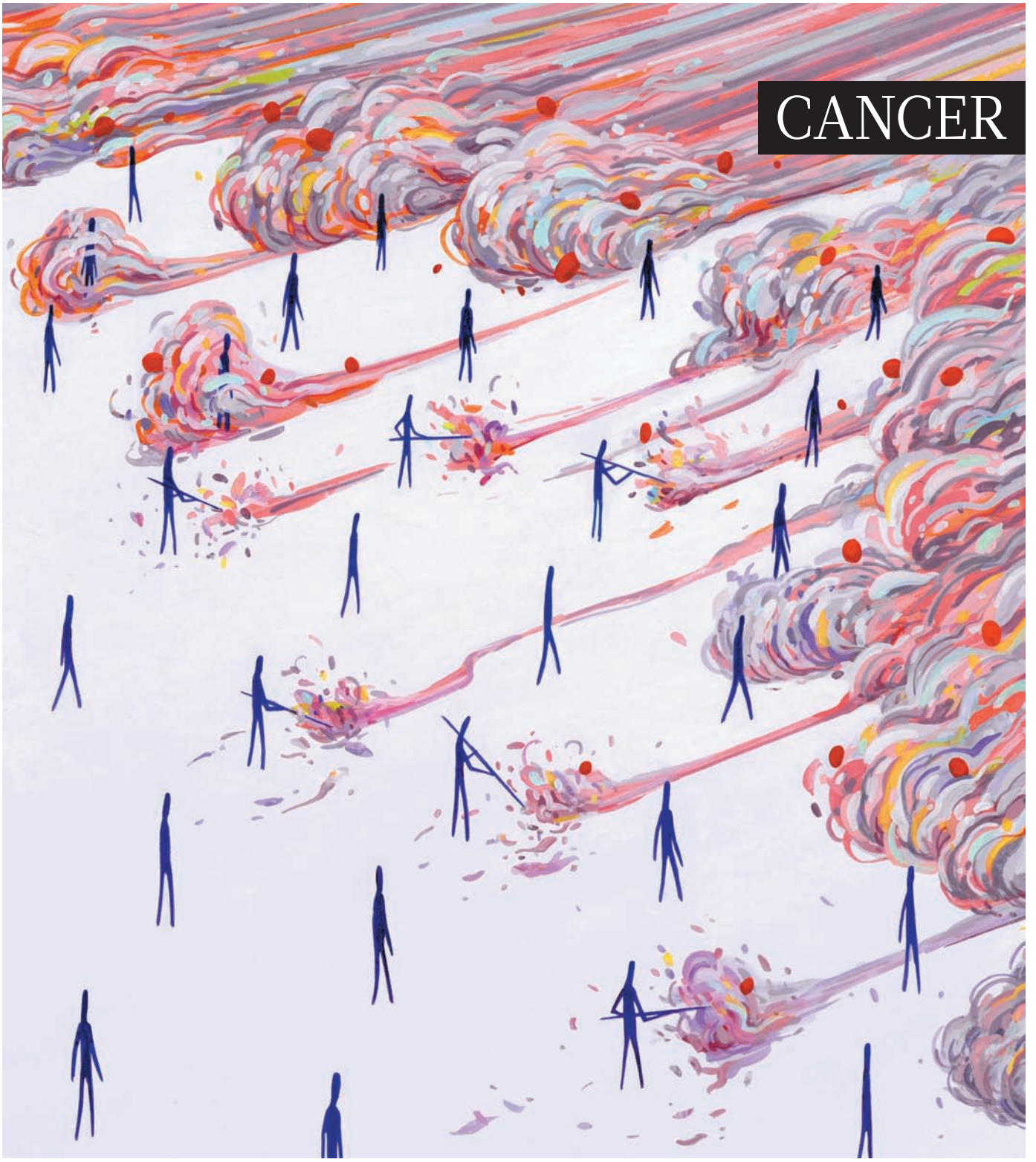

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The march on malignancy

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nature OUTLOOK

CANCER

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For millennia, humans have met their demise through violence, accidents and a fearsome array of infectious diseases. In 1900, the leading causes of death in the United States were pneumonia, influenza and tuberculosis. A century later, they are heart disease and cancer.

Antibiotics and other modern medicines have reduced the lethality of the microbial illnesses that killed our ancestors. Still, we all die of something. So we now find lying in wait for us scores of disorders characterized by the uncontrolled growth of cells. More than forty years since 'war' was declared on cancer, malignancy still casts a shadow over humanity: in 2012, 15% of deaths worldwide were attributable to cancer (page S4). The toll will almost certainly rise in the decades ahead, especially as developing countries adopt Western diets and lifestyles (S18).

This Outlook presents an overview of the current battles against cancer. We examine advances in personalized treatments (S6), nanodevices that will precisely deliver drugs to tumours (S12) and the radical changes that may be needed in clinical research as a result (S9). We explain how the terabytes of data produced by cancer research could be too much of a good thing until we figure out better ways to manage the information (S20 and S22). Clues to potential therapies may lie in an animal that is close to cancer-free (S14), but prevention seems daunting given how much of the environment is potentially carcinogenic (S16). And even as scientists begin to solve the great puzzles concerning cancer, three fundamental mysteries are proving tough to crack (S23).

To deliver this broad view of cancer widely, this Outlook is being published in both *Nature* and *Scientific American* — a collaboration that we expect to be the first of many.

We are pleased to acknowledge the financial support of Celgene Corporation in producing this Outlook. *Nature* has sole responsibility for all editorial content in this special report.

Herb Brody
Supplements Editor

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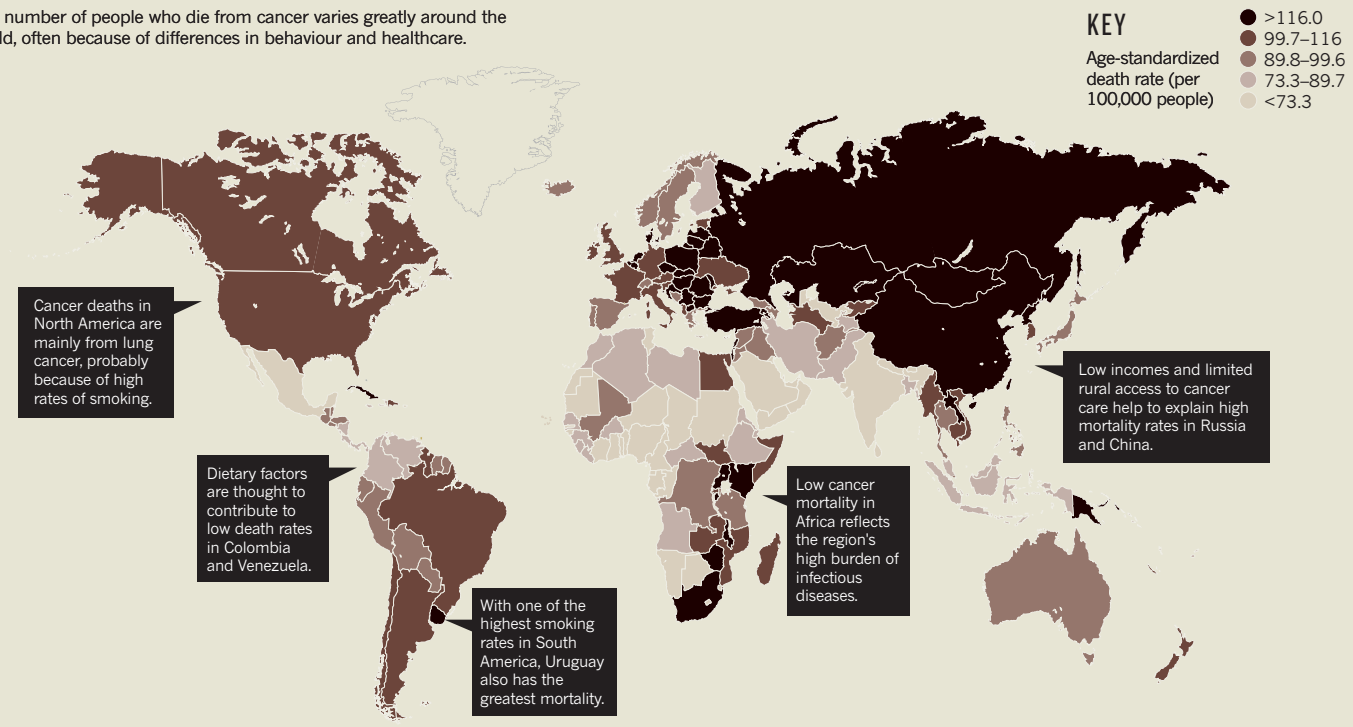
ATTACKING AN EPIDEMIC

Despite a huge amount of funding and research, regional and individual differences in cancer trends make it a hard disease to wipe out. By **Mike May**.

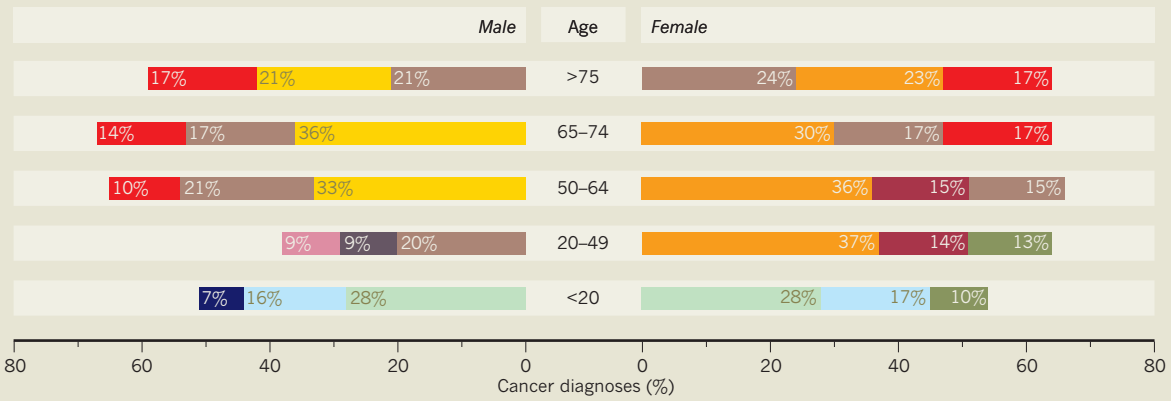
A GLOBAL KILLER

The number of people who die from cancer varies greatly around the world, often because of differences in behaviour and healthcare.



AGE-OLD PROBLEM

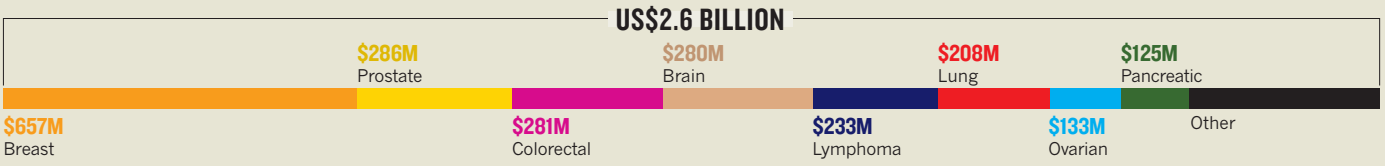
A dramatic change happens around the age of 20, when the main cancers being diagnosed in the United States start to shift from mainly leukaemia to predominantly digestive, prostate, lung and breast.



KEY
- Breast
- Colorectal
- Digestive system
- Female reproductive system
- Leukaemia
- Lung
- Nervous system
- Non-Hodgkin's lymphoma
- Prostate
- Skin
- Testes
- Thyroid

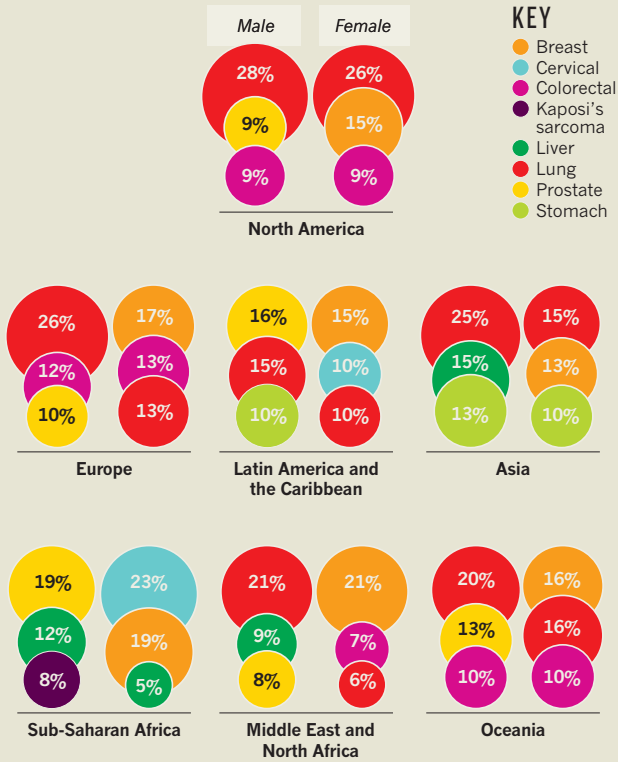
MONEY MATTERS

In 2013, the US National Institutes of Health spent US$2.6 billion on cancer research, and more than one-quarter of that went to breast cancer.



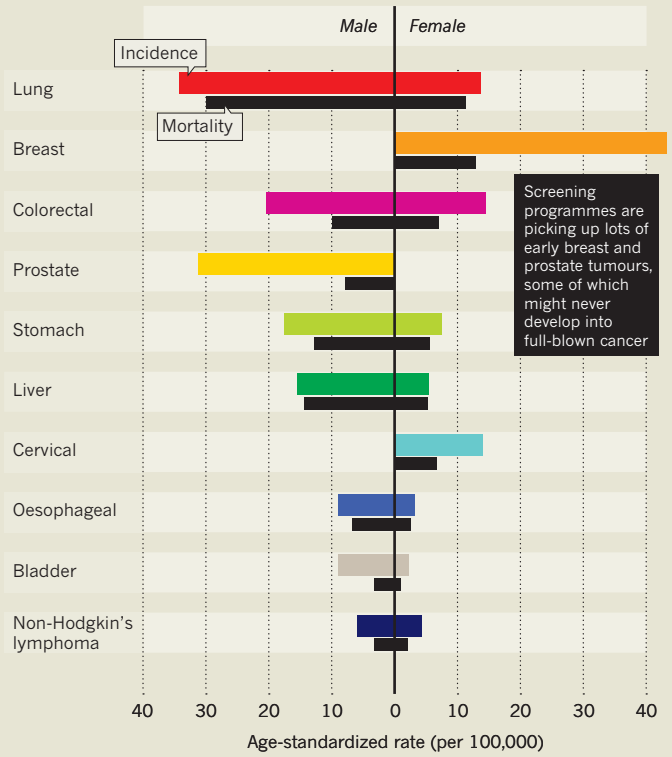
POINTS OF ATTACK

With the exception of sub-Saharan Africa, lung cancer is one of the top three cancer killers in all regions. Breast, colorectal and prostate also feature prominently.



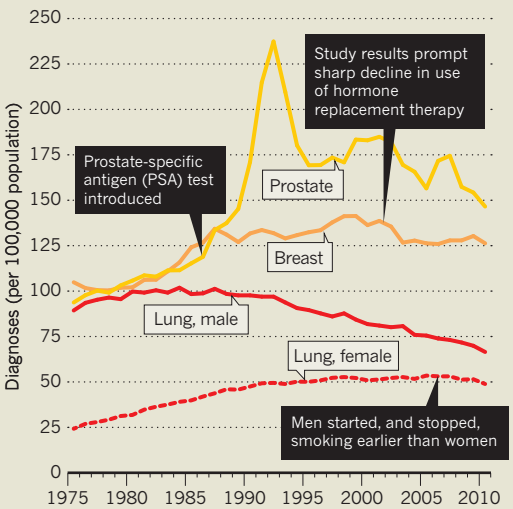
DEADLY DISCREPANCY

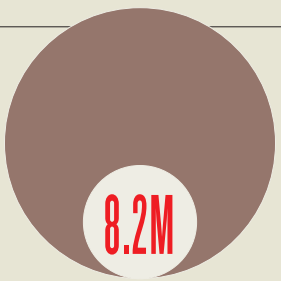
Gaps between diagnoses and mortality are most prominent for breast and prostate cancer.



RATE CHANGES

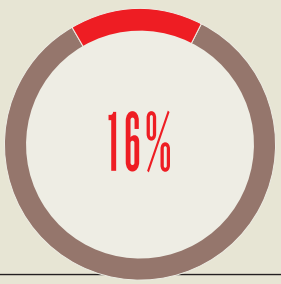
Among other factors, public-health measures have influenced the number of US people being diagnosed with certain cancers.





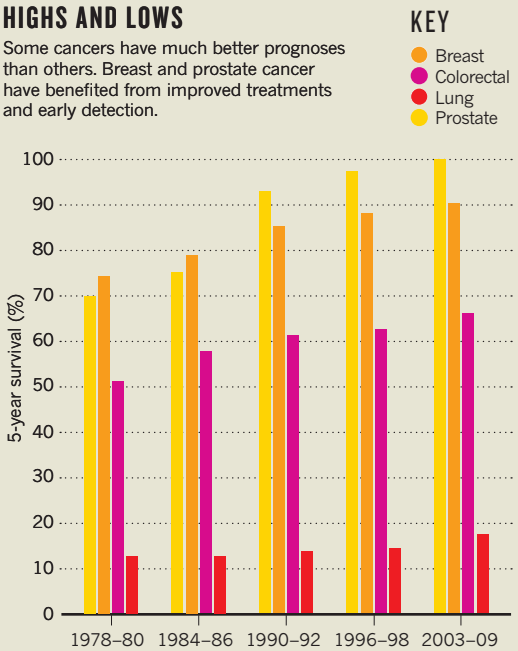
In 2012, cancer contributed to 15% of all deaths worldwide, with 8.2 million in total.

Infections caused 16% of all cancers in 2008

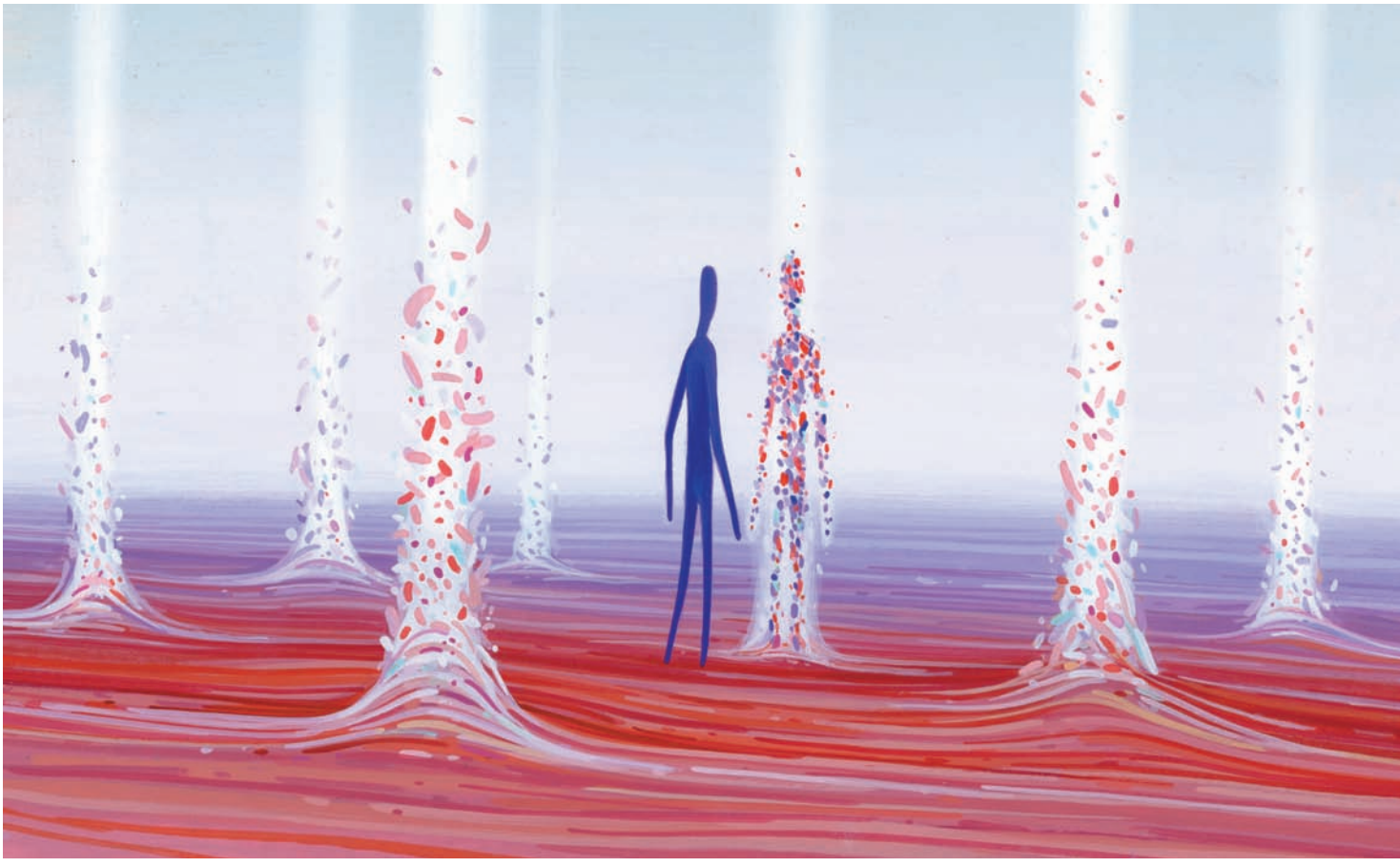


HIGHS AND LOWS

Some cancers have much better prognoses than others. Breast and prostate cancer have benefited from improved treatments and early detection.



A global killer and Points of attack: International Agency for Research on Cancer. Age-old problem, Rate changes and Highs and lows: Surveillance, Epidemiology, and End Results Program. Money matters: National Institutes of Health. Deadly discrepancy: *World Cancer Report 2014.*



BRENDAN MONROE

THERAPY

This time it's personal

Tailoring cancer treatment to individual and evolving tumours is the way of the future, but scientists are still hashing out the details.

BY LAUREN GRAVITZ

Elaine Mardis and her colleagues first encountered 39-year-old Lucy (not her real name) in 2010 at the Genome Institute at Washington University in St Louis, Missouri. Lucy had been referred there after a confusing leukaemia diagnosis. Her doctors thought she had a subtype of the disease called acute promyelocytic leukaemia (APL) — one of the most treatable forms — which usually occurs when parts of chromosomes 15 and 17 get mixed up, or translocated, triggering overproduction of blood-forming cells. But other features of her chromosomes suggested that she might have a much more dangerous form of the disease and therefore need a bone-marrow transplant.

Mardis, co-director of the Genome Institute, is involved in a university initiative to use whole-genome sequencing and other analyses to launch precision attacks against difficult cancers. While her medical colleagues treated Lucy, Mardis sequenced Lucy's genome and that of her cancer and discovered that the leukaemia was indeed caused by a piece of chromosome 15 inserting itself into chromosome 17 (ref. 1). "Our chromosomal analysis indicated that she would respond well to traditional APL therapy," Mardis says. In other words, the treatment she had already received should hold her cancer at bay — and no risky transplant would be needed.

Personalized, 'precision' medicine for cancer is in a difficult time of transition. There are promising stories like Lucy's, wherein the DNA typing of tumours suggests clear approaches to therapy, with improved results for patients. But the field is still limited by many complexities and constraints.

Researchers have learned enough about cancer to know that the way it has been tackled for decades — with cocktails of chemotherapeutic drugs that indiscriminately hit populations of rapidly growing cells — is effective only up to a point. They believe that if they can find the key genetic mutations that drive a particular cancer's growth, they will be able to target the tumour more selectively and with fewer toxic side effects. But they don't yet know enough about which genetic mutations drive a given cancer, let alone how to interrupt the aberrant cellular pathways that result.

MAKE ME A MATCH

Every cancer has a weak spot — a genetic vulnerability that could be exploited by the right drug — and many envision a day when the genome of every cancer will be sequenced, in full or in part, and then paired with an appropriate therapy.

Researchers point to the effectiveness of imatinib (marketed as Gleevec and Glivec) against chronic myelogenous leukaemia (CML) — a rare blood cancer — as perhaps the greatest success in the personalized cancer field so far. CML is most often caused by an abnormal gene rearrangement in which pieces of two chromosomes switch places with each other. Assessing whether a patient is a candidate for the drug requires the analysis of a small group of genes in what is referred to as a gene panel.

"In the 1980s, unless you got a bone-marrow transplant, the disease was an absolute death sentence in four to six years," says Razelle Kurzrock, director of the Center for Personalized Cancer Therapy at the University of California, San Diego. "Today, average survival is more than 20 years. And because the average age at diagnosis is 60, it's almost a normal life expectancy." That success comes at a price: in 2012, a year's worth of the therapy cost US$92,000.

Imatinib's success has not been easy to duplicate. Every tumour has a unique set of genetic mutations — tumours are commonly likened to snowflakes, each is slightly different from the next. And this heterogeneity, which is found even between cells in a single tumour, means that matching a patient with the appropriate therapy can be a complex proposition.

Vulnerabilities such as the one that imatinib capitalizes on are known as driver oncogenes, genetic changes that generate the proteins driving a cancer's growth. Disabling these proteins should, at least in theory, beat back the disease. The number of driver oncogenes seems to be limited — perhaps as few as 200–300 common ones, says Robert Nussbaum, a medical geneticist at the University of California, San Francisco. Understanding how to disable the common driver oncogenes should therefore enable the treatment of a large number of cancers. "First, we have to know what the genes are and how are they mutating. Then, the second challenge is developing drugs that target these abnormally activated proteins," Nussbaum says.

Such an approach means that oncologists are no longer limited to treating cancer on the basis of the organ in which it first appeared. "The whole idea of starting to classify tumours by their mutations and expression profile as opposed to the way they look under the microscope is another branch of this precision oncology that's developing," Nussbaum adds. A case in point: imatinib is not only good at keeping CML in check, it works for certain gastrointestinal cancers and other tumours as well.

"For the first time, we have a landscape of all the frequent mutations that occur in every single major cancer type," says José Baselga, a cancer biologist at the Memorial Sloan-Kettering Cancer Center in New York. "We know which are the frequent mutations that occur in breast cancer, we know which occur in all forms of thyroid cancer, leukaemia, lymphoma, CML — you name it."

Baselga and his colleagues are using this information to design clinical trials that group patients by genotype rather than by a cancer's organ of origin. For example, mutations in the gene *BRAF* can cause the protein it encodes to become oncogenic. The team has been testing a drug called vemurafenib (Zelboraf), which is effective against melanomas that contain a mutation in the BRAF protein known as BRAF(V600E), in patients with other types of cancer who test positive for the same mutation.

"We are beginning to see responses in tumour types that we would have never guessed," Baselga says. "We have very high responses in histiocytosis, hairy-cell leukaemia and some forms of thyroid cancer."

CATCH 22

Drugs with precise molecular targets such as the one that Baselga is testing can be dazzlingly effective in the short term. But that brilliance is dimmed by a massive cloud: because cancer is a continually evolving disease, such therapies rarely retain potency in the long term. Adapting mutations eventually allow cancer cells to grow back in treatment-resistant forms. "Tumours evolve for a living," Nussbaum says. "When you treat them with a targeted therapy, it's a perfect Darwinian system for selecting exactly the cells you don't want."

Because cancer cells evolve ways to survive when one oncogenic pathway is blocked, researchers are seeking to identify not just one but all of the potentially malignant pathways so as to hit them simultaneously — and curtail the ability of tumours to evolve resistance. "Mutations are occurring all the time," Kurzrock says. "Targeting just one abnormality means you're constantly chasing your tail."

Kurzrock ran into this problem in a study in which her group used a gene panel from a company in Cambridge, Massachusetts, called Foundation Medicine (see 'Testing times') to test 75 women with advanced breast cancer. Although the patients each had, on average, five or six malignancy-linked mutations, none had the same combination.

"Not only do we have next-generation sequencing-based methods, we also have this incredible growth in our general knowledge."

Why is it, then, Kurzrock asks, that we have been trying to fit these differently shaped pegs into the same round hole? Instead, she says, "we should take a patient and ask: 'What cocktail of drugs does this particular patient need based on their particular profile?'".

Another problem with the targeted approach is that therapies are typically tested only on patients with advanced cancers, which are much harder to treat than those in their early stages. Trying out drugs earlier in the course of a disease, when the cancer is more likely to be driven by just one or two key mutations, would require a major shift in the clinical trial system (see page S9).

But perhaps the biggest obstacle in targeting the products of mutated genes is that so many of the causative mutations result not in something's presence but in its absence. Most of the driver oncogenes have what is known as loss-of-function mutations — changes that disable the genes or proteins normally

TESTING TIMES

Biotechnology companies are developing sophisticated ways to match patients to therapies — and even determine whether therapy is necessary. Here are some of the most prominent.

Company	Goal	Technology	Developmental stage
Genomic Health, Redwood City, California	Risk assessment	Assesses molecular markers in tumours. Predicts whether chemotherapy will be beneficial, as well as likelihood of recurrence.	Launched onco*type* DX test for breast cancer in 2004. Tests now also available for colon and prostate cancers.
Epic Sciences, San Diego, California	Diagnosis and monitoring	Isolates tumour cells circulating in blood, and tests them for receptors and enzymes that indicate effectiveness of therapeutics.	Partnering with pharmaceutical and biotechnology companies and cancer centres. Tests are currently in clinical trials and not yet commercially available.
Foundation Medicine, Cambridge, Massachusetts	Match tumour to drug	Screens biopsies for alterations in 236 cancer-related genes for solid tumours and 405 genes for haematological cancers. Then matches mutations to drugs that are either approved by the US Food and Drug Administration or in clinical trials.	Two clinical products are available to oncologists: FoundationOne for solid tumours, launched in 2012; and FoundationOne Heme for haematological cancers, launched in 2013.
Qiagen, Hillden, Germany	Targeting appropriate patient subgroups	Uses the polymerase chain reaction analysis to detect mutations in epidermal growth factor receptor and determine whether the drug afatinib is the appropriate treatment.	Approved by US Food and Drug Administration for testing in conjunction with afatinib to select metastatic non-small-cell lung cancer patients for first-line treatment with afatinib.
Trovagene, San Diego, California	Monitoring	Analyses cell-free cancer DNA in urine to detect mutations and monitor disease progression, recurrence and therapeutic response.	Urine testing available for *KRAS* and *BRAF* mutations, which are predictive of response to colon cancer and melanoma therapies.

responsible for preventing cancerous cells from growing out of control. "It's one thing to develop a drug that blocks an activated protein. It's quite another to develop a method to compensate for the loss of a tumour-suppressor protein," Nussbaum says. Attacking these kinds of cancers will require a more nuanced approach — one that tinkers with the DNA itself rather than the proteins for which it codes.

TIME IT RIGHT

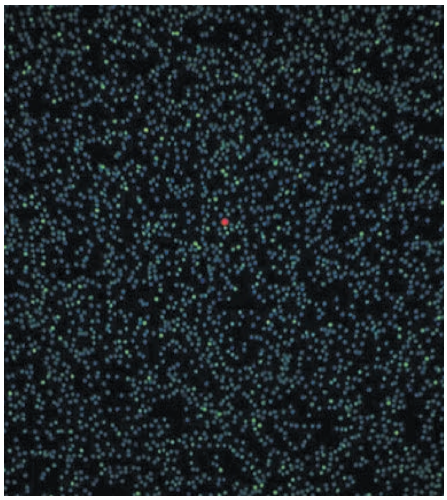
Beyond matching tumour to drug, precision medicine also depends on providing the drugs at the right time — something that requires knowing not only which mutations got a tumour started, but also how the tumour is likely to change. To ensure that therapies that start out personalized remain that way, a doctor needs to know when new oncogenic pathways pop up and when it is time to change course. But repeated biopsies are difficult, and often impossible.

Researchers have therefore been working on non-invasive ways to monitor mutations. Technology is getting good enough to separate out tumour cells or sequenceable scraps of DNA from blood samples, making it possible to do 'fluid' biopsies that provide accurate biomarkers for assessing the disease over time[2]. For instance, Epic Sciences in San Diego, California, in collaboration with cell biologist Peter Kuhn at the nearby Scripps Research Institute, has developed a way to separate tumour cells from blood and assess them for mutations and abnormal protein expression. Others are focusing on bits of DNA that have leaked from dying cells and can be analysed for cancer-driving mutations.

Such methods could one day allow real-time assessment of a patient's tumour make-up. Sarah-Jane Dawson, a molecular biologist and oncologist at the Peter MacCallum Cancer Centre in Melbourne, Australia, studies cell-free DNA — DNA that has escaped from dying cells and is circulating in the blood. She and her colleagues have found that changes in cell-free tumour DNA are detectable, on average, five months before any changes to a patient's cancer are seen in computed tomography (CT) or other scans. "That's not an insignificant amount of time for someone to remain on a therapy they're growing resistant to," Dawson says.

Researchers are also beginning to understand more about how the body fights cancer, and how to take advantage of that. Certain types of immunotherapy — treatments that prompt the body's immune system to detect and attack a tumour — seem to work better if the disease is slightly more advanced: the more mutations a cancer has, the more foreign proteins there are for immune cells to detect.

Tumour cells can be adept at exhausting, or simply turning off, the body's immune response. The best approach to treatment, therefore, might be to combine precision therapy with immunotherapy. First, prune back the cancer with molecularly targeted drugs. Next, use immunotherapy to help the patient's immune system recognize and attack the mutant cells at the first sign of danger[3]. "The vast majority of patients respond to genomically targeted therapies, but with short durability," says James Allison, a cancer immunologist at the University of Texas MD Anderson Cancer Center in Houston. Immunotherapy, he says, is the opposite. "A fraction of patients respond, but with long durability." Combining the approaches, he says, should dramatically improve outcomes.



Using just a blood sample, Epic Sciences can detect a single cancer cell (red) among a field of white blood cells (blue and green).

EPIC SCIENCES

ATTACK FROM WITHIN

Allison has pioneered a class of immunotherapy drugs called checkpoint inhibitors, which can set loose an otherwise-blocked immune system and allow it to break through the defences of certain cancers. Most notably, drugs that inhibit the a protein found on the surface of T cells called PD1, or the PDL1 protein to which it binds, have been shown in numerous clinical trials to be effective against various types of advanced cancers[4]. And Allison's colleague, oncologist and immunologist Padmanee Sharma, is seeking markers that could indicate whether a patient is responding to another checkpoint inhibitor that works against a T-cell surface receptor, CTLA4. One of the markers she has found — inducible co-stimulator (ICOS) — seems to increase when someone is responding to treatment that targets that receptor[5].

Another, still-more personalized form of immunotherapy genetically engineers a patient's immune cells (or those from a matched donor) so that they can recognize and attack cancer cells. The approach, called chimaeric antigen receptor (CAR) T-cell therapy, has produced encouraging results in several small unpublished clinical trials for advanced blood cancers: some patients achieved complete remission.

Ideally, a treatment should be personalized and hit multiple pathways simultaneously. Chemical engineer Mark Davis from the California Institute of Technology in Pasadena and cancer biologist Frank McCormick from the University of California, San Francisco, believe that the answer lies in RNA interference, a technique that uses double-stranded sequences of 'short interfering' RNA (siRNA) to mute specific genes.

Davis has created a way to encapsulate cancer drugs in nanoparticles that have the right size and surface properties to be taken up by tumour cells (see page S12). He is now working with McCormick to infuse these nanoparticles with siRNA. Until now, delivering these fragile molecules to cancer cells had proved nearly impossible, but Davis's nanoparticles provided an elegant solution. The approach has been tested in a phase I clinical trial in solid cancers[6], and the results are now being assessed.

The siRNA method could disable cancer at its very origin by silencing the genes responsible. "In a dream situation, you find a set of genes that affect your tumour, load them up and go," McCormick says. As a patient's tumour evolves, an oncologist can simply swap old siRNAs for new ones. "Once the delivery system works, you could just plug and play different payloads."

Combining a single delivery system with pluggable siRNAs would make drug development faster, cheaper and more routine, and also present less risk to the patient, McCormick says. The multi-siRNA technique has been tested successfully in mice, but human trials using a combination of siRNAs may still be a few years off — such fast-turnaround, individualized therapies pose a challenge for regulatory bodies such as the US Food and Drug Administration.

Cancer is a wily enemy and protects its secrets well. Precision approaches, such as the one Lucy received, are not yet available for most patients. But the rush of research suggests that it is only a matter of time before they are. "Not only do we have next-generation sequencing-based methods," Mardis says, "we also have this incredible growth in our general knowledge."

For Lucy, at least, that knowledge is everything. Four years on, she is still cancer free. ■

Lauren Gravitz *is a freelance science writer based in Los Angeles, California.*

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For more on immunotherapy approaches, see:
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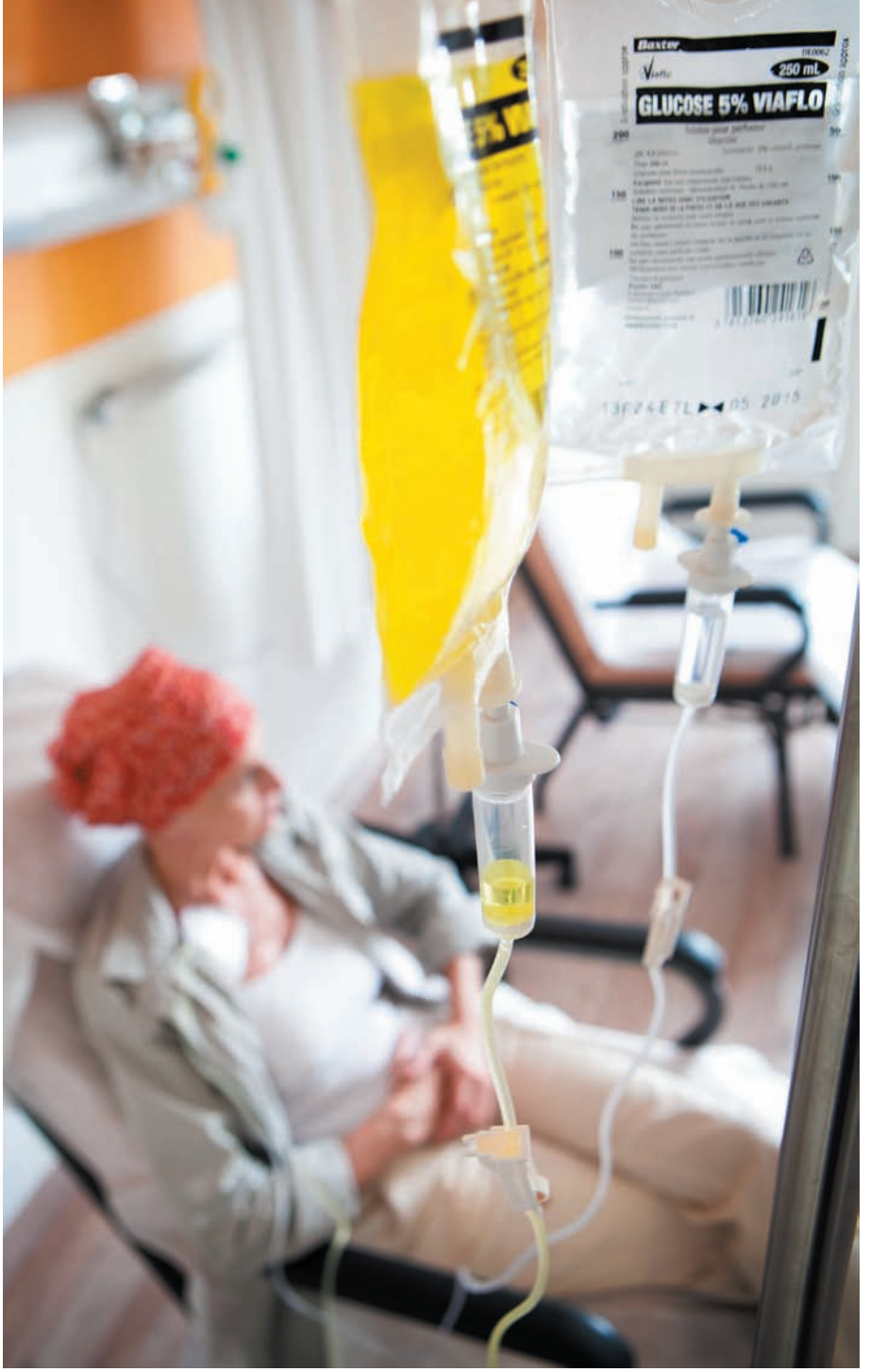


AMELIE-BENOIST/BSIP/BSIP/CORBIS

With standard treatments being replaced by more personalized ones, trial design needs to change, too.

CLINICAL TRIALS

More trials, fewer tribulations

Clinical studies that group patients according to their molecular profile can make for better and faster drug approval decisions.

BY MICHAEL EISENSTEIN

In December last year, a breast-cancer trial for the experimental drug neratinib captured industry attention — but the buzz was not just about the drug.

What was unusual was the trial itself. Known as I-SPY 2, it assesses multiple drug candidates in parallel, instead of the usual practice of one at a time. The approach is part of a wave of efforts to reform the costly and time-consuming process of drug approval that often fails to take into account the complex realities of cancer biology.

In I-SPY 2, each drug is screened in patients whose tumours have specific molecular profiles. The trial 'learns' as it accumulates data, so rather than randomly assigning new patients to just treatment or control, it uses early results to adjust recruitment. Made by Puma Biotechnology in Los Angeles, California, neratinib was just one of five targeted compounds being tested, and all were designed to selectively block signalling pathways involved in tumour growth.

The standard road to drug approval involves demonstrating safety in phase I, clinical effect in phase II and then a phase III randomized controlled trial (RCT) to confirm whether the experimental treatment provides a statistically meaningful improvement over the current standard of care. RCTs have enabled the discovery of valuable treatments that bolster both survival time and quality of life. "We actually had some outstanding successes early on — like childhood leukaemia, where we saw small improvements from various drugs stack up until the disease turned into something that is usually cured," says Richard Kaplan, a medical oncologist at the UK Medical Research Council's Clinical Trials Unit in London.

Progress against cancer has since slowed down, but many oncologists are hopeful that it is poised to accelerate once more. Thanks to a deeper knowledge of genetics and cell biology, the blunt instrument of cytotoxic chemotherapy — which indiscriminately targets all rapidly dividing cells — is now being supplemented by drugs created for tumours with specific molecular features, or biomarkers. But clinical-study design has not kept pace. Many RCTs still tend to take a broad view, making relatively simple comparisons of drug performance in two roughly identical patient groups. But their failure to account for individual genetics means that they can give rise to misleading results.

Witness the tale of gefitinib, a targeted drug developed by AstraZeneca in London and marketed as Iressa. After showing early promise in some patients with non-small-cell lung cancer (NSCLC), the drug failed in a phase III trial in 2005 (ref. 1). The trial's nearly 1,700 patients had not been selected on the basis of their tumour mutational profile. "The company took the tack of trying to get all of NSCLC," says Donald Berry, a biostatistician at the MD Anderson Cancer Center in Houston, Texas. "It hoped that the benefit in this small subset would drive things." The poor results of the trial led the US Food and Drug Administration (FDA) to put

severe restrictions on who could be prescribed the drug. Later analyses[2], however, revealed that the drug was effective in a specific subset of patients, and gefitinib is now available in Europe to patients with the appropriate mutations.

Critics point to the gefitinib story as a collision between new drugs and old trial design. They assert that conventional randomized trials are too costly, delay the identification of good therapies and mask the benefits of good drugs that work in only a subset of patients.

OPEN ARMS

In one way, however, gefitinib is an example of progress in getting drugs to patients more quickly. It is one of a number of oncology drugs to be approved for use by the FDA through its accelerated approval programme. The programme allows drugs to be marketed if they show strong evidence of clinical effect in a phase II study as long as a subsequent phase III trial is done to confirm the effect. (This is where gefitinib fell down and gained its tight restrictions).

With numerous candidates in their pipelines, pharmaceutical companies must make difficult decisions about how to invest their resources. When many separate trials are done in parallel, they compete for a limited pool of patients. One study[3] showed that filling all pancreatic-cancer trials in the United States in 2011 would have required the participation of 83% of patients with surgically treatable tumours. Yet only about 5% of patients volunteer for trials, according to the American Cancer Society.

Multi-armed adaptive trials such as I-SPY 2 and FOCUS4 — a colorectal cancer trial that started recruitment in January — offer a way to tackle limits on both company resources and the number of available patients. These phase II trials study several markers and drug candidates at once, responding to results by expanding studies for promising treatments and discontinuing them for those that are not showing any effect (see 'Adaptive design').

I-SPY 2 divides patients with breast cancer into ten subgroups on the basis of their tumour's molecular profile. Each subgroup is then divided among the treatment and control groups. Responses to each drug are compared against a single control arm. Future recruitment is not strictly randomized, but rather is informed by incoming trial data. This way, drug–biomarker combinations with early promise are allocated more patients with the same biomarker profile.

"We will need to test a new strategy of customization."

"This is about updating knowledge as you go and modifying your actions on the basis of that knowledge," says Berry, who co-organized the trial with breast-cancer specialist Laura Esserman from the University of California, San Francisco. I-SPY 2 has a second graduate moving on to phase III trials — the drug veliparib from AbbVie in North Chicago, Illinois. Five other compounds are still being tested.

FOCUS4 is recruiting patients to four treatment arms. Unlike in I-SPY 2, patients are assigned to the treatment for which their biomarker profile is thought to be a match. Each treatment arm has its own control group, made up of patients with the same biomarkers. Drugs that perform well in their biomarker-matched group will also be given to individuals whose tumours lack that marker to test for broader effects. A separate chemotherapy-only arm will treat patients who, for whatever reason, cannot participate in the other groups, as well as those who have not responded to the treatment on trial but might benefit from future drugs that target their tumour subtype.

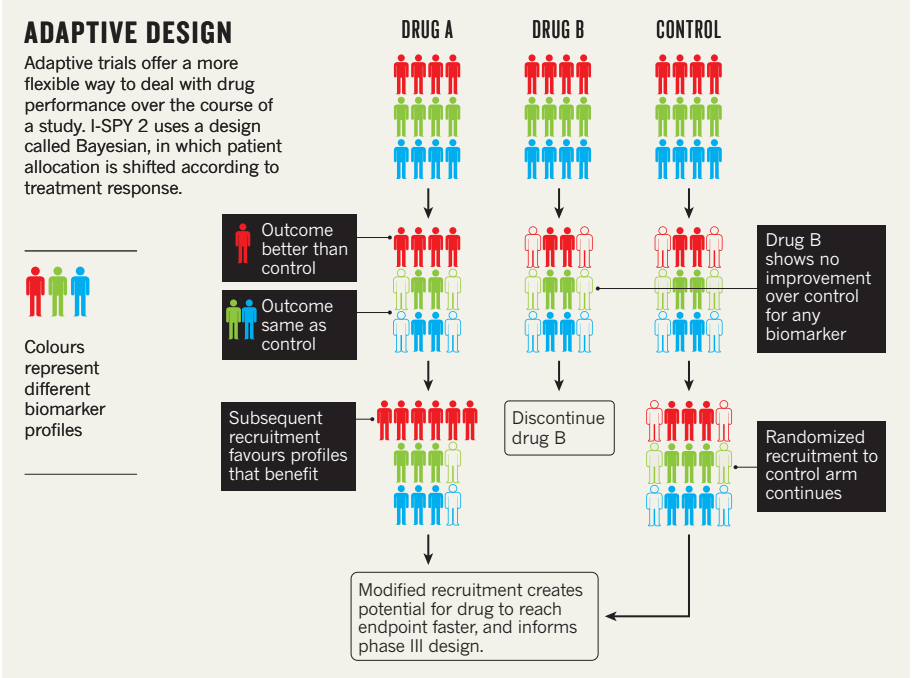
In another shift from business as usual, I-SPY 2 is focusing on initial treatment, rather than limiting itself to patients facing poor prognoses from advanced, metastatic or drug-resistant disease. "Looking at metastatic disease is always first in cancer, and if nothing happens you don't continue," says Berry. "We have to look earlier." Women in I-SPY 2 receive 'neoadjuvant' treatment that is intended to shrink their tumours before they are removed. Trial designers have tended to shy away from early-stage patients who might already be curable with standard treatments, but early-stage tumours often have fewer mutations and are more homogeneous, so could be easier to target.

Such early-stage testing has led to improved outcomes in chronic myelogenous leukaemia (CML), says Razelle Kurzrock, director of the Center for Personalized Cancer Therapy at the University of California, San Diego. There is already an effective targeted drug for CML: imatinib, which Novartis markets as Gleevec or Glivec. When physicians were using this drug only as a last resort, imatinib offered limited returns. But Kurzrock says that when doctors started giving it to patients upon diagnosis, the improvement in performance was dramatic. "The response rate is no longer just 10%," she says. "It's close to 100%."

Encouragingly, the FDA declared in mid-2012 that it would consider accelerated approval for breast-cancer drugs that can eliminate detectable tumour tissue without surgery[4], based in part on data from trials such as I-SPY 2. In September 2013, the agency issued its first such approval for the neoadjuvant use of pertuzumab, which Roche markets as Perjeta.

These trial designs offer greater opportunities for patient participation by creating treatment groups for almost all comers, rather than simply rejecting patients who do not match a single-biomarker criterion. Furthermore, I-SPY 2's sole control arm yields considerable savings relative to the expense of having a control group for each treatment. Both FOCUS4 and I-SPY 2 also offer the potential for even greater cost-cutting by seeking stronger gains from the drugs than those generally sought in clinical trials — typically, a doubling of survival without tumour progression on the treatment drug than on the control. This reduces the number of patients needed to obtain robust phase III data and ensures that only high-performance candidates move forward. "If a drug doesn't meet its prespecified outcome during interim analysis, we're going to close that arm," says Kaplan.

Successful graduation from I-SPY 2 requires a projection that a drug has an 85% chance of succeeding in a 300-patient phase III trial, and treatment arms in FOCUS4 can move seamlessly into phase III if participating companies opt to continue. This is also a feature of the



Lung Cancer Master Protocol, an adaptive trial for squamous-cell lung cancer developed with support from the advocacy group Friends of Cancer Research in Washington DC. The trial is expected to start recruiting soon.

DISEASE REDEFINED

As genomic studies start to provide further information about the mutation profiles of different cancers and as more biomarkers emerge, researchers are re-evaluating cancer classification (see 'Second chance'). A colorectal cancer that shares a mutation with a breast carcinoma may have more in common than two breast carcinomas with different mutations, for example. If this proves to be the case, then these should be the similarities that inform drug testing.

Kurzrock is among many who favour molecular profiling over tissue-based definitions. "If you have a drug that targets a specific abnormality, you would want to look at that abnormality — not whether you're dealing with breast cancer," she says. Evidence to support this model is mounting. For example, although the FDA has approved crizotinib (marketed by Pfizer as Xalkori) for NSCLC, clinical studies suggest that the drug could also be effective for children with aggressive brain tumours that have the same mutation[5].

Such approvals must now be won gradually through trials on different diseases. To speed things up, several companies are pursuing 'basket' trials that test treatments on multiple cancers with common genetic disruptions. GlaxoSmithKline is testing two melanoma drugs, dabrafenib and trametinib, in nine cancers — including brain, thyroid and intestine — that share mutations in the gene *BRAF* that could render them susceptible to these drugs. Rafael Amado, senior vice-president for oncology research and development at the firm, argues that this approach offers hope to patients with rare cancers who might otherwise slip through the cracks. By performing analyses that take data from across tumour groups, even small sets of positive outcomes can become statistically meaningful. As a result, says Amado, "we don't have to run very large randomized trials in these ultra-rare populations".

The US National Cancer Institute is exploring this approach through its Molecular Analysis for Therapy Choice programme, using targeted gene sequencing to match various drugs to people with solid tumours or lymphomas whose disease has progressed on existing treatments. "We'll have about 20 arms to start with, targeting the usual suspect mutations that you might find in cancer," says Barbara Conley, associate director of the institute's cancer-diagnosis programme. "If we can get 35% or more patients across tumour types to survive six months or more, that's an interesting signal." These are essentially phase II trials looking for indications that could justify a move to phase III, but regulators say that they are willing to formally recognize robust evidence of cross-tumour efficacy. "The FDA could approve a drug based on a molecularly defined population rather than a disease-site-specific indication," says Richard Pazdur, director of the agency's Office of Oncology and Hematology Products.

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Additional complexity could confound this broad biomarker-informed research, however. For instance, *BRAF* inhibitors that work in some melanomas are ineffective in colorectal tumours with the same mutations. But Kurzrock maintains that universal effectiveness is an unrealistic expectation. "If you look at drugs that were approved for lung cancer, the response rates were usually in the range of 15–20% of patients," she says. "We cannot expect 100% of patients treated on the basis of a genomic classification to respond."

Indeed, tumours often contain multiple mutations that might drive drug resistance — a common roadblock for targeted agents suggesting that each patient's cancer may require a specialized cocktail of agents. "We will need to test a new strategy of customization per patient and patient-centric care," says Kurzrock, "rather than just the old way of testing a drug or combination of drugs."

This complexity will mean a steep learning curve for researchers and oncologists. Berry believes that oncology will ultimately undergo a broad transformation — approaching drug testing as an opportunity to gain insight into the disease rather than merely validate existing hypotheses. "The future really is combining clinical practice and clinical trials, and having a notion of both learning and confirming in the trial," he says. "It will mean a completely different regulatory perspective and an entirely different business model for companies." ■

Michael Eisenstein *is a freelance science writer based in Philadelphia, Pennsylvania.*

SECOND CHANCE

A new perspective for past drug decisions

A drug's journey to the clinic doesn't necessarily end with a regulator's decision. As clinical oncologists learn more about the interplay between a patient's response to a drug and his or her genetics, it is becoming clear that some failed drugs might be rehabilitated by looking at instances in which a small subgroup of participants showed significant benefit.

Take everolimus, developed by Novartis. This drug failed a phase II trial for metastatic bladder cancer — but one patient's cancer went away and stayed away for more than two years. Researchers at the Memorial Sloan-Kettering Cancer Center in New York subsequently found that about 8% of people with bladder cancer carry a mutation that makes their tumour susceptible to the drug[6]. The US National Cancer Institute is now examining other reports of rare but significant drug responses through its Exceptional Responders programme, which might see some failed drugs put back into development. "We've looked at some of the phase II trials that didn't get approval over the past few years, and in lots of them as many as 10% of the people had exceptional responses," says Barbara Conley, associate director of the institute's cancer-diagnosis programme.

Conversely, even when a drug is approved, its success can only really be assessed in the real world. "Trial subjects don't have cardiac or renal disease," says Ian Tannock, an oncology researcher at Princess Margaret Cancer Centre in Toronto, Canada. "But then that result is taken out into a community of unselected patients where there is a lot of comorbidity." As a result, small benefits may disappear and rare toxicities may become apparent. Tannock advocates large-scale research to track the performance of drugs after they have been approved. But such observational studies require close collaboration across clinical centres — a process made difficult in the United States, at least, by the lack of a central national cancer registry.

The American Society for Clinical Oncology hopes to rectify this problem with CancerLinQ, which integrates patient treatment and outcome data. "This would allow us to query data for a group of patients with a particular set of molecular characteristics, look at what treatments those patients received and identify the treatment that seemed to work the best in that subset of patients," says Neal Meropol, a medical oncologist at Case Western Reserve University in Cleveland, Ohio, and a member of society's board of directors. "We can now ask questions that simply could not be answered in a standard clinical trial." **M.E.**

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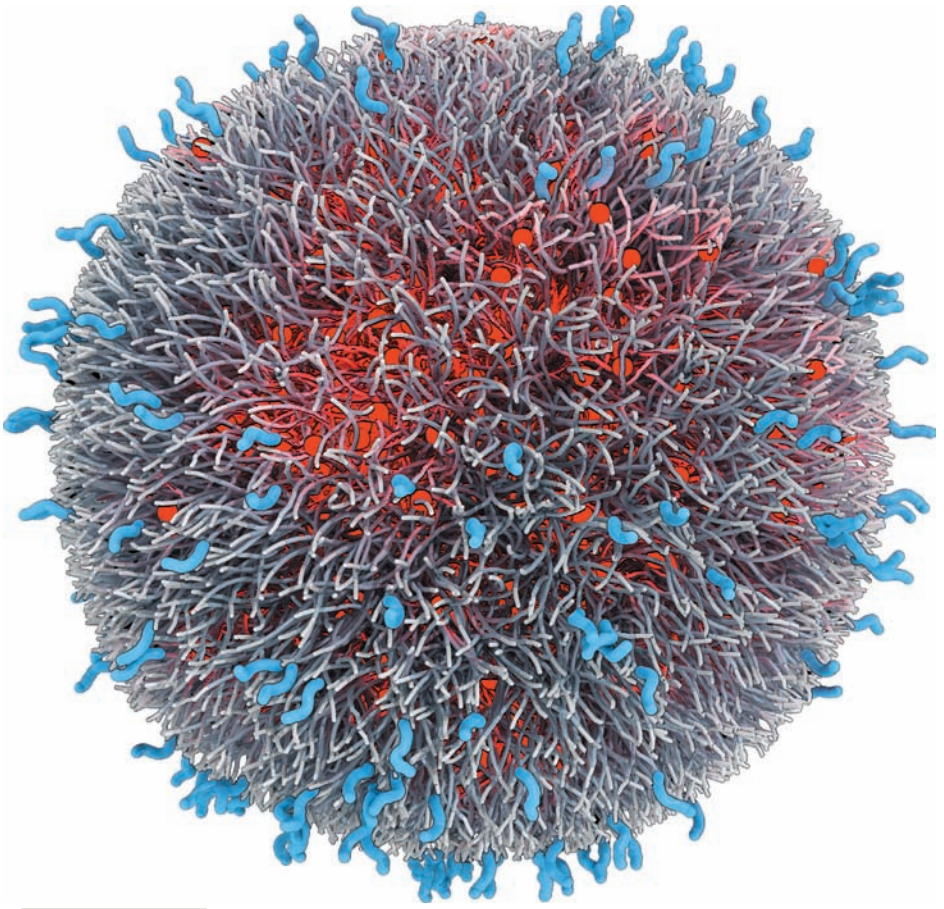

DIGIZYME/ MIT

The Accurin nano-drug BIND-014 encases a toxic payload (red) in a layer of biodegradable polymers (grey), and uses molecules on the surface (blue) to target the tumour.

NANOTECHNOLOGY

Deliver on a promise

Effective treatment of cancer requires getting the drugs precisely to the target. Enter the nanoparticle.

BY JESSICA WRIGHT

When Mary Davis nearly died from the drug used to treat her breast cancer, she issued a challenge to her scientist husband: would he switch his research focus to the design of better cancer treatments? As a chemical engineer at the California Institute of Technology in Pasadena, Mark Davis was creating solid catalysts for use in chemical synthesis. But in 1996, after Mary's experience with the highly toxic chemotherapy drug doxorubicin — dubbed the 'red death' — he heeded her plea and went to work.

Davis used his engineering know-how to design an armour-like particle less than one-thousandth the width of a human hair to encase the drug camptothecin. About ten years after his wife's treatment, he watched doctors inject this molecule, now called CRLX101, into the first patient, Ray Natha. "It was the scariest thing I've ever done," Davis recalls. During the six-month safety trial, Natha's pancreatic cancer, which had spread to his lungs, stalled. And the nanoparticle-coated drug seemed to cause fewer side effects than did unprotected drugs.

Building protective coats around toxic molecules could address one of cancer treatment's biggest remaining challenges — how to spare healthy cells when attacking cancerous ones. Chemotherapy drugs kill rapidly dividing cells to prevent the rampant cell growth that results in tumours. But these drugs reach cancer cells through the same network of blood vessels that supplies the whole body. And, as Mary Davis's experience shows, they are just as likely to poison healthy cells as cancerous ones.

Researchers are therefore working on ways to deliver drugs directly to cancerous tissue. Drug delivery is a multi-stage journey: the active agent needs to enter the body, travel through the bloodstream to arrive at the tumour site, penetrate the tumour mass and then gain entry to the cells (see 'Hole in one'). By refining each step, researchers aim to do more than just protect the body from toxic medication. Pioneering drug-delivery systems are designed to transport payloads — from highly toxic molecules to genetic material — that should never travel through the body alone, and to target cancer cells more precisely than is now possible.

ARMED ANTIBODIES

Much of the excitement over developments in cancer therapy has focused on drugs that target cancer-specific biological pathways, says Steven Libutti, a cancer surgeon at the Albert Einstein College of Medicine in New York. "But this method may not deliver the promise that we hoped, because the tumours themselves evade that strategy," he says. The alternative is to use potent drugs that are toxic to all cells, but to corral these in a benign 'Trojan horse' until they reach the tumour, he says.

One of the simplest ways to do this is to arm cancer-seeking proteins with a cell-killing drug. In the late 1990s, drug companies developed antibodies that bind to the surface of certain types of cancer cell. Fusing these proteins to drugs with a stable chemical linker yields a potent combination: the antibodies encourage uptake of the drug into cancer cells and the linker keeps the drug from working until it gets inside. "It's a simple idea," says John Lambert, chief scientific officer at ImmunoGen in Waltham, Massachusetts, which develops and licenses the technology that links the antibody to the drug. "But it has taken a long time to put all the pieces together."

Only two antibody–drug conjugate (ADC) therapies are on the market. The first, called brentuximab vedotin (marketed by Seattle Genetics in Washington as Adcetris), was approved by the US Food and Drug Administration (FDA) in 2011 to treat some types of lymphoma, cancers of the lymph system, that had not responded to previous treatment. The second, trastuzumab emtansine (marketed by Genentech of South San Francisco, California, as Kadcycla), was approved in 2013 as a treatment for late-stage breast cancer after treatment with conventional chemotherapeutics.

Trastuzumab emtansine fuses emtansine, a toxic chemotherapeutic, to antibodies that bind to a protein receptor called HER2, which is overproduced by about 20% of breast cancers. In a phase III trial that finished in 2012, the nearly 500 women who took the drug lived about

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five months longer and had fewer side effects than did those on the standard treatment[1]. All women in the study were in advanced stages of the disease, but the drug is now in clinical testing as a first-line treatment thanks to the positive results from the trial, says Lambert. Several similar drugs are now in advanced clinical trials, and ImmunoGen is trying to link emtansine to antibodies that target other cancers, from lymphoma to lung and ovarian cancers.

COATED NANOPARTICLES

Like conventional monoclonal antibodies, ADCs need to make their own way to the tumour site. "The molecules you inject have no idea where the cancer cell is," says Lambert. "If they pass by the cancer cell they can attach, but most go elsewhere."

One approach is to add a coat around chemotherapy drugs. The resulting nanoparticles, which range from about 20 to 100 nanometres in diameter, are too large to escape most blood vessels. But they do find their way out of the leakier ones hastily built by a rapidly growing tumour. As a result, they are thought to accumulate preferentially at the tumour site. However, this phenomenon has been studied mostly in animal models and not in people, says Rudolph Juliano, a pharmacologist at the University of North Carolina at Chapel Hill.

Nanoparticles can carry a stronger payload than can antibodies, encasing thousands of drugs in a single molecule. Unfortunately, however, they can also accumulate in the liver and the spleen, where they provide no therapeutic benefit and can cause side effects. To minimize unwanted effects, researchers coat the particles with a layer of polyethylene glycol, which mimics water and effectively hides the drug from the liver cells that detect and engulf intruders. But minimizing liver uptake is still an important part of nanoparticle design, says Juliano.

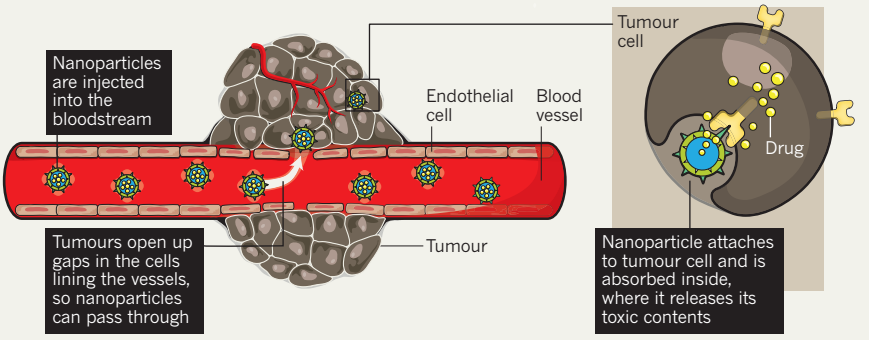
The first nanoparticles to be developed for drug delivery coated the active agent with lipids. The first drug of this type to be approved was Doxil, in 1995. Doxil carries doxorubicin and is used to treat Kaposi's sarcoma and other solid tumours, including breast and ovarian cancer.

According to the US National Cancer Institute, six such nanoparticles are currently approved for use on the market worldwide. So far, they seem to improve safety — Doxil does not end up in the heart, where doxorubicin causes toxicity — but not efficacy. As a result, some researchers have questioned whether nanotechnology is worth the high price tag that accompanies its production: it can cost ten times more than conventional treatment. "New nanoparticle-based drug delivery will be expensive and it has to be justified by improved therapeutic outcomes," says Juliano. "We're still at too early a stage to ascertain that."

Still, nanoparticle drug delivery can have a dramatic and worthwhile effect, says Yun Yen, an oncologist at the City of Hope cancer centre in Duarte, California, who administered CRLX101 (developed by Cerulean Pharma in Cambridge, Massachusetts) to Natha. "It's quite amazing when you see a patient and you're expecting their blood count to drop and you're expecting them to be nauseous, but they do so well," he says.

HOLE IN ONE

Drug-carrying nanoparticles exploit the increased permeability of tumour blood vessels to gain entry to the cell.



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ENGINEERED FOR DELIVERY

Nanotechnology has yet to achieve its full potential because it has so far been used only to ferry drugs intended to be administered through conventional methods, says Omid Farokhzad, a physician-scientist at Harvard Medical School in Boston, Massachusetts, and founder of three nanotechnology-based biotech companies in Massachusetts. One of Farokhzad's companies, Blend Therapeutics in Watertown, is working to engineer drugs specifically for use in nanoparticles.

Farokhzad's other two companies — BIND Therapeutics of Cambridge and Selecta Biosciences of Watertown — use technology that engineers a long polymeric string that spontaneously folds to form a particle. The polymers are interspersed with targeted ligands designed to link the particles to cancer cells. The self-assembly makes it easier for scientists to reproduce the molecule in different batches — a key advantage for translating the technology into the clinic. In a 2012 study, Farokhzad and his colleagues screened 100 polymers that incorporate a molecule that binds to a prostate-specific membrane antigen (PSMA), which is displayed on the surface of most prostate tumours[2]. The particles enclose a chemotherapeutic, docetaxel. The most promising of the nanoparticles, BIND-014, is in phase II trials for treatment of lung and prostate cancer.

"We've built a truck and we have a GPS system. You can load anything on the truck."

Some researchers are branching out from conventional chemotherapy and using nanoparticles to deliver small pieces of RNA to cancer cells, where they decrease expression of certain genes in a method called RNA interference. Davis says that the use of nanoparticles to deliver RNA is promising because it allows researchers to reach multiple genes, and thus pathways, in one hit. He developed the first RNA-carrying nanoparticle to enter clinical trials for cancer. The particle, called CALAA-01, targets the gene *RRM2*, which is involved in cell division and uses molecules that bind to the transferrin receptor, which is highly expressed on cancer cells, to gain access to the cell interior[3]. CALAA-01 entered phase I clinical trials to treat melanoma, but the follow-up trial was halted for reasons that have not been made clear.

Other efforts aim to bring drugs directly to the tumour. Sylvain Martel, a biomedical engineer at Montreal Polytechnic in Canada, is building magnetic particles that researchers will be able to guide to the tumour. These particles use the same contrast agent as in magnetic resonance imaging (MRI), so when a patient is in an MRI scanner researchers can use a strong magnetic field on top of the tumour to guide drugs to the correct site. Martel and his colleagues have tested the method in pigs and aim to try it in people. The magnetic particles can enclose other targeting particles, Martel says. "We've built a truck and we have a GPS system," he says. "You can load anything into the truck."

This vision of a researcher driving a drug directly to the site of a tumour is far from the whole-body onslaught that Mary Davis experienced nearly 20 years ago. Today, the drug she encouraged her husband to develop is nearing the end of phase II clinical trials and has been used to treat hundreds of patients. Future therapies may strike even more efficiently, with fewer side effects, says Mark Davis. "We need to think about ways of driving down cancer so people can have a reasonable life without all the added side effects and toxicities." ■

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PHOTOTAKE/ALAMY

The naked mole rat has been extensively studied, but no cancer has ever been spotted in this species.

COMPARATIVE BIOLOGY

Naked ambition

A subterranean species that seems to be cancer-proof is providing promising clues on how we might prevent the disease in humans.

BY SARAH DEWEERDT

There is a lot not to envy about the life of the naked mole rat: imagine passing your days in a stuffy, pitch-black system of tunnels two or three metres underground with 100 of your closest relatives. But there is one thing that humans might covet: as far as anyone knows, the animal never gets cancer.

Native to the Horn of Africa, this small rodent (*Heterocephalus glaber*) is neither a mole nor a rat; it is actually more closely related to porcupines and guinea pigs. The animal's pale-pink, wrinkled skin is nearly hairless, the better to slip through those narrow burrows. But there is yet another more compelling fact: in all the thousands of naked mole rats that have lived and died in research labs and zoos over the past several decades, not a single instance of spontaneous cancer has been recorded[1].

So far, the animal provides little more than a footnote to the vast body of cancer literature based largely on studies of laboratory mice. But the species has a few fierce advocates in the scientific community, who say that to truly defeat cancer we need to pay a lot more attention to naked mole rats and species like them.

"If we want to learn what naturally occurring resistance mechanisms protect from cancer, we may not find them in mice because mice are even more prone to cancer than humans," says biologist Vera Gorbunova, who co-leads naked-mole-rat studies at the University of Rochester in New York. In some strains of mice, for example, cancer kills 90% of animals.

In other words, although mice are an excellent model for cancer development, progression and treatment, naked mole rats may be better for prevention. "We have to study species that are more resistant," Gorbunova explains.

Researchers have found it tough to induce cancer in naked mole rats. Working in culture, they have infected cells from the creatures with a genetically engineered virus that contains a pair of oncogenes, or cancer-promoting genes, that reliably turns mouse cells malignant[2,3]. "This common oncogenic cocktail had no effect on the naked-mole-rat cells," says Rochelle Buffenstein, a physiologist at the University of Texas, San Antonio, and a pioneer of naked-mole-rat research. "They did not become tumorigenic, they didn't rapidly proliferate, they didn't invade tissues."

Naked-mole-rat cells also seem to be highly sensitive to their neighbours. Normally when cells are grown in culture dishes, they stop proliferating when they touch neighbouring cells; the end result is a smooth, uniform layer covering the surface of the dish. This property, called contact inhibition, is absent in cancer cells. But Gorbunova's team observed that naked-mole-rat cells stop proliferating after just a few cell-to-cell contacts, rather than when all the spaces on the culture plate have been filled in.

The researchers dubbed this hypersensitivity early contact inhibition, and found that it

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is regulated by two genes: *p16* and *p27* (ref. 2). If *p16* is disabled, they showed, *p27* stops cell growth — but at higher cell densities. In humans and mice, *p27* is the main player in contact inhibition, with *p16* taking a minor supporting role. But in naked mole rats, the two genes have become decoupled, resulting in two layers of protection against runaway growth.

In trying to understand what was activating *p16*, Gorbunova's team noticed that naked-mole-rat cells were secreting something into the growth medium that was making it viscous. "We spent some time trying to isolate the goo, and identify what kind of chemical it is," Gorbunova says.

The goo turned out to be hyaluronan, a long polymer of sugars that occupies the spaces between cells in the skin and connective tissues of vertebrates. But in naked mole rats, hyaluronan production is in overdrive: the animals make a large quantity of an unusually large type of the polymer, and break it down more slowly than do other species[4].

That extra dollop of hyaluronan seems to be key to early contact inhibition, because adding enzymes that degrade it to the culture dish blocks the phenomenon[4]. So does blocking CD44, a receptor found on the surface of cells that binds to hyaluronan. How *p16* and CD44 are functionally connected is unknown, Gorbunova says. "We know the beginning point and the end point of the pathway, but we don't understand what's in between."

Others disagree with this interpretation of the results. "We don't see early contact inhibition in our lab," says Buffenstein, who uses a different protocol for growing naked-mole-rat cells. Under optimal culture conditions, she says, the cells will grow to cover a culture dish.

WEIRD AND WONDERFUL

But the cells behave unusually in other respects, Buffenstein has found. They can survive remarkably high doses of heavy metals and carcinogens, although such agents do stop the cells proliferating. By contrast, a high proportion of mouse cells die at low doses — and those that survive continue to proliferate. These multiplying, damaged cells may be the ultimate source of cancers[5].

In a sense, these results parallel Gorbunova's, Buffenstein believes. "We think it's the same mechanism," she says. "When things aren't exactly the way the cell thinks they should be, the cells just sit tight and stop proliferating."

The recognition that something isn't right probably involves *p53*, a tumour-suppressor gene found in many species, including humans. In most species, *p53* is activated only when cells are stressed, but naked-mole-rat cells produce high levels of the protein even under normal conditions. They also express high levels of another protein — nrf2, a master regulator of hundreds of cell-protection genes[6].

All of this suggests that naked mole rats rely on many of the same cancer-protection mechanisms as do humans, just kicked into high gear. "They've upregulated the system to really be extra careful about changes in the cell and when to replicate and when not to," Buffenstein says.

Applying the model of the naked mole rat to human cancer resistance is unlikely to be as simple as upregulating existing anticancer genes. Too much activity of *p16*, for example, can cause cell ageing and death. "My bet would be to try to somehow manipulate turnover of hyaluronan," Gorbunova says. After all, she points out, hyaluronan is already used as a cosmetic treatment for wrinkles, so it may be a relatively feasible target.

Further research may pinpoint other resistance mechanisms in the naked mole rat. "Perhaps many pathways are involved," says Vadim Gladyshev, a cancer biologist at Harvard Medical School in Boston, Massachusetts, who helped to sequence the animal's genome in 2011. "The problem," he adds, "is that the naked mole rat is quite distant from other organisms with completely sequenced genomes." For precisely this reason, he is now sequencing the genome of the Damaraland mole rat (*Fukomys damarensis*). This close cousin of the naked mole rat also lives underground in groups but does develop cancer, so differences between the species could help to identify genomic regions relevant to resistance.

"To some degree we still lack the molecular tools to study them."

Another challenge in working with such an unexplored model is that "to some degree we still lack the molecular tools to study them", says João Pedro de Magalhães at the University of Liverpool, UK, who specializes in the genomics of ageing. But DNA sequencing and gene-expression technologies can be applied across species, so his lab is surveying how gene expression changes in cells from mice, rats and naked mole rats after exposure to DNA-damaging chemicals. Such patterns may shed more light on exactly how damaged naked-mole-rat cells decide when to stop proliferating.

The naked mole rat is not the only cancer-resistant animal. Scientists are increasingly focusing their attention on the blind mole rat (*Spalax* spp.). These are furry brown torpedoes of rodents that are agricultural pests in the Mediterranean region. "In none of the *Spalax* we've raised, thousands of individuals, have we ever found any cancer," says Eviatar Nevo, founder of the Institute of Evolution at the University of Haifa in Israel.

Despite their similar names, blind mole rats are not closely related to naked mole rats (they are more closely related to rats and mice). The two animals evolved their resistance independently, making for intriguing similarities and differences in the underlying mechanisms.

For example, blind mole rats produce hyaluronan in a form similar to that of naked mole rats, but their cells do not show early contact inhibition when grown in the lab. However, the contact inhibition they do show is not normal: instead of filling a culture dish and then holding steady, blind-mole-rat cells undergo mass cell death when they reach high densities[7].

But the species have in common a *p53* tumour-suppressor gene that functions in an unusual way. In the blind mole rat, this gene has a sequence almost identical to a mutated form of *p53* found in many human cancers, and it seems to encourage cells to stop proliferating rather than to self-destruct[8].

DIRECT ATTACK

Researchers at the University of Haifa have also discovered a tantalizing clue that anticancer mechanisms in the blind mole rat may involve selective destruction of malignant cells. When placed in the same laboratory dish as cells derived from human breast or liver cancers, blind-mole-rat cells reduce survival of the cancer cells[9] — suggesting that they secrete an anti-proliferation factor into the medium.

Many researchers believe that these species' cancer resistance is related to their ability to tolerate the oxygen-poor environment of underground burrows, which is similar to the oxygen-poor environment experienced by cells in rapidly growing tumours. "The idea that an animal living in a cancer-like environment would be able to generate adaptations against cancer is very, very natural," Nevo says. "There are 200 species of subterranean mammal," he adds, suggesting that additional anticancer mechanisms may be found by studying this group of species more thoroughly.

Other researchers are looking more broadly across the animal kingdom, plumbing the genomes of long-lived, cancer-resistant species such as Brandt's bat (*Myotis brandtii*) and the bowhead whale (*Balaena mysticetus*). "Harnessing the power of natural selection to increase our knowledge of cancer and hopefully develop therapies against cancer or for cancer prevention is a very unexplored area," says de Magalhães. The end of cancer may yet prove to be underground — or in the seas or in the air. ■

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Shanghai is one of 74 cities that has yet to meet the air-quality standards set by the Chinese government.

IMAGINECHINA/CORBIS

PREVENTION

Air of danger

Carcinogens are all around us, so scientists are broadening their ideas of environmental risk.

BY REBECCA KESSLER

In November last year, an eight-year-old girl became China's youngest person to get lung cancer. The cause, according to her doctor, was fine particulate matter that accumulated in her lungs and led to malignant changes in her cells. Air pollution has been enveloping Chinese cities in smog, periodically closing schools and businesses, and drastically reducing visibility.

A month before the girl's diagnosis, outdoor air pollution and one of its main constituents, particulate matter, were declared carcinogenic to humans by the International Agency for Research on Cancer (IARC). The announcement capped a decade-long review that examined the cancer-causing potential of several airborne pollutants, including dusts, solvents and metals emitted by vehicles, industry, farms, homes and natural sources.

Scientists have suspected since the 1940s that air pollution causes lung cancer, but it has taken seven decades of research to establish the connection. During that time it became clear that smoking causes most lung-cancer deaths (70% globally) and that air pollution kills more people through cardiovascular disease than through cancer. Nevertheless, air pollution's cancer toll adds up. Researchers blamed it for 223,000 lung-cancer deaths in 2010, nearly 15% of all such deaths. The IARC also noted evidence linking air pollution to bladder cancer[1].

"Everybody is exposed to it," says Aaron Cohen, an epidemiologist at the Health Effects Institute in Boston, Massachusetts, a research organization funded by the US government and the motor-vehicle industry. "You can't avoid breathing the air no matter who you are."

Scientists are making progress in understanding the effects of air pollution and other environmental carcinogens. They are learning that certain chemicals may increase cancer risk at lower-than-expected doses, that people may be particularly vulnerable during certain periods of their lives and that the consequences of exposure may cause ripples for generations. Researchers are also looking into environmental triggers that can lead to the onset of particular cancers. Although it is the quest for a cancer cure that draws the most funding and talent, a small but vocal chorus is calling for more attention to environmental carcinogens, in the hope that reducing exposure to them will help to keep the disease from starting.

The IARC has evaluated a total of 970 natural and artificial agents and identified 464 as having some level of carcinogenicity to humans. With some overlap, a catalogue by the US National Toxicology Program lists 240 substances as 'known' or 'reasonably anticipated' human carcinogens. Some cancer-causing agents occur naturally, such as aflatoxins — poisonous compounds produced by moulds that grow in nuts, seeds and legumes. Others are man-made, such as ionizing radiation from medical imaging and various commercial chemicals. Yet of the 80,000 chemicals in commerce, only a tiny fraction has been tested for carcinogenicity.

The proportion of cancers attributable to environmental carcinogens is subject to debate. The most widely cited estimate, made in 1981, attributes 2% of US cancer deaths to pollution

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go.nature.com/srjaod

and 4% to occupational exposures[2]. Those figures are dwarfed by the numbers for smoking and diet, which claimed 30% and 35% of the burden, respectively. But a 2010 report by the US President's Cancer Panel assailed the 1981 estimate and stated that "the true burden of environmentally induced cancer has been grossly underestimated"[3]. And a global estimate by the World Health Organization (WHO) is much higher: 19% of the world's cancers — and 1.3 million deaths annually — are attributed to environmental and occupational factors.

Even so, many researchers, charitable foundations and government agencies continue to underestimate the importance of environmental carcinogens, says Richard Clapp, an epidemiologist at the University of Massachusetts Lowell. "There's more to it than is generally given credence that environmental exposures are causing a portion of our cancer burden and that we can do something about it," he says.

Designating a substance as a carcinogen and making recommendations about its use can be controversial. For example, in 2011, the US National Toxicology Program listed formaldehyde, a chemical common in building materials and household products, as a carcinogen, and styrene, which is used to make plastics and rubber, as reasonably anticipated to be a human carcinogen[4]. Despite similar designations by the IARC and other agencies, industry groups such as the American Chemistry Council successfully advocated for a review of the report by the National Academies in an effort to get the chemicals delisted and avoid further regulation. The outcome of the review is expected soon.

A QUESTION OF QUANTITY

Research is painting an increasingly complex picture of how the body reacts to environmental chemicals. In the past two years, debate has peaked about the behaviour of endocrine-disrupting chemicals. A 2012 review[5] of more than 800 studies concluded that it is "remarkably common" for these chemicals to induce biological responses at much lower doses than expected, and for the responses to be non-monotonic — that is, for higher doses not necessarily to produce greater effects than lower doses. The assertion has huge regulatory implications because safety testing for most chemicals is done not at the low doses at which agents occur in the environment, but at high doses. The results are extrapolated to lower doses, a methodology that would be unsound if non-monotonic behaviour were widespread.

These phenomena have been highly contentious. The US Environmental Protection Agency (EPA) has concluded that non-monotonic responses do occur but are uncommon. Its draft report is currently under review by a National Academies committee. Even so, the WHO, the United Nations Environment Programme and the US Endocrine Society all underscore the importance of low-dose and non-monotonic responses.

Another idea gathering steam is that people are particularly vulnerable at certain times, such as during gestation, puberty and pregnancy, and after giving birth. For example, a study[6] on human prostate stem cells implanted into mice indicated that early-life exposure to low doses of the endocrine-disrupting chemical bisphenol A, which is used in the manufacture of food containers and drink bottles, may increase the risk of a man developing prostate cancer.

Human studies, too, support 'windows of susceptibility'. The Child Health and Development Studies (CHDS) have found that women who have high levels of polychlorinated biphenyls (PCBs) in their blood immediately after giving birth have a tripled risk of developing breast cancer nearly two decades later[7]. The pesticide DDT has an even greater effect[8].

Another CHDS study[9] found that mothers of sons who developed testicular cancer in their thirties tended to have had a suite of DDT-related compounds in their blood when they gave birth. It is now becoming clear "that those really early exposures and events in life could influence the health trajectory of a lifetime", says epidemiologist and CHDS director Barbara Cohn.

"We've got to stop pouring this carcinogenic stuff out into the economy."

Dozens of environmental chemicals are regularly detected in people. Figuring out how these mixtures influence the risk of cancer and other problems may be the most puzzling question for researchers. Most studies investigate the effect of just one chemical at a time, and even that is tricky. "It is very unlikely for us to unravel what we need to know about chemicals until we can understand the implications of mixtures," says Cohn. "We're just learning how to do this."

Looking ahead, Cohn says that she plans to study whether chemical exposures reverberate into the third and fourth generations; the first great-grandchildren of the women who originally participated in the study will soon be born. Rodent studies have shown that exposure to toxic agents can increase the risk of cancer and other illnesses not only in the exposed animal and its offspring, but also in its offsprings' offspring — often as a result of epigenetic alterations to gene expression[10].

IARC director Christopher Wild has coined the term 'exposome' to describe every exposure a person experiences during his or her lifetime — including chemicals, infectious agents, diet, social milieu and more. To better understand what might trigger cancer, Wild suggests that researchers hunt for the hallmarks of exposures, for instance in metabolic products or the pool of RNA molecules transcribed in certain cells.

A promising advance is that the genomes of some tumours have been found to contain distinct mutations when the person has been exposed to particular environmental risks such as tobacco or ultraviolet light. "The tumour starts to reveal its own secrets of its origins," Wild says. Wild has spent three decades researching cancer. During that time, he says, "I don't think anybody's ever asked me: 'Have we found out how to prevent it?' It's always, 'Have we found a cure?'"

Moreover, Wild and others say, prevention efforts usually focus on lifestyle changes for which the individual is responsible, such as stopping smoking and eating well, rather than regulatory changes that would place the responsibility on companies or governments to protect people from exposure to carcinogens.

A CALL TO PREVENT

The IARC's *World Cancer Report 2014* notes that cancer rates are rising fastest in developing countries (see page S18) and that some of the latest treatments will be too expensive for most people to access. It calls for a renewed commitment to prevention, including legislation limiting exposure to environmental carcinogens. "It just seemed an obvious conclusion that you couldn't treat your way out of cancer," Wild says.

Clapp agrees. He points to the promise of green chemistry, the development of safe molecules and techniques to replace harmful ones. An example is replacing dry-cleaning that uses perchloroethylene (classified by the IARC as probably carcinogenic) with soap-based 'wet-cleaning'. Clapp also applauds the European Union's chemical regulation, known as REACH, which puts the onus on companies to demonstrate a chemical's safety before it hits the market. "We've got to stop pouring this carcinogenic stuff out into the economy so that people don't get cancer in the first place," he says

China has started to do just that with air pollution. But curbs on exhaust and industrial emissions and fines for polluters have not yet had much effect: just 3 of the 74 cities the government monitors have met air-quality standards. For now, some citizens resort to wearing face masks outdoors and running air filters in their homes — but that only goes so far. "To clean up the air — that's the solution," Cohen says. "It's not to make people sit in their houses or walk around with masks on." ■

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JACQUELINE KOCH/FRED HUTCHINSON CANCER RESEARCH CENTER

In Uganda, families dealing with cancer find support from fellow patients in treatment clinics.

DEVELOPING WORLD

Global warning

Much of the world is ill-equipped to cope with its rising cancer burden and are pushing prevention and screening.

BY ERIC BENDER

In the villages outside Bangalore in southern India "there's a lot of fear around cancer", says social epidemiologist Suneeta Krishnan. "Women know other women who have breast cancer, or died of cervical cancer. They have little awareness that early detection can lead to good outcomes — and a feeling that they'd rather just not know, because they couldn't afford treatment."

The concerns noted by Krishnan, who works with RTI International's Women's Global Health Imperative in San Francisco, California, are common in the developing world, where prevalence of cancer is climbing rapidly. Experts are raising the alarm over an incoming tidal wave of diagnoses in low- and middle-income countries (LMICs) that will be met with health-care resources that are starkly limited at best.

Of the 14 million people diagnosed with cancer worldwide in 2012, more than 60% live in Africa, Asia and Central and South America, according to the *World Cancer Report 2014*; these regions also account for about 70% of the world's 8 million cancer deaths[1].

Global cancer incidence is predicted to reach 25 million by 2032. The share of the burden borne by LMICs will almost certainly grow, say public-health experts, as populations expand, live longer and adopt the Western lifestyles that are associated with risks of numerous types of cancer (see 'Driving demographics'). "As life expectancies go up, cancer goes up, and these countries are totally unprepared to deal with it," says Mary Gospodarowicz, medical director of the Princess Margaret Cancer Centre in Toronto, Canada, and president of the Union for International Cancer Control (UICC) in Geneva, Switzerland.

Some nations have only a handful of oncologists, and doctors who leave to get trained in developed countries often stay abroad. Underlying these problems are severe limits on health-care funding. "Cancer care is a huge expenditure, and governments and private institutions universally are struggling to cover the costs," says Corey Casper, co-director of the Uganda Cancer Institute/Hutchinson Center Cancer Alliance in Seattle, Washington.

The dearth of health-care resources in developing countries is compounded by fears and stigmas associated with cancer. Public-awareness challenge number one is to dislodge the common conviction that cancer is an automatic death sentence.

In Latin American nations, women shy away from breast screening because they expect those diagnosed with cancer to die of the disease. "If they've only seen women die, they won't run forward to getting a mammogram," says Felicia Knaul, director of the Harvard Global Equity Initiative in Boston, Massachusetts.

Education campaigns must target not just patients or potential patients but also their families and the communities around them. One key is persuading men that the women in their families should get screened, because a wife, for example, may not feel free to take that step without her husband's permission. "Men can be obstacles," says Princess Dina Mired, director-general of the King Hussein Cancer Foundation in Amman. "We tell them that these are your daughters, your wives and your mothers, and you need to support them."

In addition to calling for ramped-up access to screening, advocates around the world are also speaking up on the need for improved end-of-life pain control. "There is zero access to morphine in the poorest countries," says Knaul. "The vast majority of cancer patients die in excruciating pain, and it isn't really an issue of money." Legal restrictions are often the cause; India is one of several countries that are thinking about easing constraints on the use of opiates in palliative care.

The successes of the global campaign against HIV/AIDS offer lessons. "Just as advocates acted up and spoke out on HIV, we need to act up and speak out on cancer and other chronic diseases," says Knaul.

PREVENTION IS A PRIORITY

One-third of the deaths from cancer in LMICS are preventable, according to the World Health Organization (WHO). Measures to reduce exposure to carcinogens such as tobacco; boost vaccinations against infections that can cause cancer; and encourage healthy lifestyles that lower cancer risks can help to avert the rising tide of cancer in LMICs, says Gospodarowicz. "And if you can prevent a lot of cancers, hopefully you will have more resources to deal with the cancers that are not preventable."

The WHO attributes just under one-quarter of global cancer deaths to tobacco, and the news on anti-smoking efforts is mixed. Encouragingly, 177 countries are implementing the WHO Framework Convention on Tobacco Control, says Hana Ross, head of international tobacco control research at the American Cancer Society in Atlanta, Georgia. The convention came into force in 2005 and offers a proven set of tools to reduce tobacco use, ranging from boosting health education and increasing taxation to establishing smoke-free zones and putting pictorial warnings on cigarette packages.

But putting the anti-smoking ideas into practice is another matter. "The battle is changing because of the strength of the tobacco companies, which can make it difficult to implement and enforce those provisions," Ross says. In China, which has about 350 million smokers (including more than half of all males) and where the government owns the world's largest tobacco firm, progress remains particularly difficult. Across Africa, as the population grows and people are increasingly targeted by marketing, "it's going to be catastrophic", she says.

Viral infections are another major contributor to cancer mortality. Up to 20% of cancer deaths in low-income countries arise from hepatitis viruses, which can cause liver cancer, or human papillomavirus (HPV), which is linked to cervical and other cancers. In recent progress against HPV, drug manufacturers are lowering the price of vaccines for low-income countries. Additionally, clinical trials have indicated that a single dose of HPV vaccine may offer the same level of protection against cervical cancer as the customary three doses[2], and is considerably easier to administer. Moreover, an unpublished phase III study showed that a Merck vaccine called V503 is effective against nine strains of HPV, with the potential to prevent about 90% of cervical cancers, as opposed to about 70% prevention from four strains covered by the company's current vaccine, Gardasil.

UNIQUE CHARACTER

Some aspects of cancer in the developing world contradict conventional understanding of the disease, and researchers do not yet know why. Breast cancer provides an example. "Women in the developing world often get breast cancer at a much younger age and in a much more aggressive form than women in the developed world," says Princess Dina. "These women marry early, have children early, breastfeed and probably don't use birth control. Those are supposed to be factors that prevent against breast cancer, so why are they getting this kind of cancer?"

Another major puzzle is why the number of cancers that are driven by infections is so high in the developing world. Some causes are well-known, such as a dearth of the pap-smear tests widely used in the West to identify HPV-linked abnormalities before they develop into full-blown cancers. But others remain a mystery.

In one effort, the Uganda Cancer Institute/Hutchinson Center Cancer Alliance is studying how newborn babies acquire the infections that can lead to cancer. The work has found that viruses such as Epstein–Barr (associated with Burkitt's lymphoma and other cancers) show up in almost all Ugandan children within the first two years of life and often can be detected for years afterwards, says Casper.

Cost-effective approaches to screening and diagnostics are also undergoing intense testing. For instance, a pilot programme in Uganda, run by the non-profit organization Imaging the World in Naalya, has successfully trained local health workers to use rugged portable ultrasound machines to help detect breast cancer, according to Casper. Suspicious lumps are given fine-needle biopsies, which can be analysed by equipment that is already widespread in Africa for use in HIV care.

Elsewhere, work is examining the effectiveness of screening that can be done with locally available resources — such as visual inspections of the cervix after dabbing it with acetic acid. The approach is not as accurate as pap smears, but is much less expensive and demanding of expertise, and it means that abnormal cells can be immediately removed by cell-freezing methods. A randomized study[3] of 150,000 Indian women indicated that the technique can cut cervical-cancer deaths by 31%.

Even if health care is available and affordable, front-line health-care workers in LMICs are often not properly trained to diagnose and treat cancer. And because of cultural norms, women in many countries may not permit a male doctor to examine them. As a result, the doctor may have no option but to make a diagnosis based on a woman's description of her symptoms. This restriction is one of the reasons that a very high proportion of women arriving at major care centres already have advanced tumours that have never been examined by a health-care worker.

'Twinning' partnerships, in which health-care institutions in developed nations offer expertise to colleagues in developing countries, offer a way to improve cancer care. The concept could also be applied within a country, with national and state centres working with smaller, local centres, Knaul suggests. Given proper training and supervision, it may be possible to complete certain drug treatments in the local centres, making cancer therapy practical for patients who live far from clinics. And the near ubiquity of mobile phones is making telemedicine more practical. "We have a mechanism to make sure patients don't get lost in follow-up," says Edward Trimble, director of the US National Cancer Institute's Center for Global Health in Rockville, Maryland.

Trimble also points to promising early experiments using mobile phones to take images of tumours at remote locations and send them to oncology specialists. This approach could aid in diagnosing the eye cancer retinoblastoma, for example, and apps are being developed to help diagnose other types of cancer as well. "There aren't any apps that have been shown to be 100% effective around the world, but this is an important area of research," says Trimble.

SETTING GLOBAL GOALS

The worldwide conversation about cancer is changing, says Tezer Kutluk, a paediatric oncologist at Hacettepe University's Faculty of Medicine in Ankara. Since it became the leading killer worldwide in 2011, "cancer is more and more on the agenda of LMICs, and its priority is increasing", he says.

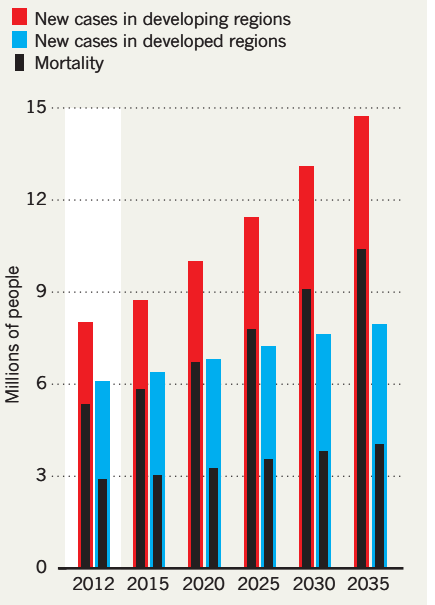
On a positive note, he adds, the WHO, governments, public and private institutions, and other stakeholders are learning to work together more efficiently on both cancer and other non-communicable diseases — one example being the UICC's global public-awareness campaign held each year on World Cancer Day.

Given predictions of an incoming wave of cancer cases in LMICs and in view of the constraints on resources, "there's a lot of controversy and a lot of effort right now to find the best buys for LMICs to invest in", says Gospodarowicz. "You need to have all the pieces in the puzzle for cancer control."

The quest to solve this puzzle, she says, is accelerating the demand for evidence of the most effective and efficient ways to control cancer — and the demand to share the results of that science globally. "The world is now thinking not just about developing new cancer drugs or X-ray machines or other technologies but about how to actually apply them," she says. "That's a very exciting development." ■

DRIVING DEMOGRAPHICS

The number of people who will develop and die from cancer is predicted to climb more steeply in developing countries than in developed nations as populations grow and age. Lifestyle changes, such as Westernization, are likely to boost the numbers further.



SOURCE: WHO

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BRENDAN MONROE

BIOINFORMATICS

Big data versus the big C

The torrents of data flowing out of cancer research and treatment are yielding fresh insight into the disease.

BY NEIL SAVAGE

In 2013, geneticist Stephen Elledge answered a question that had puzzled cancer researchers for nearly 100 years. In 1914, German biologist Theodor Boveri suggested that the abnormal number of chromosomes — called aneuploidy — seen in cancers might drive the growth of tumours. For most of the next century, researchers made little progress on the matter. They knew that cancers often have extra or missing chromosomes or pieces of chromosomes, but they did not know whether this was important or simply a by-product of tumour growth — and they had no way of finding out.

"People had ignored it for a long time, primarily because it's really hard to understand," says Elledge, of Brigham and Women's Hospital in Boston, Massachusetts. "What we didn't know before is that it's actually driving cancer."

Elledge found that where aneuploidy had resulted in missing tumour-suppressor genes, or extra copies of the oncogenes that promote cancer, tumours grow more aggressively (T. Davoli *et al. Cell* **155,** 948–962; 2013). His insight — that aneuploidy is not merely an odd feature of tumours, but an engine of their growth — came from mining voluminous amounts of cellular data. And, says Elledge, it shows how the ability of computers to sift through ever-growing troves of information can help us to deepen our understanding of cancer and open the door to discoveries.

Modern cancer care has the potential to generate huge amounts of data. When a patient is diagnosed, the tumour's genome might be sequenced to see if it is likely to respond to a particular drug. The sequencing might be repeated as treatment progresses to detect changes. The patient might have his or her normal tissue sequenced as well, a practice that is likely to grow as costs come down. The doctor will record the patient's test results and medical history, including dietary and smoking habits, in an electronic health record. The patient may also have computed tomography (CT) and magnetic resonance imaging (MRI) scans to determine the stage of the disease. Multiply all that by the nearly 1.7 million people diagnosed with cancer in 2013 in the United States alone and it becomes clear that oncology is going to generate even more data than it does now. Computers can mine the data for patterns that may advance the understanding of cancer biology and suggest targets for therapy.

Elledge's discovery was the result of a computational method that he and his colleagues developed called the Tumor Suppressor and Oncogene Explorer. They used it to mine large data sets, including the Cancer Genome Atlas, maintained by the US National Cancer Institute, based in Bethesda, Maryland, and the Catalogue of Somatic Mutations in Cancer, run by the Wellcome Trust Sanger Institute in Hinxton, UK. The databases contained roughly 1.2 million mutations from 8,207 tissue samples of more than 20 types of tumour.

The researchers selected a set of parameters that helped to identify the genes they were looking for, such as the mutation rate or the ratio of benign mutations to those that cause a gene to stop functioning. They then applied statistical classification methods to differentiate between suppressor genes and oncogenes. About 70 suppressor genes and 50 oncogenes were already known for these tumour types, but Elledge and his colleagues increased that to about 320 and 200, respectively (although

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that number could fall, because some genes could turn out to be false positives). They also identified pathways in the growth process that might make good drug targets.

Making this sort of finding requires large data sets. "Any individual cancer cell's a mess, but if you look at enough tumours, you get a pattern," Elledge says. "The only way you can figure this out is if you look at them globally."

EASY TO USE

Analysing the genomes of 8,200 tumours is just a start. Researchers are "trying to figure out how we can bring together and analyse, over the next few years, a million genomes", says Robert Grossman, who directs the Initiative in Data Intensive Science at the University of Chicago in Illinois. This is an immense undertaking; the combined cancer genome and normal genome from a single patient constitutes about 1 terabyte (10^{12} bytes) of data, so a million genomes would generate an exabyte (10^{18} bytes). Storing and analysing this much data could cost US$100 million a year, Grossman says.

To make it easier to access whatever subset of data researchers need, Grossman and his colleagues have developed Bionimbus, a cloud-based, open-source platform for sharing and analysing genomic data from the Cancer Genome Atlas.

The results can be powerful. Megan McNerney, a pathologist at the University of Chicago, used Bionimbus to track down a gene involved in acute myeloid leukaemia (AML). Scientists already knew that some patients with the disease had lost part of chromosome 7, but could narrow down the gene involved only to 15–20 candidates. McNerney selected 23 patients from the database and used the computer to compare their RNA sequences to see if something might be missing. She discovered that one copy of the gene *CUX1*, which normally encodes a tumour-suppressor protein, had been deleted in these patients (M. E. McNerney *et al. Blood* **121,** 975–983; 2012). Testing in fruit flies and mice showed that removal of one copy of the gene led to an overgrowth of certain blood cells and, eventually, to leukaemia. Her discovery may not have produced a cure for AML, but it has increased the understanding of a disease for which the median survival time has been stuck at less than a year for four decades, and it might also lead to more-accurate prognoses.

McNerney says that even her small-scale project has shown the benefits of mining data. "It's transforming cancer biology enormously," she says. "Big data has made leaps that we couldn't make otherwise."

Genomics — and data from other '-omics, such as proteomics and epigenomics — are not the only sources of data being sifted. The American Society of Clinical Oncology (ASCO) in Alexandria, Virginia, is developing a platform called CancerLinQ, which trawls through patients' electronic health records. These records increasingly include genomic data, as well as diagnoses and notes on treatment, and measures of how well patients are responding to therapy. The system has gathered records from 177,000 people with breast cancer for a pilot project. Developers hope that the system will be fully operational by the summer of 2015, with other solid tumours to follow.

Clifford Hudis, a breast-cancer specialist at the Memorial Sloan Kettering Cancer Center in New York and president of ASCO, says that CancerLinQ could make discoveries missed by clinical trials. As approved drugs are deployed more widely, the system could gather data on side effects, drug interactions and outcomes in different patient populations. It might also notice, for instance, if doctors stray from US Food and Drug Administration guidelines for drug dosage, based on their assessment of how the dose affects their patients. "If there are 100 cases in a row of doctors independently disregarding the guideline, it helps to teach the computer that the guideline's wrong," Hudis says. The computer might discover, for instance, that doctors get better results when they adjust the dosage according to the patient's age.

"There are some fundamental challenges being caused by our ability to capture so much data."

Discoveries can also be made from combining genomics and standard medical-imaging records. "High-performance computing and big data are enabling us to look across modalities," says David Foran, a pathologist and head of informatics at the Rutgers Cancer Institute of New Jersey in New Brunswick. The centre produces high-resolution digital images of tissue samples and compares them between patients, looking for patterns that might aid prognosis. It expects to generate 40,000–100,000 images.

Researchers might see genetic clues indicating that some patients will respond to a particular drug therapy, for instance, and then look at their CT and MRI scans to see whether changes in the cancer match up with the genetic prediction. Or they might find a correlation between mutations, therapy choice and smoking history. "The computer program can simultaneously look at the patterns in all of them," Foran says.

Comparing so much data greatly expands doctors' expertise, Foran adds. "When you go to see a physician, especially an oncologist, you're relying on his past experience. What we're doing now is training the computer to look at large cohorts of thousands and hundreds of thousands." It is as if the doctor were making treatment decisions based on personal experience of hundreds of thousands of patients.

Gene sequences and electronic health records are new sources of data, but there is a lot of historical information available, too. Johns Hopkins Hospital in Baltimore, Maryland, for instance, has paper-based pathology reports that date back to its opening in 1889. Before it switched to computer records in 1984, the hospital generated more than half-a-million records. Every US state has years or decades of historical cancer records, as do other countries. Denmark, for instance, has cancer records going back to 1943. And Public Health England last year launched a database of all cancers currently being diagnosed across the country, including 11 million records going back 30 years. Adding all that history into the mix widens the field of possible clues that computers can search through.

HARD TO ANALYSE

But it is the new technologies that are creating an information boom. "We can collect data faster than we can physically do anything with them," says Manish Parashar, a computer scientist and head of the Rutgers Discovery Informatics Institute in Piscataway, New Jersey, who collaborates with Foran to find ways of handling the information. "There are some fundamental challenges being caused by our ability to capture so much data," he says.

A major problem with data sets at the terabyte-and-beyond level is figuring out how to manipulate all the data. A single high-resolution medical image can take up tens of gigabytes, and a researcher might want the computer to compare tens of thousands of such images. Breaking down just one image in the Rutgers project into sets of pixels that the computer can identify takes about 15 minutes, and moving that much information from where it is stored to where it can be processed is difficult. "Already we have people walking around with disk drives because you can't effectively use the network," Parashar says.

Informatics researchers are developing algorithms to split data into smaller packets for parallel processing on separate processors, and to compress files without omitting any relevant information. And they are relying on advances in computer science to speed up processing and communications in general.

Foran emphasizes that the understanding and treatment of cancer has undergone a dramatic shift as oncology has moved from one-size-fits-all attacks on tumours towards personalized medicine. But cancers are complex diseases controlled by many genes and other factors. "It's not as if you're going to solve cancer," he says. But big data can provide new, better-targeted ways of grappling with the disease. "You're going to come up with probably a whole new set of blueprints for how to treat patients." ■

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PERSPECTIVE

Learning to share

Genomics can provide powerful tools against cancer — but only once clinical information can be made broadly available, says **John Quackenbush**.

The unveiling of the draft sequence of the human genome in 2000 was met with enthusiastic predictions about how genomics would dramatically change the treatment of diseases such as cancer. The years since have brought a 100,000-fold drop in the cost of sequencing a human genome (to just a few thousand US dollars), and the time needed to sequence it has been cut from months to little more than a day. Researchers can therefore now generate unprecedented quantities of data to help in the battle against cancer (see page S20).

So far, however, our expanded data-generation capacity has not transformed medicine or our understanding of disease to the degree that some expected. A major contributor to this disappointing outcome has been the failure to deal effectively with the problem of capturing and sharing appropriate clinical data on large collections of samples.

The ultimate goal of cancer researchers is to deliver actionable point-of-care information to doctors treating patients. This means, for example, producing easy-to-read reports that detail the associations between a patient's disease state and their probable response to available therapeutics — associations that are defined by a variety of clinical and genomic attributes and that should be supported by a large, well-curated knowledge base. This information can then help doctors to make rapid decisions about which course of therapy is likely to work best for each patient.

Research has already established associations between a few gene variants or gene-expression profiles and clinical endpoints such as drug response. But given the ability to generate large-scale genomic profiling data, they have identified many fewer variants than might have been expected. This shortfall can be attributed to failings in current clinical-research paradigms.

The fundamental design of most clinical and translational-research studies involves comparisons between well-defined patient cohorts. Researchers may divide patients into groups on the basis of outcome — for example, response to a therapy — and ask whether there are genomic features such as mutations or patterns of gene expression that can robustly distinguish between responders and non-responders. Or they can define patient groups according to genomic status and then ask whether there are meaningful differences in some relevant endpoint, such as survival. Cancer research has produced thousands of such genomic studies, with data on hundreds of thousands of patients. But very few of the published studies have been thoroughly validated and fewer still have proved clinically useful.

Although researchers have rushed to generate genomic data, that alone is not sufficient to advance the field. One challenge is to develop analytical methods that are effective for huge amounts of genomic data. In particular, better methods are needed to 'normalize' the data generated by different technologies or at different sites, so that results can be compared across studies — a problem that may seem trivial but that nevertheless has defied a general solution. Methods are also needed to synthesize different types of information more effectively to make predictions, including ways to model the complex interacting networks of factors that drive disease. And standards must be developed to support reproducible research, facilitating validation of the results of any single study in the context of a collective body of data.

But the greatest barrier to the use of 'big data' in biomedical research is not one of methodology. It is, rather, the lack of uniform, anonymized clinical data about the patients whose samples are being analysed. Without such data, even defining experimental cohorts is difficult, and there is a risk of missing potentially obvious confounding factors. Unfortunately, nearly every published study lacks the clinical data to address fundamental research questions fully or to allow the findings of one study to be validated in others.

The first step towards solving this problem is to develop more flexible patient-consent procedures so as to allow the broad use of anonymized clinical data in research. This is particularly important because, at the start of a study, researchers may not know which variables could be important for defining a relevant cohort or could turn out to be confounding an analysis.

The second step is to develop hospital and laboratory computational-infrastructure and data-security protocols to improve the sharing, access and fair use of clinical data. A major barrier to reproducing results is that publicly available data sets rarely include the right clinical information to define appropriate cohorts or test the relevance of a genomic signature.

And, finally, the culture of data sharing must change. Although the publication of the results of genomics studies generally requires the sharing of genomic data, the sharing of clinical data is frequently limited to a bare minimum: just the details described in a manuscript. Even common clinical variables, such as patients' sex, treatment history, smoking history, ethnicity or even standard disease subtype are often not provided. The absence of such key information again makes it difficult to reproduce the results of an analysis or to validate other published data sets.

Big data has tremendous potential to provide fresh insights into diseases such as cancer. But that potential will be realized only by tackling how best to share the clinical information necessary to interpret it. And developing a more complete understanding is essential if we are ultimately to create the knowledge base necessary to provide clear, concise, reliable and actionable information to doctors and their patients. ■

PUBLICLY AVAILABLE DATA SETS **RARELY INCLUDE** THE RIGHT CLINICAL INFORMATION TO **DEFINE** APPROPRIATE COHORTS OR TEST THE **RELEVANCE** OF A GENOMIC SIGNATURE.

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BRENDAN MONROE

BIOLOGY

Three known unknowns

Even as cancer therapies improve, basic questions about drug resistance, tumour spread and the role of normal tissue remain unanswered.

BY KATHERINE BOURZAC

In 1996, Charles Sawyers designed early clinical trials for one of the first drugs aimed at a cancer-specific genetic mutation. The drug was imatinib, the cancer was chronic myeloid leukaemia and Sawyers — a clinical oncologist at the Memorial Sloan Kettering Cancer Center in New York — saw patients who had been debilitated by the disease rapidly improve when given the medicine. "It was unbelievably satisfying," he says.

Unfortunately, he then saw many of those cancers come roaring back as they became resistant to the drug.

The experience with imatinib has given cancer biologists mixed messages. The medicine, now marketed by Novartis in Basel, Switzerland, as Gleevec or Glivec, highlights the potential of personalized medicine. Figuring out what mutation caused the disease and designing a drug to target it was a technological triumph, and it was followed by two further drugs to combat the emerging drug resistance.

But treating cancer by chasing mutation after mutation with drug after expensive drug is not a sustainable model — not least because few cancers other than leukaemia have simple, known genetic causes. "When we know the mutations and can get to a treatment strategy it's exciting," says Sawyers. But so far in the age of gene sequencing, he adds, "we've grabbed the low-hanging fruit".

Biologists now know a huge amount about cancer — much more than they did even ten years ago. About 500 genes have been implicated in the disease, and the list is growing. There are also about 100 approved cancer drugs, some of which, like imatinib, specifically target mutations in those genes, on top of older therapies such as surgery and radiation.

But all this knowledge is not enough: even in countries where people have access to the newest therapies, improvements in death rates have slowed. Up to half of cancers could be prevented by changes in diet and exercise, encouraging people to stop smoking and eliminating environmental risks such as pollution, but other gains will be harder. To conquer cancer, researchers will need to answer some basic scientific questions. Here, *Nature* looks at three of the most pressing.

HOW CAN DRUG RESISTANCE BE OVERCOME?

To combat resistance, researchers are studying the cancer genome, coming up with new ways to design drugs, concocting

combination therapies — and even looking back to Darwin's theory of evolution.

"Seen through a Darwinian lens, the tumour is an ecosystem, a mixture of cells that are continuously mutating," says Paul Workman, head of cancer therapeutics at the Institute of Cancer Research in London. "You put into that mix a very strong selective pressure, which is the drug." At that point it becomes survival of the fittest. Many cells die; others use a combination of strategies to survive and thrive. These may include producing protein pumps that flush the drug out, increasing the rate of DNA repair or using an alternative molecular pathway to restore whatever function the drug blocks. Targeted drugs contribute to the genetic complexity: "These therapies themselves may be driving tumours to become more heterogeneous," says Charles Swanton, a medical oncologist at Cancer Research UK's London Research Institute.

A better understanding of the underlying genetic diversity of tumour cells may help researchers to work out how to tackle drug resistance. Swanton and others are therefore exploiting ever-faster and cheaper DNA-sequencing technologies. So far, Swanton says, it looks as though every tumour has a set of core mutations that are shared by all its cells. He calls these the tumour's 'trunk'. Subpopulations of cells within the tumour have their own unique sets of shared mutations; he calls these subpopulations 'branches'. Therapy prunes some branches while sparing others, which then repopulate the tumour.

Researchers are now trying to look at tumour evolution in patients. One study, called TRACERx (Tracking Cancer Evolution through Therapy), will allow Swanton and a large group of collaborators to observe 850 people with lung cancer from diagnosis through therapy. Biopsies are taken from multiple spots within tumours both before and after treatment, then analysed by sequencing the parts of the tumour genomes that code for proteins. Comparing these biopsies should identify which mutations are associated with drug resistance. These kinds of studies may help geneticists to write what Swanton calls "an evolutionary rulebook of cancer" that can be used to predict tumour evolution without having to do repeated sequencing studies to get future patients on the right therapies.

Other researchers caution that genetics will provide only part of the picture of tumour heterogeneity and drug resistance. Variations in how tumours use these genes — the way they are regulated and expressed — also enable tumours to develop drug resistance. "Cells that are not intrinsically resistant to a drug will rewire their circuitry during treatment to become resistant" without any genetic changes at all, says cell biologist Joan Brugge at Harvard Medical School in Boston, Massachusetts.

Even without a full understanding of the way that tumours evolve in the face of chemotherapy, researchers are coming up with ways to overcome resistance. Using a combination of drugs can reduce a tumour's options. Here, scientists take inspiration from the success of the antiretroviral cocktails that keep HIV in check. Like cancer, HIV has tremendous genetic diversity and evolves rapidly, but the right cocktail of drugs has transformed HIV infection from a death sentence for many into a manageable, long-term condition. Cancer presents a tougher challenge. HIV has just nine genes, compared with our approximately 20,000, making human cancer cells much more complex. Researchers are still trying to figure out how to make smart combination therapies that really work.

"Cells that are not intrinsically resistant to a drug will rewire their circuitry during treatment to become resistant."

James Doroshow, head of cancer treatment and diagnosis at the US National Cancer Institute (NCI) in Bethesda, Maryland, believes that the best way to figure out combination therapies is to test the possibilities through brute force. The NCI has been testing 5,000 drug combinations against 60 cancer cell lines *in vitro*; promising candidates are then screened for toxicity in mice. The results have not yet been published, but Doroshow says that new and unexpected combinations are showing up.

Workman's group is using computer models of gene networks to sort through thousands of possible drug combinations and genes to find likely synergies. He agrees that combination therapy is the only way to overcome resistance, but thinks that new drugs are also needed. He estimates that just 5% of known cancer genes are targeted by drugs. "If we can't make drugs against the other 95%," he asks, "how on Earth are we going to build the combination therapies that will lead to a cure?"

To make matters more difficult, some cancer-causing mutations work by silencing the tumour-suppressor genes that normally help to stop tumours from forming. Developing a drug to block the absence of something is a major challenge, says Workman. And some of the genes associated with cancer make proteins whose structures are unknown; without the structure, chemists have nothing to go on. Many cancer genes therefore remain, for the time being at least, untargetable.

HOW ARE HEALTHY TISSUE AND GENES INVOLVED?

Cancer is caused not just by bad cells or bad genes, but also by good ones not doing the right thing — an aspect of cancer that is highly complicated to study and to combat.

Mina Bissell, a bioengineer at the Lawrence Berkeley National Laboratory in California, sees potential in an area that has been largely ignored by the pharmaceutical industry: the supportive structures and non-cancer cells in and around tumours, called the tumour microenvironment. Signals from this microenvironment can stop a cell that has cancer-causing mutations from becoming cancerous, and putting a tumour cell in a different environment can render it benign. "We need to therapeutically fix the microenvironment," she says.

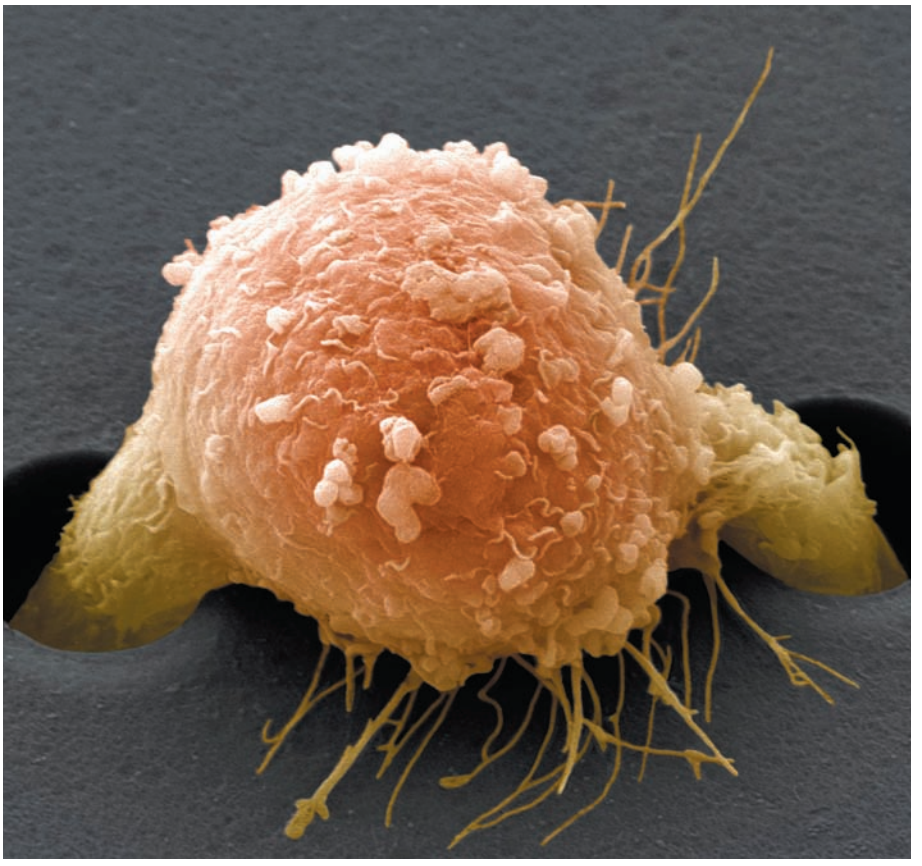
Jacqueline Lees, associate director of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology in Cambridge, agrees. It is important, she says, to think not just about killing cancer cells but also about targeting the processes that support them, the interactions between tumour and non-tumour cells and the immune system. Tumours cannot thrive without certain kinds of signalling patterns from their neighbouring cells. "Traditional drug screening has missed that," Lees says.

Lees is studying a process called cancer dormancy. Some cancer cells are quiescent during the tumour's boom times but can become reactivated if left behind after surgery. Lees is trying to determine how this works, and what role normal cells have in the dormancy and activation process.

Quiescent tumour cells are less vulnerable to chemotherapy because the treatments are aimed at dividing cells, and quiescent ones are not taking part in the normal cell cycle of growth and division.

What signals from the microenvironment are needed to wake these cells? Lees says that inflammation — a sign of activation of the immune system — after surgery and treatment may jump-start quiescent cells. Then, a tumour cell has to warm up its engines. "It has to switch back on a whole protein program that takes 48 hours, and during that time it's taking advantage of interactions with normal surrounding cells," she says. The right drugs in the right order could help to control this process. Chemotherapy could be preceded by drugs that wake up the quiescent cells. Then drugs that suppress crosstalk could prevent them from restarting a tumour after therapy.

If it can be revved up, the immune system might be able to do this itself. Cancer cells put up many defences against attack from the immune system, including expressing receptors that deactivate an important class of immune cell. In the past few years, drugs that block these receptors have generated much excitement in clinical trials. These drugs, called immune checkpoint inhibitors, seem to let loose the immune system's natural cancer-fighting activity. But they do not work in all patients, and researchers have yet to figure out why, says Sawyers. For these



STEVE GSCHMEISSNER/SPL

Breast-cancer cells can become motile and start to spread around the body.

patients, a combination of drugs that target the tumour, the support cells and the immune system "could save the day", he says.

Lees agrees. Successfully treating cancer may require attacking tumours on multiple fronts, she says, with conventional therapies bolstered by new ones that activate the immune system and silence certain interactions between tumours and their environment.

HOW DOES CANCER SPREAD?

The cause of most cancer deaths — about 90% — is not the primary tumour, but secondary tumours called metastases that have developed elsewhere in the body. Sometimes these metastatic tumours become apparent decades after a patient was thought to be cured. So a better understanding of metastasis would help to prevent a great deal of cancer deaths. "We need to focus more on secondary tumours," says Ann Chambers, director of translational breast-cancer research at the London Health Sciences Centre in Canada.

The beginning of the metastatic process is by now pretty well understood, says Robert Weinberg, a cancer biologist at Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. Some cancer cells become motile and aggressive, and enter the bloodstream. Some exit the circulation at distant sites, and a fraction of these can start new tumours there (C. L. Chaffer and R. A. Weinberg *Science* **331,** 1559–1564; 2011). What is incredible, says Weinberg, is that any of these cells live, let alone seed new tumours. "The big remaining mystery is how cancer cells are able to adapt and make a living in a distant tissue," he says. The environment in the brain or bone marrow, say, is very different from that in the prostate or breast, where the tumour may have started its journey. There may be different levels of glucose and oxygen, or the foreign tissue might be more or less acidic. Tumour cells are thought to be dependent on growth factors, protein signals and other encouraging messages in their native tissue. Still, some cells form new tumours at other sites. Weinberg speculates that this involves not mutations, but extensive changes in gene expression.

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Perhaps even more puzzling than how cells can thrive in a new place is what they do in the time between their arrival and the growth spurt that initiates secondary disease. "Cancer cells make it to a distant organ, escape the bloodstream — and then they sit there for ten years while nothing happens," says tumour biologist Klaus Pantel of the University Medical Center Hamburg-Eppendorf in Germany. "Something keeps them from proliferating, and then something activates these cells."

What those signals are is unknown. And not enough people are studying the problem, says Chambers. "Tumour dormancy is frustrating — like watching paint dry," she says. "People don't want to watch tumours not grow."

There are other barriers to studying metastasis. Secondary tumours that have grown large enough to cause health problems and be detected are often not biopsied because patients are in fragile health. And it is difficult to get a picture of the early stages of growth of metastases: they are too small to show up in imaging scans. Furthermore, Chambers notes, even when people have ideas for drugs to prevent or slow tumour spread, today's clinical trials are not designed to show this effect. Trials tend to enrol patients with advanced disease and established metastatic tumours. The potential of a drug to prevent the spread of cancer cannot be seen in this group because it is too late, she says.

To treat cancers that have already spread will require knowing more about the mechanics of metastasis. First, researchers must figure out which of the heterogeneous mix of cells in a tumour are capable of spreading, and how they differ from the other cells.

Brugge has developed a way to find these tumour-initiating cells. Researchers in her lab take about 100 cells from a primary tumour biopsy, separate them, clone them and give each its own genetic bar code. They then maintain one set *in vitro* and inject another into mice, says Brugge. Cells with metastatic tendencies will grow into tumours, and once they do, the researchers remove them and note, using the bar codes, which cells started the new tumours. Brugge can then go back to the cells in culture to study what differentiates them from cells that did not metastasize.

Another approach involves looking for tumour cells in patients' blood, cancer's metastatic thoroughfare. These circulating tumour cells may hold some answers to the mystery of metastasis — their ranks must include some that will form secondary tumours. Once isolated, they can be sequenced and imaged, and the expression of their genes can be compared with that of the primary tumour's.

Many key details of cancer biology remain elusive, but new technologies are helping researchers to gain access to them. Quickly advancing genomic and bioinformatics techniques are helping to overcome drug resistance by predicting which drugs to use and in what combinations; new models are providing insight into the interactions between normal and cancerous tissues; and metastatic cells can now be found before they make tumours.

Given this progress, veteran researchers find reason for optimism. "Twenty years ago, I would have thought some of these problems were intractable," says Doroshow. "But now, I don't." ■

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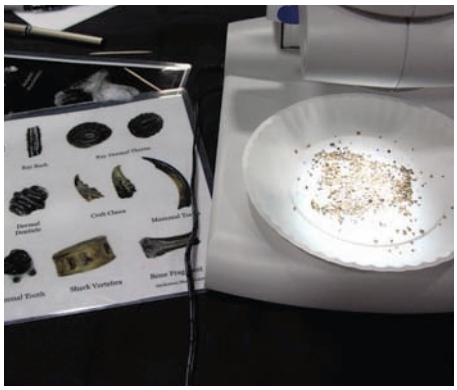

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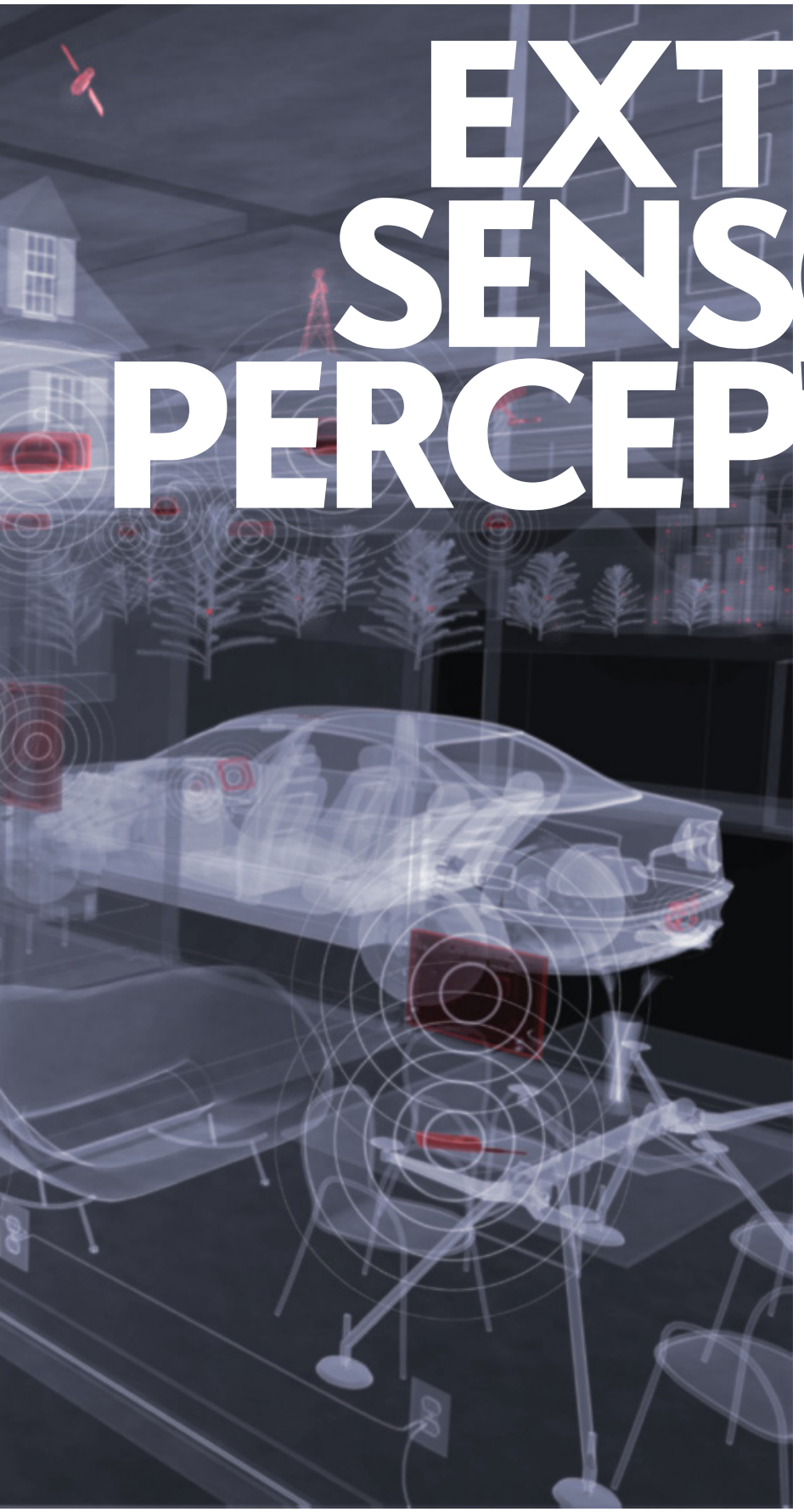

COMPUTER SCIENCE

EXTRA SENSORY PERCEPTION

How a world filled with sensors will change the way we see, hear, think and live

By Gershon Dublon and Joseph A. Paradiso

IN BRIEF

The modern world is filled with network-connected electronic sensors, but most of the data they produce are invisible to us, "siloed" for use by specific applications. If we eliminate those silos and enable sensor data to be used by any network-connected device, the era of ubiquitous computing will truly arrive.

Although it is impossible to know precisely how ubiquitous computing will change our life, a likely possibility is that electronic sensors embedded in the environment will function as extensions of the human nervous system. Wearable computing devices could become, in effect, sensory prosthetics.

Sensors and computers could make it possible to virtually travel to distant environments and "be" there in real time, which would have profound implications for our concepts of privacy and physical presence.

Illustration by Mirko Ilić

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Gershon Dublon is a Ph.D. student at the M.I.T. Media Lab, where he develops new tools for exploring and understanding sensor data.

Joseph A. Paradiso is an associate professor of media arts and sciences at the Media Lab. He directs the Media Lab's Responsive Environments Group, which explores how sensor networks augment and mediate human experience, interaction and perception.

HERE'S A FUN EXPERIMENT: TRY COUNTING THE ELECTRONIC SENSORS surrounding you right now. There are cameras and microphones in your computer. GPS sensors and gyroscopes in your smartphone. Accelerometers in your fitness tracker. If you work in a modern office building or live in a newly renovated house, you are constantly in the presence of sensors that measure motion, temperature and humidity.

Sensors have become abundant because they have, for the most part, followed Moore's law: they just keep getting smaller, cheaper and more powerful. A few decades ago the gyroscopes and accelerometers that are now in every smartphone were bulky and expensive, limited to applications such as spacecraft and missile guidance. Meanwhile, as you might have heard, network connectivity has exploded. Thanks to progress in microelectronics design as well as management of energy and the electromagnetic spectrum, a microchip that costs less than a dollar can now link an array of sensors to a low-power wireless communications network.

The amount of information this vast network of sensors generates is staggering—almost incomprehensible. Yet most of these data are invisible to us. Today sensor data tend to be "siloed," accessible by only one device for use in one specific application, such as controlling your thermostat or tracking the number of steps you take in a day.

Eliminate these silos, and computing and communications will change in profound ways. Once we have protocols that enable devices and applications to exchange data (several contenders exist already), sensors in anything can be made available to any application. When that happens, we will enter the long-predicted era of ubiquitous computing, which Mark Weiser envisioned in this magazine a quarter of a century ago [see "The Computer for the 21st Century"; September 1991].

We doubt the transition to ubiquitous computing will be incremental. Instead we suspect it will be a revolutionary phase shift much like the arrival of the World Wide Web. We see the beginnings of this change with smartphone applications such as Google Maps and Twitter and the huge enterprises that have emerged around them. But innovation will explode once ubiquitous sensor data become freely available across devices. The next wave of billion-dollar tech companies will be context aggregators, who will assemble the sensor information around us into a new generation of applications.

Predicting what ubiquitous computing and sensor data will mean for daily life is as difficult as predicting 30 years ago how the Internet would change the world. Fortunately, media theory can serve as a guide. In the 1960s communications theorist Marshall McLuhan spoke of electronic media, mainly television, becoming an extension of the human nervous system. If only McLuhan were around today. When sensors are everywhere—and when the information they gather can be grafted onto human perception in new ways—where do our senses stop? What will "presence" mean when we can funnel our perception freely across time, space and scale?

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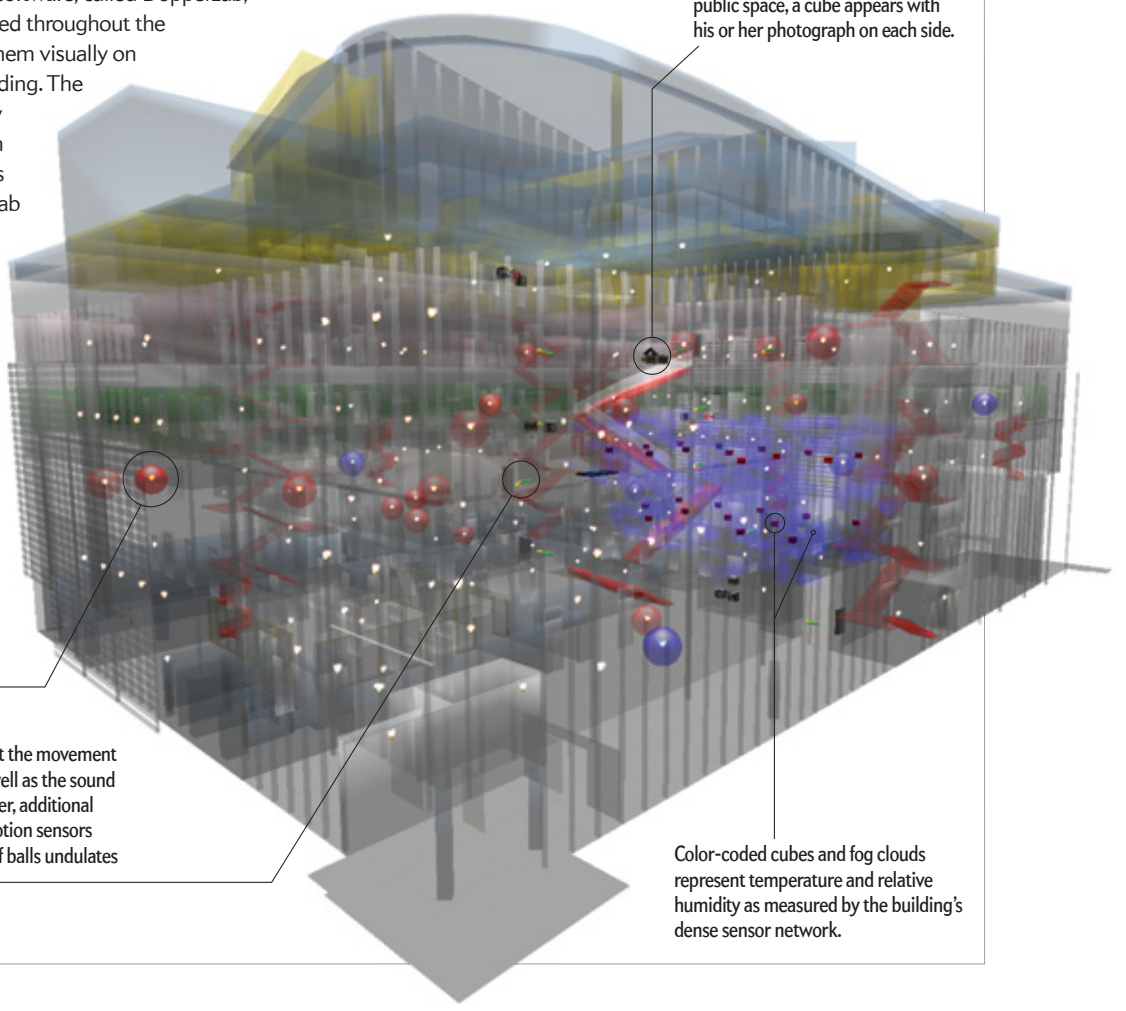
The Reality Browser

The authors' sensor-browsing software, called DoppelLab, gathers data from sensors placed throughout the M.I.T. Media Lab and depicts them visually on a translucent model of the building. The browser updates automatically in real time, so users can log on from anywhere and see what is happening in any room in the lab at any moment. Temperature, motion, sound and other properties are depicted with icons.



COURTESY OF GERSHON DUBLON AND DOPPELLAB DEVELOPMENT TEAM

VISUALIZING SENSOR DATA

WE PERCEIVE THE WORLD using all our senses, but we digest most digital data through tiny two-dimensional screens on mobile devices. It is no surprise, then, that we are stuck in an information bottleneck. As the amount of information about the world explodes, we find ourselves less able to remain present in that world. Yet there is a silver lining to this abundance of data, as long as we can learn to use it properly. That is why our group at the M.I.T. Media Lab has been working for years on ways to translate information gathered by networks of sensors into the language of human perception.

Just as browsers like Netscape gave us access to the mass of data contained on the Internet, so will software browsers enable us to make sense of the flood of sensor data that is on the way. So far the best tool for developing such a browser is the video game engine—the same software that lets millions of players interact with one another in vivid, ever changing three-dimensional environments. Working with the game engine Unity 3D, we have developed an application called DoppelLab that takes streams of data collected by sensors placed throughout an environment and renders the information in graphic form, overlaying it on an architectural computer-aided design (CAD) model of the building. At the Media Lab, for example, DoppelLab collects data from sensors throughout the building and displays the results on a computer screen in real time. A user looking at the screen can see the temperature in every room, or the foot traffic in any given area, or even the location of the ball on our smart Ping-Pong table.

DoppelLab can do much more than visualize data. It also gathers sounds collected by microphones scattered about the building and uses them to create a virtual sonic environment. To guarantee privacy, audio streams are obfuscated at the originating sensor device, before they are transmitted. This renders speech unintelligible while maintaining the ambience of the space and the vocal character of its occupants. DoppelLab also makes it possible to experience data recorded in the past. One can observe a moment in time from various perspectives or fast-forward to examine the data at different timescales, uncovering hidden cycles in the life of a building.

Sensor browsers such as DoppelLab have immediate commercial applications—for example, as virtual-control panels for large,

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sensor-equipped buildings. In the past a building manager who wanted to track down a problem in the heating system might have sorted through spreadsheets and graphs, cataloguing anomalous temperature measurements and searching for patterns that would point to the source. Using DoppelLab, that person can see the current and desired temperature in every room at once and quickly spot issues that span multiple rooms or floors. More than that, planners, designers and building occupants alike can see how the infrastructure is being used. Where do people gather and when? What effects do changes in the building have on how people interact and work within it?

But we did not make DoppelLab with commercial potential in mind. We built it to explore a bigger and more intriguing matter: the impact of ubiquitous computing on the basic meaning of presence.

REDEFINING PRESENCE

WHEN SENSORS AND COMPUTERS make it possible to virtually travel to distant environments and "be" there in real time, "here" and "now" may begin to take on new meanings. We plan to explore this shifting concept of presence with DoppelLab and with a project called the Living Observatory at Tidmarsh Farms, which aims to immerse both physical and virtual visitors in a changing natural environment.

Since 2010 a combination of public and private environmental organizations have been transforming 250 acres of cranberry bogs in southern Massachusetts into a protected coastal wetland system. The bogs, collectively called Tidmarsh Farms, are co-owned by one of our colleagues, Glorianna Davenport. Having built her career at the Media Lab on the future of documentary, Davenport is fascinated by the idea of a sensor-rich environment producing its own "documentary." With her help, we are developing sensor networks that document ecological processes and enable people to experience the data those sensors produce. We have begun populating Tidmarsh with hundreds of wireless sensors that measure temperature, humidity, moisture, light, motion, wind, sound, tree sap flow and, in some cases, levels of various chemicals.

Efficient power management schemes will enable these sensors to live off their batteries for years. Some of the sensors will be equipped with solar cells, which will provide enough of a power boost to enable them to stream audio—the sound of the breeze, of nearby birds chirping, of raindrops falling on the surrounding leaves. Our geosciences colleagues at the University of Massachusetts Amherst are outfitting Tidmarsh with sophisticated ecological sensors, including submersible fiber-optic temperature gauges and instruments that measure dissolved oxygen levels in the water. All these data will flow to a database on our servers, which users can query and explore with a variety of applications.

Some of these applications will help ecologists view environmental data collected at the marsh. Others will be designed for the general public. For example, we are developing a DoppelLab-like browser that can be used to virtually visit Tidmarsh from any computer with an Internet connection. In this case, the backdrop is a digital rendering of the topography of the bog, filled with virtual trees and vegetation. The game engine adds noises and data collected by the sensors in the marsh. Sound from the microphone array is blended and cross-faded according to a user's virtual position; you will be able to soar above the bog and hear everything happening at once, listen closely to a small region, or swim underwater and hear sound collected by hydrophones. Virtual wind driven by real-time data collected from the site will blow through the digital trees.

INFRARED CAMERAS in a sensor-laden bog spot groundwater (*seen here in yellow*) flowing into colder surface water. While surface water tracks closely to the air temperature, groundwater maintains a steady temperature year-round.

The Living Observatory is more of a demonstration project than a practical prototype, but real-world applications are easy to imagine. Farmers could use a similar system to monitor sensor-laden plots, tracking the flow of moisture, pesticides, fertilizers or animals in and around their cropland. City agencies could use it to monitor the progression of storms and floods across a city while finding people in danger and getting them help. It is not a stretch to imagine using this technology in our everyday life. Many of us already look up restaurants on Yelp before going out. One day we will be able to check out a restaurant's atmosphere (is it crowded and noisy right now?) before heading across town.

Eventually this kind of remote presence could provide the next best thing to teleportation. We sometimes use DoppelLab to connect to the Media Lab while away on travel because hearing the buzz and seeing the activity brings us a little bit closer to home. In the same way, travelers could project themselves into their homes to spend time with their families while on the road.

AUGMENTING OUR SENSES

IT IS A SAFE BET that wearable devices will dominate the next wave of computing. We view this as an opportunity to create much more natural ways to interact with sensor data. Wearable computers could, in effect, become sensory prostheses.

Researchers have long experimented with wearable sensors and actuators on the body as assistive devices, mapping electrical signals from sensors to a person's existing senses in a process known as sensory substitution. Recent work suggests that neuroplasticity—the ability of our brain to physically adapt to new stimuli—may enable perceptual-level cognition of "extra senso-

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ry" stimuli delivered through our existing sensory channels. Yet there is still a huge gap between sensor network data and human sensory experience.

We believe one key to unlocking the potential of sensory prostheses will be gaining a better handle on the wearer's state of attention. Today's highest-tech wearables, such as Google Glass, tend to act as third-party agents on our shoulders, suggesting contextually relevant information to their wearer (recommending a particular movie as a wearer passes a movie theater, for example). But these suggestions come out of the blue. They are often disruptive, even annoying, in a way that our sensory systems would never be. Our sensory systems allow us to tune in and out dynamically, attending to stimuli if they demand it but otherwise focusing on the task at hand. We are conducting experiments to see if wearable computers can tap into the brain's inherent ability to focus on tasks while maintaining a preattentive connection to the environment.

When sensors and computers make it possible to virtually travel to distant environments, "here" and "now" may begin to take on new meanings.

Our first experiment will determine whether a wearable device in the field can pick out which of a set of audio sources a user is listening to. We would like to use this information to enable the wearer of a device to tune into the live microphones and hydrophones at Tidmarsh in much the same way that they would tune into different natural sources of sounds. Imagine concentrating on a distant island in a pond and slowly beginning to hear the faraway sounds, as if your ears were sensitive enough to extend the distance. Imagine walking along a stream and hearing sound from under the water or looking up at the trees and hearing the birdsong at the top of the canopy. This approach to delivering digital information could mark the beginning of a fluid connection between our sensory systems and networked sensor data. There will probably come a time when sensory or neural implants provide that connection; we hope these devices, and the information they provide, will fold into our existing systems of sensory processing rather than further displacing them.

DREAM OR NIGHTMARE?

FOR MANY PEOPLE, ourselves included, the world we have just described has the potential to be frightening. Redefining presence means changing our relationship with our surroundings and with one another. Even more concerning, ubiquitous computing has tremendous privacy implications. Yet we believe there are many ways to build safeguards into technology.

A decade ago, in one of our group's projects, Mat Laibowitz deployed 40 cameras and sensors in the Media Lab. He designed a huge lamp switch into each device so it could be easily and obviously deactivated. In today's world, there are too many cameras, microphones and other sensors scattered for any one person to deactivate—even if they do have an off switch. We will have to come up with other solutions.

One approach is to make sensors respond to context and a person's preferences. Nan-Wei Gong explored an idea of this kind when she was with our research group several years ago. She built a special key fob that emitted a wireless beacon informing nearby sensor devices of its user's personal privacy preferences. Each badge had a large button labeled "No"; on pressing the button, a user was guaranteed an interval of total privacy wherein all sensors in range were blocked from transmitting his or her data.

Any solution will have to guarantee that all the sensor nodes around a person both receive and honor such requests. Designing such a protocol presents technical and legal challenges. Yet research groups around the world are already studying various approaches to this conundrum. For example, the law could give a person ownership or control of data generated in his or her vicinity; a person could then choose to encrypt or restrict those data from entering the network. One goal of both DoppelLab and the Living Observatory is to see how these privacy implications play out in the safe space of an open research laboratory. As pitfalls and sinister implications reveal themselves, we can find solutions. And as the recent revelations from former NSA contractor Edward Snowden have shown us, transparency is critical, and threats to privacy need to be dealt with legislatively, in an open forum. Barring that, we believe that grassroots, open-source hardware and software development is the best defense against systemic invasions of privacy.

Meanwhile we will be able to start seeing what kinds of new experiences await us in a sensor-driven world. We are excited about the prospects. We think it is entirely possible to develop technologies that will fold into our surroundings and our bodies. These tools will get our noses off the smartphone screen and back into our environments. They will make us more, rather than less, present in the world around us. SA

MORE TO EXPLORE

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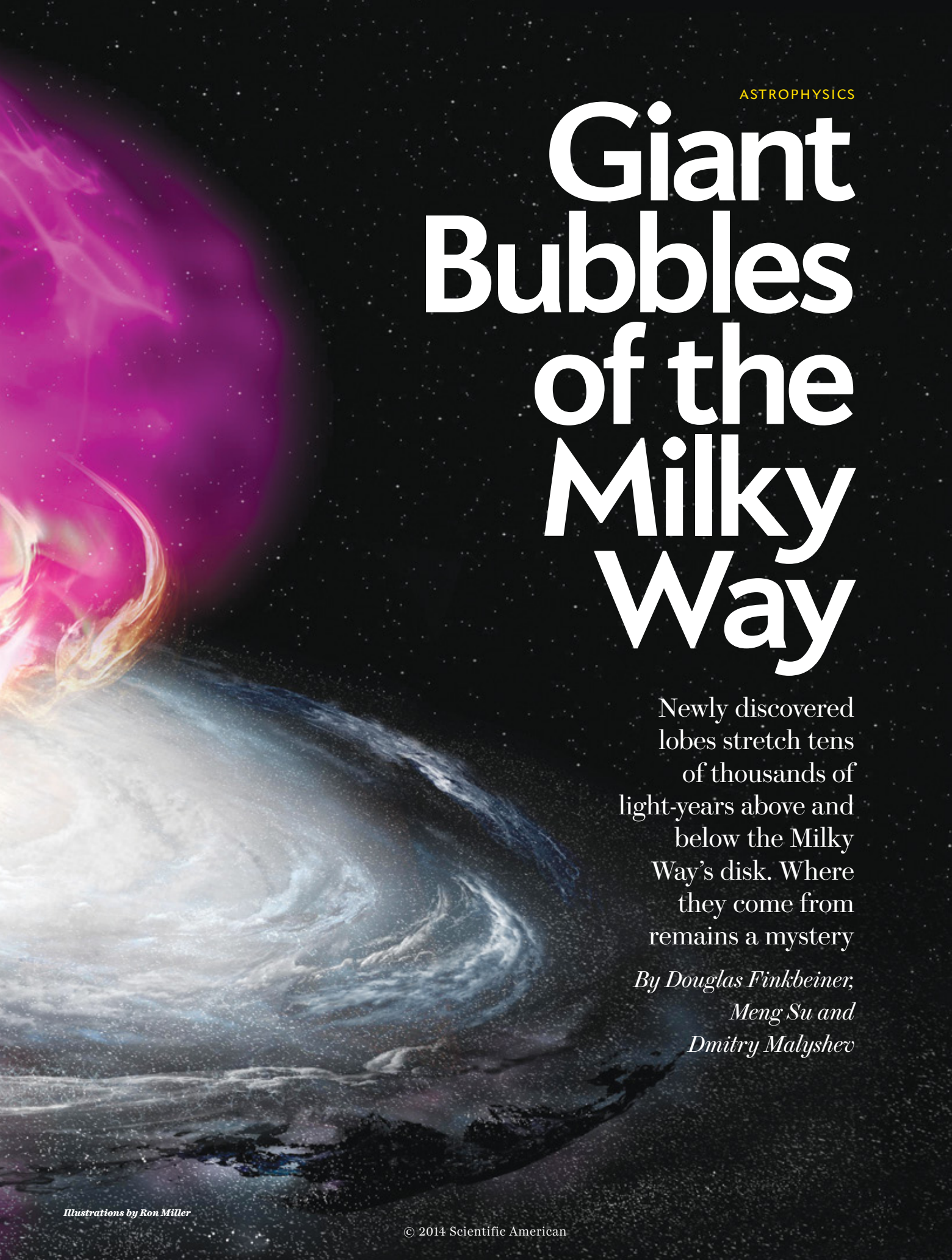

ASTROPHYSICS

Giant Bubbles of the Milky Way

Newly discovered lobes stretch tens of thousands of light-years above and below the Milky Way's disk. Where they come from remains a mystery

By Douglas Finkbeiner, Meng Su and Dmitry Malyshev

Illustrations by Ron Miller

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Douglas Finkbeiner is professor of astronomy and of physics at Harvard University and a member of the Institute for Theory and Computation at the Harvard-Smithsonian Center for Astrophysics.

Meng Su is a Pappalardo Fellow and an Einstein Fellow at the Massachusetts Institute of Technology and the M.I.T. Kavli Institute for Astrophysics and Space Research.

Dmitry Malyshev is a postdoctoral fellow at Stanford University and the SLAC National Accelerator Laboratory, as well as a member of the Fermi Large Area Telescope team.

On a clear night, away from city lights, you might see a beautiful structure arched across the sky: our home galaxy, the Milky Way. Since ancient times, humans have marveled at the dark dust clouds silhouetted against the milky background. Just four centuries ago Galileo pointed his telescope at the heavens and found that the milk was the blended light of countless stars.

The architecture of the Milky Way has just been revised again. Using an entirely new type of telescope, we and our collaborators have discovered colossal structures that tower over the galactic center and extend tens of thousands of light-years into space. These luminous lobes have gone unnoticed for so long because they glow brightest in gamma rays, which cannot pass through our atmosphere.

We do not yet know what is creating these Fermi bubbles, as we have called them. But they appear to be driven by mysterious processes happening deep within the center of our Milky Way galaxy—a chaotic region where a supermassive black hole churns whirlpools of hot gas, while violent supernovae bloom like daffodils out of the rich soil of stellar nurseries.

Like many unexpected discoveries, we found the Fermi bubbles nearly by accident. But now that we have found them, we have begun to meticulously map out their features. Our giant bubbles of the Milky Way promise to reveal deep secrets about the structure and history of our galaxy.

THE SURPRISE DISCOVERY

THE FIRST HINT that something was amiss in the inner galaxy came not from gamma rays but from microwaves. The year was 2003, and I (Finkbeiner) was trying to better understand the origin of the universe using data from the Wilkinson Microwave Anisotropy Probe (WMAP), at the time the latest, greatest cosmology satellite. I was a postdoctoral fellow at Princeton University, studying how nearby interstellar dust obscured the signal from WMAP's intended target—microwaves from the dim afterglow of the big bang. The dust is interesting in its own right, but to a cosmologist it is like smudges on a windshield, something to be modeled and subtracted from the data.

The dust was not the only thing I had to remove. Since astronomers are forced to observe the cosmos from inside the Milky Way, I also had to subtract the microwave signals created by energetic particles such as electrons that fly through the galaxy. In 2003 astronomers already had a fairly sophisticated understanding of these signals, but something did not fit. I could model most of the galactic emission, but when I tried to subtract it in the inner part of the galaxy, there was always something left over. I named this leftover signal the "microwave haze."

This mysterious signal coming from the center of the galaxy

IN BRIEF

The Fermi Gamma-ray Space Telescope has revealed massive structures that tower tens of thousands of light-years over the galactic center. These lobes have been named the Fermi bubbles.

Astronomers do not understand the processes that created the Fermi bubbles, but they suspect that the bubbles are evidence of recent, violent events at work in our galaxy.

Two leading explanations exist. The bubbles may be inflated by a jet of energy coming from our galaxy's central black hole or the accumulated wind of a swarm of supernovae.

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had no known explanation, but astronomers quickly came up with ideas. The most exciting possibility was that the haze was evidence of hidden dark matter. No one knows what dark matter is, only that it interacts with ordinary matter through gravity. Scientists expect that gravity will pull dark matter toward the center of the galaxy. In the dense cloud of dark matter in the Milky Way's core, dark matter particles will occasionally collide, perhaps creating an electron and a positron in the process.

Even if we cannot see dark matter, we should be able to see these particles. As they twist and turn through the galactic center's tangled knot of magnetic fields, they should emit what is called synchrotron radiation—the luminous exhaust of charged particles forced to make a turn [*see box at right*].

The microwave haze we were seeing could have been an artifact of synchrotron radiation generated by dark matter. But how were we to tell for sure? The very same electrons that produce synchrotron microwaves would have an additional consequence: they should also be colliding with existing photons and accelerating those photons up to extremely high energies in a process called inverse Compton scattering [*see box at right*].

Soon a consensus developed: if the microwave haze was being caused by high-energy electrons—perhaps as a consequence of dark matter annihilation—then we should also be able to find high-energy gamma rays. We turned to the Fermi Gamma-ray Space Telescope, which was designed to study gamma rays in space [*see box on page 47*].

Data from the Fermi satellite was released to the public on August 24, 2009. By this time I had become a professor, and my then postdoctoral fellow Gregory Dobler and I rushed to make our first gamma-ray maps of the galaxy. After a few long days and nights, we found a hazy excess of gamma rays in the inner galaxy that appeared to match the microwave haze. We and our collaborators quickly submitted a paper arguing that the signals were related. We asserted that they are both probably caused by a high-energy population of electrons in the center of the galaxy, but we did not speculate about the source of the electrons.

The next shoe took a bit longer to drop. In October 2009 I was in my office remaking some figures in our first paper with newly released Fermi data. I had noticed that the original gamma-ray data showed faint edges—clear borders where the signal dropped off precipitously. In astronomy, sharp features usually come from transient events. For example, a supernova may send out a shock wave that appears as a distinct edge in our telescopes. In time, sharp features tend to smooth out and fade away.

If dark matter were causing the gamma-ray signal, then the drop-off should have been smooth—fading gently as you looked farther away from the galactic center—because dark matter annihilation would have been going on for billions of years. Any sharp edges would have dissipated long ago.

In the first batch of Fermi data, the edges had looked so ratty that we just chalked them up to noise in the signal and ignored them. Now they were appearing in the new data again, and I started to wonder. I showed them to my then graduate students Meng Su and Tracy Slatyer, who agreed that they were real. Then Su really jumped in and started to work—I think almost continuously without sleep—on deriving the exact shape of the edges. Within a matter of days we totally changed our opinion about what was in the data. Dark matter was out. Bubbles were in. In May 2010 Su, Slatyer and I submitted a paper to the *Astro-*

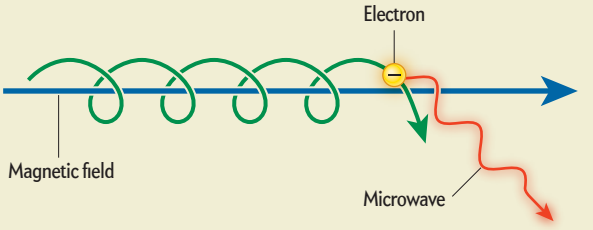
BASICS

A Field Guide to Cosmic Radiation

When astronomers find electromagnetic radiation coming from interstellar space, they must work backward to reveal its source. The three radiation-producing processes below all came into play as the authors teased out the story of the Milky Way's Fermi bubbles.

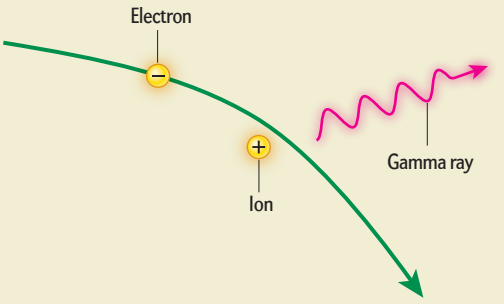
Synchrotron

When charged particles such as electrons change direction, they emit radiation. In the central Milky Way, strong magnetic fields spin electrons in circles. These accelerating particles generate so-called synchrotron radiation. Galactic synchrotron radiation comes mainly in the form of microwaves.



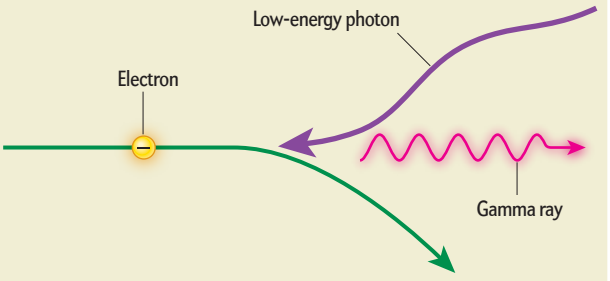
Bremsstrahlung

If an energetic electron passes by another charged particle, the electron will often slow down, losing energy in the process. This lost energy becomes a photon—a particle of light—which shoots out of the electron as bremsstrahlung radiation. In the galaxy, these photons are gamma rays.



Inverse Compton

An electron flying through the galaxy can also smack head-on into a photon. Much like a baseball encountering a well-swung bat, these photons will shoot out of the collision with much higher energies than they had going in. We see these "home run" shots as gamma rays.



Graphics by Greg Maxson

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physical Journal describing the structures and naming them "Fermi bubbles" in honor of the Fermi telescope.

BUBBLE MAKERS

EVEN THOUGH NOBODY HAD EXPECTED to find bubbles made of high-energy cosmic rays jutting tens of thousands of light-years above the Milky Way, perhaps it should not have been that shocking.

Many other galaxies have bubbles, too. We can see them in x-rays and radio waves, and if we had better gamma-ray telescopes we would probably find them shining in gamma rays as well.

We understand the processes that create the bubbles in many of these other galaxies. In some cases, the bubbles trace their origin to a gigantic black hole—often with the mass of billions of suns—that anchors the galaxy's center. As material from the galaxy falls toward the black hole, it begins to spin like the water draining out of a bathtub. This whirlpool of hot gas and dust creates intense magnetic fields that power jets of radiation and cosmic-ray particles that may inflate the bubbles.

We know that the Milky Way galaxy also has a supermassive black hole at its center, but we have never observed a strong jet of intense radiation streaming out of its core. (If a jet exists, it is not pointed our way, and thank goodness for that.) So we do not have direct evidence that this process is inflating the Fermi bubbles.

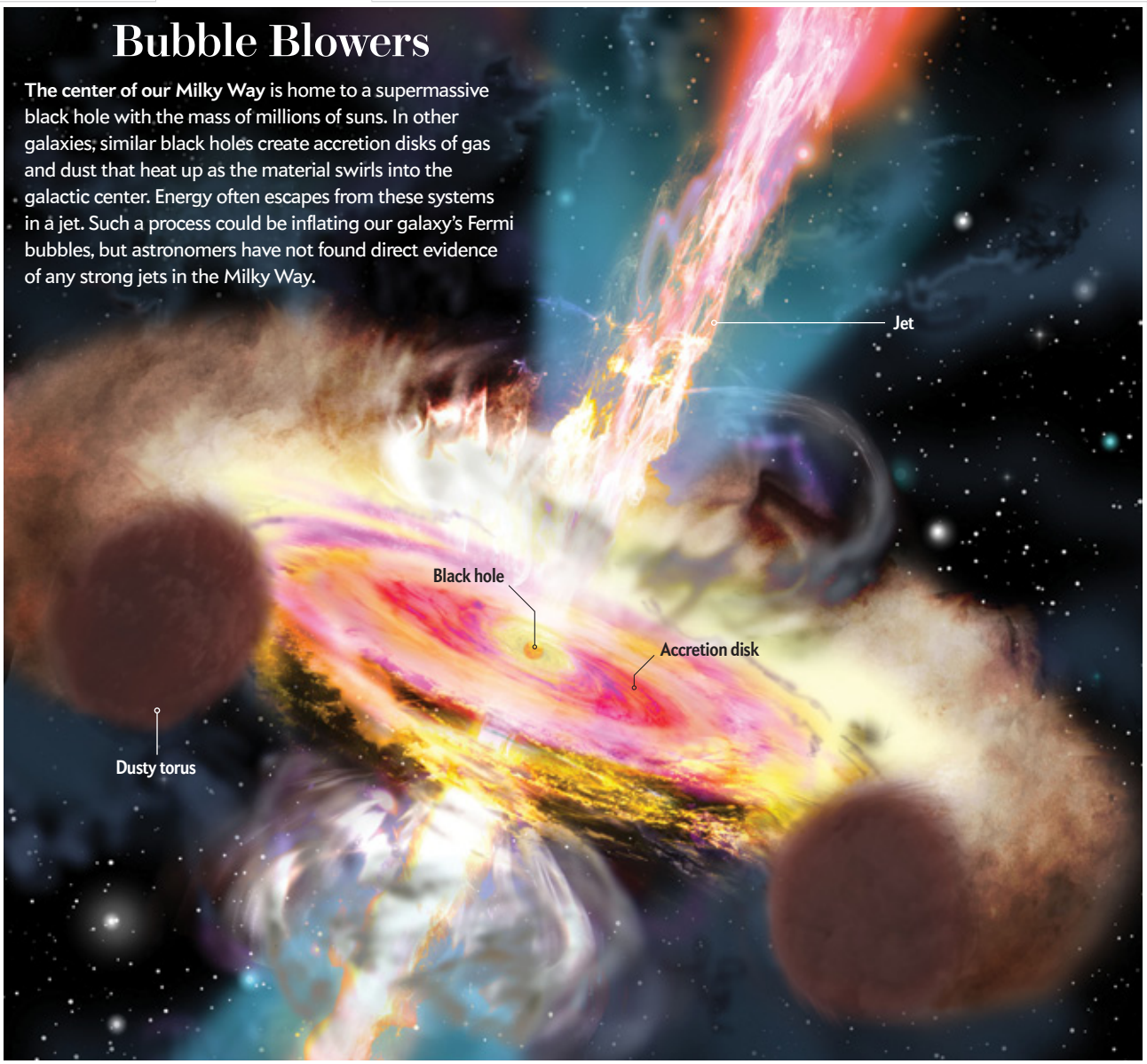
On the other hand, a large gas cloud—the Magellanic stream—sits high above the galactic center. If a jet of radiation were pointed there, it would temporarily strip electrons free from atoms in the cloud. As the electrons and ions came back together, they would produce so-called recombination radiation.

Astronomers have found exactly this. Perhaps there was an intense episode of accretion onto the Milky Way's central black hole about a million years ago—accretion that generated high-energy jets and ultraviolet radiation that knocked the electrons

HOW IT WORKS

Bubble Blowers

The center of our Milky Way is home to a supermassive black hole with the mass of millions of suns. In other galaxies, similar black holes create accretion disks of gas and dust that heat up as the material swirls into the galactic center. Energy often escapes from these systems in a jet. Such a process could be inflating our galaxy's Fermi bubbles, but astronomers have not found direct evidence of any strong jets in the Milky Way.



SCIENTIFIC AMERICAN ONLINE Take a video tour of the Fermi bubbles at ScientificAmerican.com/jul2014/bubbles

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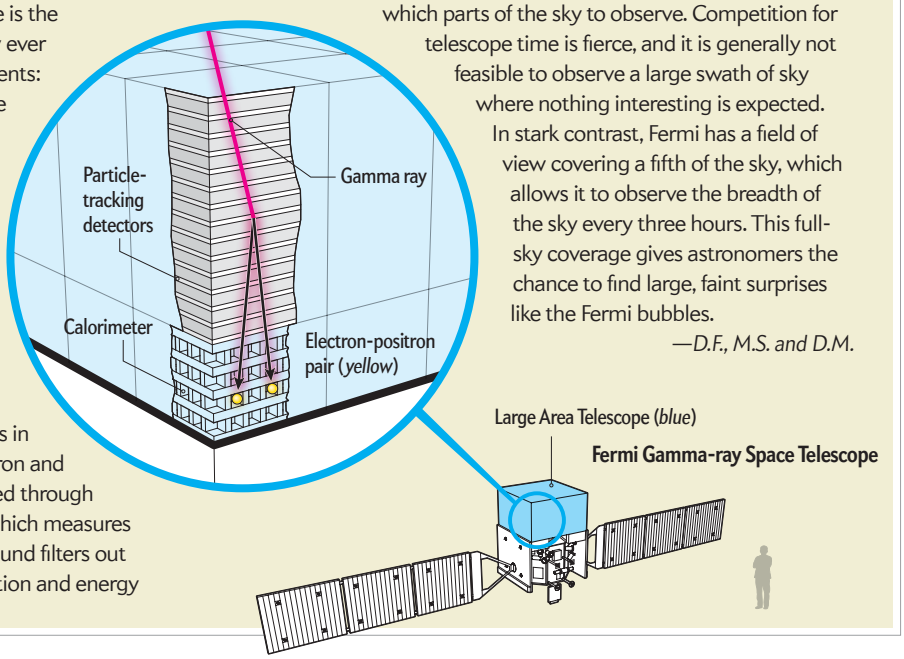
A Gamma-Ray Eye

Earth's atmosphere blocks gamma rays, which have energies billions of times that of visible light, so one way astronomers measure them is by getting above the atmosphere. The Fermi Gamma-ray Space Telescope is the most powerful gamma-ray observatory ever launched. It contains two main instruments: a burst monitor that keeps watch on the entire sky for evidence of transient gamma-ray bursts and the Large Area Telescope (LAT), which is the most sensitive and highest-resolution gamma-ray detector ever launched.

The LAT is radically different from any optical telescope: it has no mirrors, no lenses and no focal plane. Instead it operates more like a particle physics experiment. Each incoming gamma ray recoils off an atomic nucleus in the telescope and transforms to a positron and electron. These particles are then tracked through onboard detectors and a calorimeter, which measures energy. Further data analysis on the ground filters out background noise and reveals the direction and energy of the original gamma ray. Anyone can download these data.

Most telescopes can see only a tiny fraction of the sky at a time, and astronomers spend a great deal of effort deciding which parts of the sky to observe. Competition for telescope time is fierce, and it is generally not feasible to observe a large swath of sky where nothing interesting is expected. In stark contrast, Fermi has a field of view covering a fifth of the sky, which allows it to observe the breadth of the sky every three hours. This full-sky coverage gives astronomers the chance to find large, faint surprises like the Fermi bubbles.

—D.F., M.S. and D.M.



around in the Magellanic stream. This event could have also created the Fermi bubbles.

Alternatively, galaxies such as the nearby M42 galaxy have bubbles that are by-products of intense star formation near their centers. In a stellar nursery, stars form in many different sizes. The more massive a star is, the faster it burns its nuclear fuel. When the fuel runs low, the star's core collapses and releases an enormous amount of energy that rips off the outer layers of the star in a supernova explosion, leaving a neutron star or black hole behind. These supernovae create a wind of particles that can inflate bubbles around a galactic center.

We know that the center of the Milky Way has also been a region of intense star formation. Several thousand stars around the central black hole are only about six million years old—mere toddlers in cosmic time. Yet if extremely massive stars also formed in this same stellar nursery, six million years would be long enough for them to have already exploded as supernovae. These supernovae would have driven a wind of hot gas out from the galactic center—a wind that might have been powerful enough to inflate the bubbles.

NEXT STEPS

AS WE SEE, the story of the Fermi bubbles is wound tightly with the history and evolution of the Milky Way. The bubbles can also teach us about the physics of how black holes pull in nearby matter and how high-energy cosmic rays interact with interstellar gas. Although structures like the Fermi bubbles exist in other galaxies, the bubbles allow us to study these systems up close.

To this end, we are trying to observe the bubbles using the entire electromagnetic spectrum. One of the most amazing things about the bubbles is that they are large and luminous in gamma rays but nearly invisible in other frequencies. We hope that new data from the Planck spacecraft, which has mapped microwave radiation across the entire sky, will provide important clues. We are also attempting to map the bubbles in x-rays, although we are limited by current technology. The bubbles are giant structures that tower over the galaxy, but nearly all x-ray satellites have a narrow field of view. The challenge is akin to mapping a mountain range while peering through a paper towel tube.

It took three centuries after Galileo's discovery that the Milky Way is made of stars for astronomers to understand that our galaxy is just one of many billions of galaxies spread throughout the cosmos. With any luck, we will come to understand the true significance of the Fermi bubbles in less time than that. SA

MORE TO EXPLORE

Giant Gamma-ray Bubbles from *Fermi*-LAT: Active Galactic Nucleus Activity or Bipolar Galactic Wind? Meng Su et al. in *Astrophysical Journal*, Vol. 724, No. 2, pages 1044–1082; December 1, 2010.

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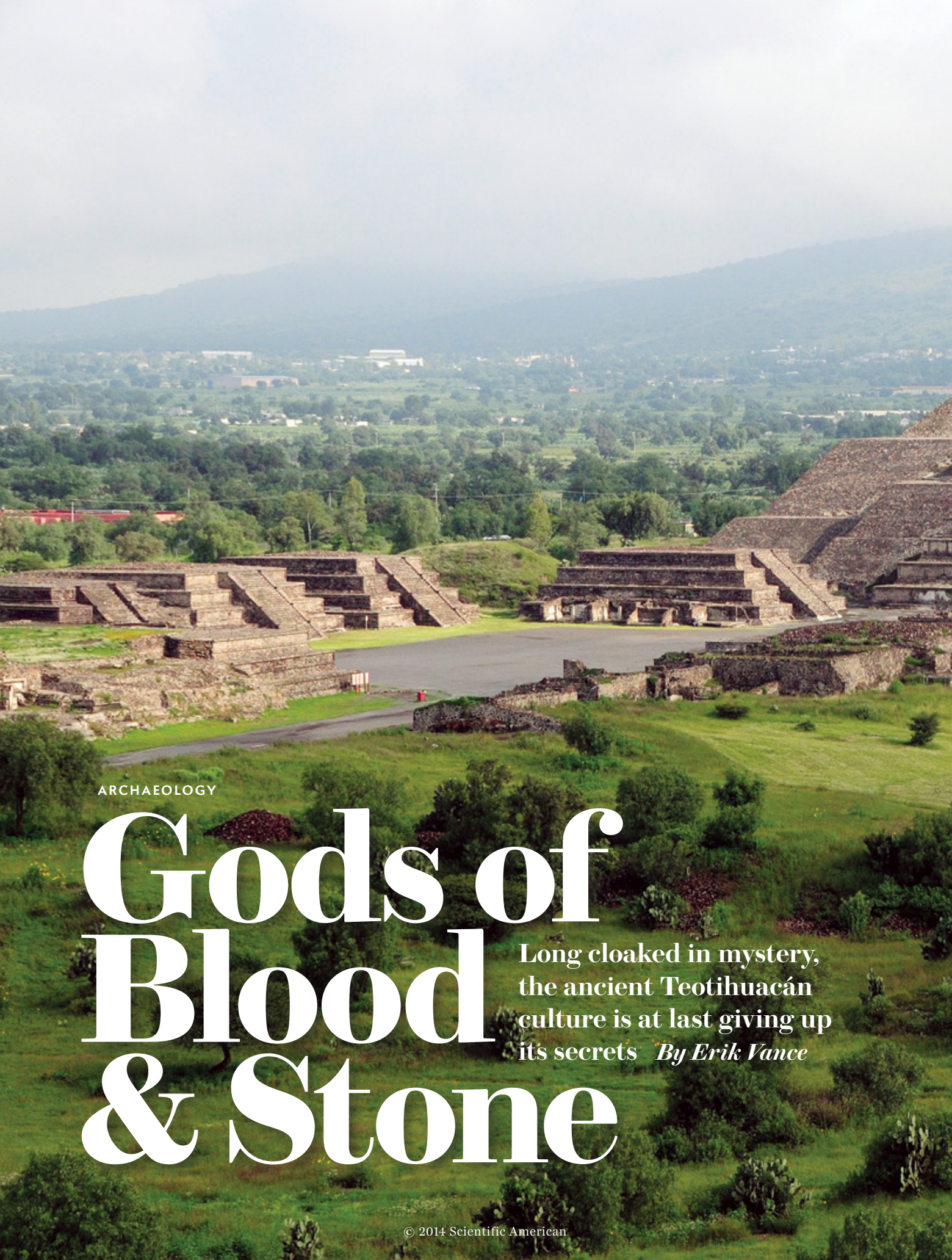

ARCHAEOLOGY

Gods of Blood & Stone

Long cloaked in mystery, the ancient Teotihuacán culture is at last giving up its secrets *By Erik Vance*

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PYRAMID OF THE MOON punctuates the Avenue of the Dead at the site of Teotihuacán near Mexico City.

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Erik Vance is a science writer based in Mexico City. His last article for *Scientific American* examined Mexico's struggle to make science pay off.

SOMETIME IN THE 14TH CENTURY, THE FIRST MEXICA FOUND THEIR WAY into the valley of Teotihuacán. The Mexica (often incorrectly called Aztecs in modern times) were new to the region. An aggressive, ambitious people from the north, they were fast becoming the dominant force in highland Mexico, conquering territory and setting up the powerful city of Tenochtitlán, which would soon rule a massive empire from what is now called Mexico City. Imagine that first search party—bold, feeling invincible as a nascent superpower—coming into a lush green expanse surrounded by rolling hills. The warriors are following tales told by the local Toltec tribes of a place in the mountains, just 25 miles from their new home, where the gods once lived. Then, turning a bend, their bravado gives way to awe as the home of the gods looms into view. Ruins of pyramids as high as 20 stories—so big they are initially mistaken for hills—line a huge road. Everywhere the explorers look lie crumbling temples, marketplaces and relics of a long-dead civilization with no name, no writing, no history. Just a vast city, once glorious beyond imagination, now abandoned.

The Mexica eventually patterned Tenochtitlán after this ghost of a city and turned the ruins into a sort of summer retreat for the elite. They named that ancient road the Avenue of the Dead and the two biggest pyramids the Pyramids of the Sun and Moon. The old city itself they called Teotihuacán—the place where gods are born.

Some 200 years later, in 1521, Spanish conquistadors toppled the Mexica's empire. And for hundreds of years Teotihuacán rested in gentle decay. When archaeologists first began excavating the site in earnest in the early 1900s, they had no better idea of who built the place than the Mexica had. Many thought it was a minor settlement erected by scattered tribes that were later subsumed by invaders. Today scholars know that Teotihuacán is actually much older and much more important than any of those early investigators could have guessed. It was the heart of an extensive empire that predates all the highland civilizations in the region and that reached as many as 700 miles away. A city that rivaled, and perhaps even dominated, the mighty Maya kingdoms in Guatemala and Honduras.

But with no written texts to guide them, archaeologists have long been puzzled about how the people of Teotihuacán lived. By tunneling into the monuments and carefully excavating the smaller structures nearby, they have been able to sketch out some answers. They now envisage a verdant, multiethnic community with rich social strata, including merchants, traders and artisans from across Mexico.

Less clear is what Teotihuacán's politics were. Two schools of thoughts have emerged. One sees a city ruled by a warlike king, unchallenged and infallible, who guided a strict state with an iron fist. The other envisions a mercantile state in which several powerful families vied for influence but could not wrest supreme control and therefore played a careful political game. Now two projects are racing to settle the debate and solve the puzzle. One thing is agreed on, though: in the end, Teotihuacán was not a

IN BRIEF

Archaeologists have puzzled over the mysteries of the ancient Mexican city of Teotihuacán for decades. Yet an understanding of this society eluded them.

Recent discoveries have furnished new clues to the lives these people led and the reach of their empire—and in so doing kindled debate over their politics.

One theory holds that Teotihuacán was ruled by a single all-powerful king; another pictures several elite families competing for control.

PRECEDING PAGES: GETTY IMAGES

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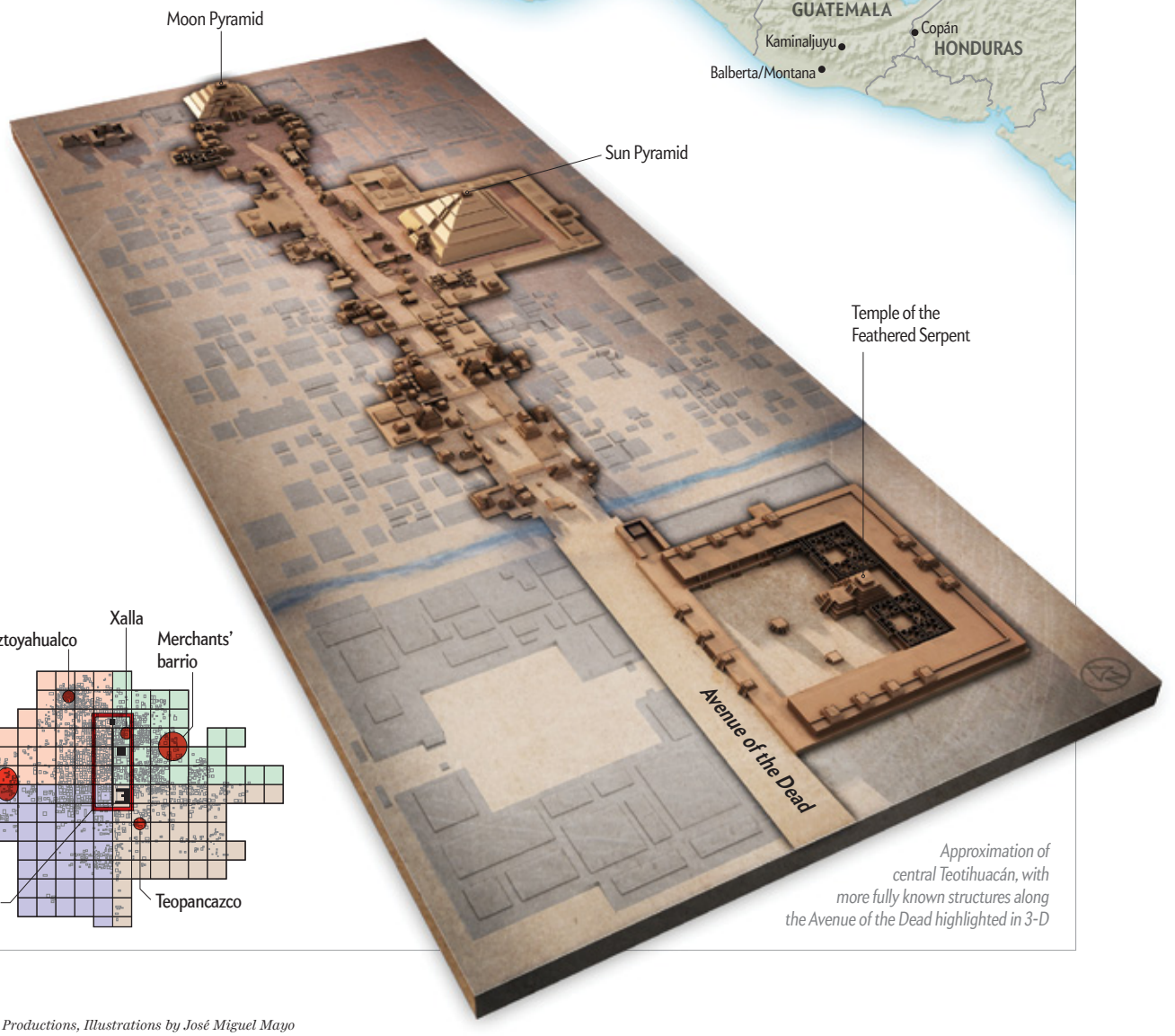
City of Gods

Once seen as a minor settlement, the ancient city of Teotihuacán is now known to have been the nucleus of a vast empire whose influence extended as far as western Honduras. Excavations under the site's monuments and in smaller structures nearby, including the everyday homes of the city's residents, have begun to illuminate this mysterious society. The findings reveal a diverse community whose members lived in ethnically distinct neighborhoods—an arrangement that has fanned debate over who ruled the city.



Approximation of central Teotihuacán, with more fully known structures along the Avenue of the Dead highlighted in 3-D

SOURCES: BASED ON WORK BY RENÉ MILLON (*all maps*); *OBSIDIAN AND THE TEOTIHUACAN STATE: WEAPONRY AND RITUAL PRODUCTION AT THE MOON PYRAMID*, BY DAVID M. CARBALLO, UNIVERSITY OF PITTSBURGH CENTER FOR COMPARATIVE ARCHAEOLOGY AND INSTITUTO DE INVESTIGACIONES ANTROPOLÓGICAS, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO, 2011 (*map of Mesoamerica*); "CORPORATE LIFE IN A APARTMENT AND BARRIO COMPOUNDS AT TEOTIHUACAN, CENTRAL MEXICO," BY LINDA R. MANZANILLA, IN *DOMESTIC LIFE IN PREHISPANIC CAPITALS: A STUDY OF SPECIALIZATION, HIERARCHY, AND ETHNICITY*. EDITED BY LINDA R. MANZANILLA AND CLAUDE CHAPDELAINE. UNIVERSITY OF MICHIGAN MUSEUM OF ANTHROPOLOGY, 2009 (*small locator map*)

Maps by XNR Productions, Illustrations by José Miguel Mayo

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place where gods were born but a place where men built them out of blood and stone—and a place where they eventually dashed them to the ground.

AN ELUSIVE KING

RECONSTRUCTING THE POLITICS of a bygone culture is no easy task. Picture landing in Washington, D.C., 1,400 years after its collapse and trying to understand its people. Did they worship Abraham Lincoln? Were they a military state? Did they conduct elaborate rituals in the reflecting pool? Which of their rulers or priests lived atop the Washington Monument? These are the kinds of questions that Saburo Sugiyama of Aichi Prefectural University in Japan has asked about Teotihuacán for more than 35 years.

Three major structures dominate the site: the Sun Pyramid is the tallest, the Moon Pyramid is the second tallest and the terminus of the Avenue of the Dead, and the smallest, on the same side of the avenue as the Sun Pyramid, is the Temple of the Feathered Serpent. (This last temple is often called Quetzalcoatl, after the similar-looking Mexica god that was probably inspired by this older version.) Although the Feathered Serpent structure is smaller than the others, many have suggested that it was the most significant and housed potent kings or priests. Located at the very center of the original city, it is made up of two pyramids, surrounded by a squat walled complex.

In 1989 Sugiyama and archaeologist Ruben Cabrera Castro of Mexico's National Institute of Anthropology and History unearthed a crucial new clue to the story of Teotihuacán: 18 bodies near the temple that had been ritually sacrificed and laid out. Soon after, the research duo found more such bodies and then, while tunneling under the temple, still more—well over 100 in all. The individuals they recovered, mostly male, seemed to be warriors from other lands, suggesting a martial society in which rule was enforced at the tip of an obsidian blade.

Sugiyama began to construct a highly specific idea of what kind of place Teotihuacán was in its heyday. He envisioned an ironfisted king who ruled with unquestioned authority in the city. "This city was created, materialized with power. You can't just suggest your ideas by saying, 'Hey, guys, let's make some buildings,'" he says. "You need to convince people with power."

Just outside of Teotihuacán, in a small town, Sugiyama is sitting in his laboratory. The building contains more than two million objects found during the decades since he started excavating. He has a quiet, thoughtful demeanor in person, and it is easy to picture him as the vagabond hippie he was in the 1970s, leaving his native Japan to travel the world. But when it comes to archaeology, few are as ambitious and driven.

In 1998, frustrated that he had not found a tomb or other direct evidence of his kings, Sugiyama decided to tunnel under the giant Moon Pyramid in search of them. It was an ambitious project, but it offered the best way to understand the power structure of the society and was a good place to search for a tomb. Like any big city, Teotihuacán was built in stages. Anthropologists think that starting in 150 B.C., various factions coalesced around this spot in a lush valley and formed an alliance of sorts. They built their city in spurts, first here, then there. Sugiyama's tunneling revealed that the Moon Pyramid was one of the first big structures they created, in A.D. 100.

But they did not erect it all at once. From 1998 to 2004, Sugiyama tunneled past seven previous versions, built one over the other, like Russian dolls. The fourth version—built early in the third century A.D., according to carbon dating—was a major upgrade from the previous one. This was a time of growth and perhaps even the birth of an empire.

ICONOGRAPHY of Teotihuacán includes the feathered serpent (*top*) and jaguar (*bottom*). According to one theory, four houses ruled the city, and the feathered serpent and jaguar were the strongest of them.

Although Sugiyama had yet to locate his kings, his discoveries fit neatly into an emerging picture of Teotihuacán's rise to power. Whether behind a king's banner or not, as Teotihuacán built up its city, it started reaching out its fingers. Some 450 miles southeast of Teotihuacán, in what is now Chiapas, lie the ruins of a small city called Los Horcones that emerged at around the same time. Even this far away from Teotihuacán, Claudia Garcia-Des Lauriers of California State Polytechnic University, Pomona, who has excavated the site, sees its definitive imprint: "The fact that you lay out your main plaza area for your entire community to kind of echo the way that one walks down the Avenue of the Dead and enters into a large open plaza—that's really powerful. You are trying to invoke [Teotihuacán]."

The similarities are subtle but noticeable to a trained eye, Garcia-Des Lauriers says. Given its layout and the style of its

CORY LANGLEY *Corbis (top)*; WERNER FORMAN *Getty Images (bottom)*

pottery, Los Horcones was either a military outpost or a close trading partner with Teotihuacán. Interestingly, the road Garcia–Des Lauriers suspects to be impersonating the Avenue of the Dead does not lead anywhere—it abruptly ends at a large boulder. Yet the dead end makes sense if people who had traveled to the parent city were trying to create a miniature version of it. "This is really just like Mecca in Islamic societies," Sugiyama says of Teotihuacán. "It would have seen pilgrimages."

Similar cities have been discovered in recent years all over Mexico. Scientists now believe that Teotihuacán controlled a region far more vast than any had expected before those ruins came to light—covering much of modern southern Mexico and stretching into Honduras. As its domain expanded, goods such as limestone and feathers poured in from the far reaches of the Mesoamerican world. In fact, in the jungle to the east, controlled by the legendary Maya kings, scientists have found references to a mysterious mountain city to the west, where the people were as thick as reeds in a marsh. Many suspect this western place was Teotihuacán, which apparently even exerted control over the Maya megacity of Tikal in Guatemala. Evidence from another Maya city, Copán in Honduras, suggests that a person from Teotihuacán assassinated its king and established his own rule.

Such an empire, Sugiyama says, needed a strong, charismatic king. He envisions one such leader living around A.D. 219, watching over monumental construction projects and ushering in an empire that would last 500 years.

Eventually, inside the fourth version of the Moon Pyramid, Sugiyama found a stamp of that empire—remains of 12 humans (most likely captives) and more than 50 animals, including wolves, jaguars and eagles, arranged in an elaborate configuration. The layout now looks to be a representation of a creation myth, with a cluster of knives in a circle like a sundial pointing north. "Again, we found very strong evidence of the state—decapitations, knives," he says. "Again, we didn't find the body of a ruler."

In ancient Maya cities, almost every building of note contains a king under the front steps or in the building itself, elegantly preserved and attended by jars of precious spices and stones. Yet to date, not a single king has been discovered in Teotihuacán.

MONARCHY OR CORPORATE SOCIETY?

DESPITE THE MISSING KING, Sugiyama is still convinced that Teotihuacán was a monarchy, like ancient Egypt, complete with a godlike head and a military apparatus focused on keeping its multiethnic citizens in line. But other experts take a different view. "You cannot have a multiethnic society ruled by one person. They would have had coups d'état all the time," insists archaeologist Linda R. Manzanilla of the National Autonomous University of Mexico. "Teotihuacán had a corporate society, which is the opposite of what the Maya had."

Based on her own excavations, Manzanilla argues that Teotihuacán was ruled not by a supreme leader but four powerful houses, all vying for dominion like something out of *Game of Thrones*. If Sugiyama's version of Teotihuacán is like Egypt, think of Manzanilla's as a little like the Roman Republic—a mighty state ruled by committee. Kings in Teotihuacán were figureheads controlled by the ruling classes from four houses, which were represented in the iconography of Teotihuacán: coyote, feathered serpent, jaguar and eagle. Each house dominated a quadrant of the city and sent representatives to a central governing building with an administrative section for each house. The feathered serpent and jaguar were the strongest houses; thus, the most ornate temples—the Pyramid of the Sun and the Feathered Serpent Temple—were on their side of the Avenue of the Dead.

Both Manzanilla's and Sugiyama's camps say the other's claims are baseless. How can two people study the same site for decades and come back with totally different conclusions? Partly, it may be that Manzanilla looks at Teotihuacán through a very different lens. Where Sugiyama has spent his career looking at the Teotihuacán equivalent of the Washington Monument, Manzanilla says she has been digging up Georgetown: her picture of Teotihuacán stems from her work over the past 20 years in the everyday homes of its people. In the 1990s Manzanilla excavated Oztoyahualco, an artisan apartment compound in the northwest of the city—an area she thinks was controlled by the house of the eagle. Unlike Maya apartment complexes, which have just one shrine, this compound had many different shrines from different traditions. For Manzanilla, this multiethnic quality defines Teotihuacán. She sees a place that could thrive only because wealthy landowners from abroad controlled trade corridors and the goods that fed the community's rapid growth. With so many powerful factions, it would have been very hard for a lone tyrant to hold the population under his thumb. When the city banded together in 150 B.C., Manzanilla says, one group would not have had a monopoly on resources as some of the Maya rulers had. She reasons that the rulers of Teotihuacán relied on taxes from the provinces to build their empire. As such, each shareholder would have leverage in the use of that power. Those with control over the richest territories, such as the Feathered Serpent Temple, had the most leverage over decisions.

This kind of forced power sharing is rare in the ancient world but not unheard of. Rome and Greece were, of course, republics for many years. Likewise Mohenjo Daro, an ancient city in Pakistan's Indus Valley in 2000 B.C., seems to have shared power with a settlement called Harappa, and Tiwanaku in Bolivia shared power with Wari to the north until A.D. 1000.

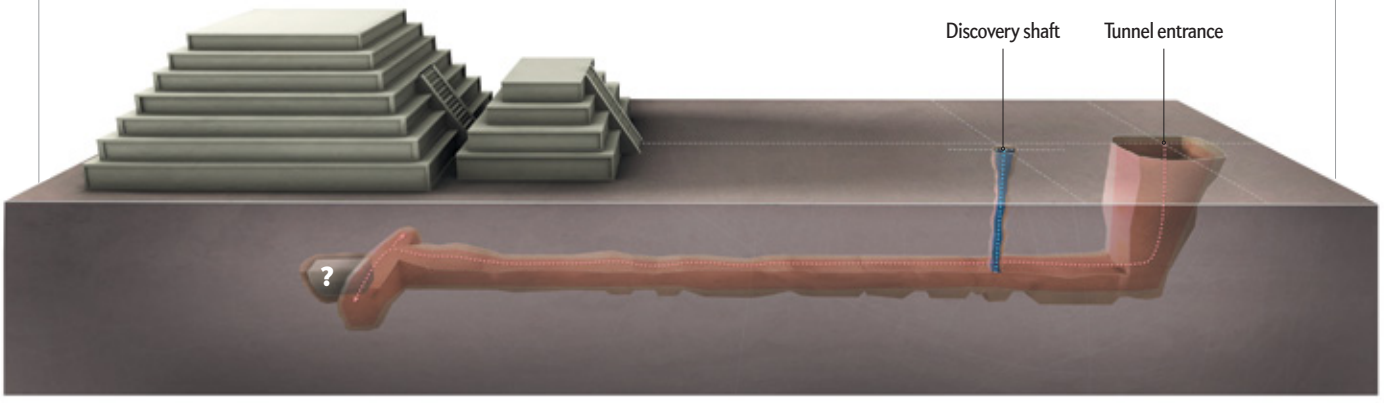
Sharing with another city you cannot defeat is different than sharing within a city, however. Manzanilla admits that most ancient civilizations had a single ruler and that the setup she proposes is a little odd. She believes, though, that in any given region, some cultures are bound to experiment with joint rule. Yet the strongest evidence she has to support her idea is not something she found but rather something she did not find. Something no one has found.

"Where is that powerful king depicted? Where is he buried? Where is his palace? Can you imagine a site like Teotihuacán, with 125,000 people, [having] a single ruler? His living place and his burial place should have been outstanding. No doubt. And we don't see that," she says. "You'd see him in the vessels, in the throne, in the stelae, in the palaces themselves."

What she does see is a four-petaled flower inscribed throughout the city. Historian Alfredo López Austin of the National Autonomous University of Mexico says that this symbol may represent the four houses that ruled the city. Like Rome, such a place would have been rife with plotting and power plays. As Teotihuacán expanded and its influence spread, the elites acquired increasingly more control. Markets were paved and expensive limestone began appearing throughout the city. The elites of all four houses became greedy and competitive.

Tunnel to the Underworld

Excavation of a secret tunnel found under the Temple of the Feathered Serpent has revealed a series of compartments and chambers containing an array of ceremonial offerings, from masks and weapons to mysterious pyrite mirrors. Archaeologist Sergio Gómez Chávez of Mexico's National Institute of Anthropology and History, who discovered a shaft into the tunnel, is on the verge of opening the final major chamber, located under the heart of the temple. This chamber is considered the best candidate yet for a royal tomb at Teotihuacán. Such a find could settle the debate over the politics of this mighty civilization.



To some extent, the data back up this scenario. Increasingly, scientists have been finding that people throughout Mexico moved to the city but maintained their ethnic heritage for hundreds of years. Just as New York City has Spanish Harlem and Chinatown, Teotihuacán had districts for people from Oaxaca to the south, for the Maya and for those from the corridor connecting to the Gulf of Mexico. For example, take the neighborhood of Teopancazco, just south of the Temple of the Feathered Serpent. In the early part of this century, Manzanilla excavated the site, which was dominated by elites from along the trade route to what is now Veracruz, east of Mexico City, and whose symbol she thinks was the feathered serpent. With such a lucrative territory, they would have controlled massive wealth and thus might have sponsored the nearby temple for their feathery emblem.

Manzanilla's work showed that these feathered serpent elites dined on 12 different fish species, salted and smoked, from their home along the Gulf of Mexico, 130 miles away, and decorated their clothing with gulf seashells. "There was a competition between elites to show the best of cosmetics, pigments, hides, cotton clothes, attire, headdresses," she says.

Nowhere was this competition more blatant than in the burials. Since 2005 Manzanilla has painstakingly analyzed several fascinating graves of elite adolescents at Teopancazco. The children are decorated in elaborate fashion, with cinnabar, greenstone and mica from around the empire, plus lots of material imported from their home region.

The wealthy lived in increasingly lavish style for centuries, building up their palaces and lining them with stones that had to be transported from miles away. But the high life could not last forever. In A.D. 350 something snapped. Twenty-nine elites seemed to have been decapitated, and their heads were adorned in a manner only found in the ancient Veracruz region. Manzanilla suspects this was a "termination" ritual, denoting some kind of cultural transformation. At this time, the Feathered Serpent Temple was replaced by one in front of it that displayed jaguars, like an artist redoing a sketch. In fact, after this point, few if any feathered serpents appear anywhere in the city, a sign that the Veracruz people no longer held much sway, in Manzanilla's view.

But they were not gone. After that, a new line of elites must have ascended, and it appears that they continued to prosper in Teopancazco for two more centuries. Then, in A.D. 550, the city of Teotihuacán burned. No one knows why. Manzanilla says that there is no sign of an invading force. What is in evidence is a large gap between the rich and poor. Analysis of human remains from the site indicates that many of the wealthy were healthy, whereas the poor were malnourished, had back problems from carrying heavy loads and even suffered conditions caused by lack of sunlight—perhaps from slaving away in some workshop. "My guess is that the intermediate elites revolted against the ruling elites," she says. "The ruling elite tried to control this movement too late. These people already had a lot of interests, a lot of alliances in the corridors, and they revolted."

After that, Manzanilla theorizes, a contrite leadership focused its building effort on housing across Teotihuacán and not on elaborate temples. Another century or so more, and the city collapsed for good. For the elites, she says, this sequence of events would have meant simply picking up and returning to their homelands in the corners of the empire.

Teopancazco reveals a slice of life from Teotihuacán separate from the grand temples. The city was diverse, but it was not a melting pot. Instead it was a patchwork, with each culture keeping its identity and operating in fierce competition with its neighbors for prestige and authority. This patchwork may explain why there was no uniform written language or images of kings as there was for the Maya. Such representation would have meant tilting the scales too far in one side's favor.

SCIENTIFIC AMERICAN ONLINE Read more about Teotihuacán at ScientificAmerican.com/jul2014/teotihuacan

Perhaps the most fascinating aspect of Teotihuacán archaeology is that both Manzanilla's and Sugiyama's theories could be true. George Cowgill, an emeritus professor at Arizona State University, has proposed that Teotihuacán vacillated between both models, occasionally switching when the right ruler grabbed power. Neither Manzanilla nor Sugiyama likes this compromise, however.

CHAMBER OF SECRETS

ARCHAEOLOGISTS MIGHT NEVER KNOW who ruled Teotihuacán for sure. But very soon Sergio Gómez Chávez may find a crucial piece of the puzzle. Gómez Chávez, an archaeologist at the National Institute of Anthropology and History, has been digging at Teotihuacán for decades, both in common people's homes, such as the city's Oaxaca neighborhood, and in the grand temples. That work included an excavation of the Temple of the Feathered Serpent's drainage system in an effort to restore it to protect the structure from further water damage during storms. It turns out the ancient drainage system works perfectly. But Gómez Chávez found that it was purposefully stuffed up with 50 bodies missing arms and legs. Who builds a drain only to ceremonially plug it? Gómez Chávez knew that the blocking of the drain occurred around the same time that the fourth version of the Moon Temple was built. What if it was done on purpose? What if the city's denizens wanted to flood the area every year, like the reflecting pool in Washington, D.C. (the people of Teotihuacán were known to divert rivers, among other waterworks projects)? It was during one such flooding episode, on a fateful Thursday in October 2003, that the archaeologist made his most shocking discovery.

"I'm coming in to work like any normal day, and [workers] inform me that a big hole has formed" near the temple, Gómez Chávez recalls. He rushed to the site, and sure enough the rain from the night before had opened a perfectly circular tunnel going straight down into blackness. He did not hesitate. He told one of the workers to find a rope. Though not a skilled mountaineer, he managed to tie himself to the rope, and several workers lowered him into the hole, hand over hand. The hole—a foot or two wider than his shoulders—went down some 50 feet and stopped. It was almost like a well except when Gómez Chávez got to the bottom, he found that the dirt and rock on either side was loose, as if it was put there to seal a horizontal tunnel going in both directions. At the top of that fill was a gap that he could almost peer through. "I couldn't sleep for a week, because you don't know what's in it," he recollects.

It seemed that a straight, horizontal tunnel, perpendicular to the shaft, had long ago been filled in with stones and dirt to seal it forever. One end went to a ceremonial entrance behind him, long hidden from view. The other, Gómez Chávez soon learned, continued beyond view—straight to the heart of the Feathered Serpent Temple. The hole he had found was perhaps for ventilation or for light or a view of the stars. Without it, the tunnel may have stayed secret forever. Thus began a 10-year effort to clear the tunnel and find what it hid. The tunnel was filled around that crucial third-century era of expansion. Using radar and sonar, Gómez Chávez learned that it led to a series of three chambers under the center of the pyramid. So he carved his way toward them, one foot at a time. Today he is almost at the end.

A few months ago Gómez Chávez invited me to see the tunnel. Now I am here at his site at the foot of the Temple of the Feathered Serpent, in the wide expanse that he believes was once allowed to flood every year. Walking along the tunnel, I am struck by how chilly it is. It is a hot autumn day outside, but down here it is moist and cool. Gómez Chávez says that when the people of Teotihuacán used this tunnel, the water table was right at their feet. This, he guesses, might have been the reason they put the tunnel at this height. A cold, dark place with water along the ground might have represented the underworld. In several places, I see remnants of a special clay they used to line the tunnel. Peppered with sparkly pyrite, the clay looks almost like twinkling stars. "This is no longer a temple dedicated to Quetzalcoatl but a temple to commemorate the beginning of mythic time," he reflects.

So far Gómez Chávez and his colleagues have removed almost 1,000 tons of filler from the tunnel. In so doing, he has found sealed compartments, one after the other, which he has opened to expose ever more elaborate offerings, including masks, weapons, even reed mats that would have functioned like thrones. "The concentration of materials—it's just amazing. It's unbelievable the things that he is finding," Sugiyama says. Now empty, the compartments appear as pits lining the tunnel floor. Walking on wood planks, I have to be careful not to slip into one.

In the spring of 2013, using a robotic drone, Gómez Chávez reached two of the three major chambers at the end of the tunnel. One contains dozens of quartz spheres, the other pyrite mirrors. No one has any idea what they were or has seen anything like them. Standing by those chambers, I squat and try to peer ahead at the last chamber, still sealed. It is a few feet lower than where I am. "It's very wet down there," Gómez Chávez says. "With all the mud and water, we have had to go slowly now."

Gómez Chávez imagines this place as an elaborate ritual site, where men left the earthly world for a moment and emerged as kings. Sugiyama, slightly irritated that he did not find the tunnel during his own investigation, says there is no better candidate for a royal tomb. Even Manzanilla admits that the discovery of a royal tomb would be a big deal for Teotihuacán. She insists it will not hurt her theory, but that depends on what is inside.

Meanwhile Manzanilla is excavating her own site, called Xalla, looking for a smoking gun. A series of five structures not far from the Sun Pyramid are arranged in a diamond shape, almost like a four-petaled flower with a shrine in the middle. This, she thinks, is the administrative center of the city, where each of the four houses sent emissaries to look after their business.

Either way—whether Manzanilla proves her theory of distributed power or Gómez Chávez discovers an all-powerful king buried at the end of the tunnel—Teotihuacán will never be the same. At long last, the lives of its people, like ships coming out of the fog, are slowly emerging from 1,300 years of mystery to tell their story. SA

MORE TO EXPLORE

Human Sacrifice, Militarism, and Rulership: Materialization of State Ideology at the Feathered Serpent Pyramid, Teotihuacan. Saburo Sugiyama. Cambridge University Press, 2005.

Corporate Life in Apartment and Barrio Compounds at Teotihuacan, Central Mexico. Linda R. Manzanilla in *Domestic Life in Prehispanic Capitals: A Study of Specialization, Hierarchy, and Ethnicity.* Edited by Linda R. Manzanilla and Claude Chapdelaine. University of Michigan Museum of Anthropology, 2009.

FROM OUR ARCHIVES

Teotihuacán. René Millon; June 1967.

FOOD TECHNOLOGY

BUILDING TASTIER FRUITS & VEGGIES*

Making modern supermarket produce so big and hardy drained a lot of its flavor. Scientists now have the technology to bring it back—without genetic engineering

By Ferris Jabr

***NO GMOS REQUIRED**

Photographs by Dan Saelinger

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THE MODERN SUPERMARKET PRODUCE AISLE IS FULL OF VISUAL ILLUSIONS.

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The strawberries are plump and glistening; the tomatoes smooth-skinned and lustrous; the melons firm and brightly colored—yet all too often devoid of flavor. We have no one to blame for these bland beauties but ourselves. By selectively breeding crops to be as prodigious as possible and to survive weeks of shipping and storage in dark, cool conditions, we have sapped flavor, aroma and nutrition from our food.

Consider the dilemma that cantaloupes presented to plant breeders. To enjoy a cantaloupe's full flavor, you must pick and eat it at peak ripeness, before it goes too soft. Toward the later stages of a cantaloupe's development, a burst of the hormone ethylene causes the fruit to ripen and soften quite quickly. This speedy puberty made transporting cantaloupes across states or from one country to another problematic: even on ice, the melons turned to mush by the voyage's end. So plant breeders decreased the levels of ethylene in cantaloupes intended for long-distance shipping by cross-pollinating only melons that naturally produced the lowest amounts of the hormone. Without a strong spurt of ethylene, the melons stay firm on the trip from field to produce aisle, but the chemical reactions that produce a ripe melon's aroma and taste never happen.

Breeders have had some success in overcoming this predicament. In the 1990s Dominique Chambeyron—a plant breeder employed by the Dutch De Ruiter Seeds Group—managed to create a variety of small, striped cantaloupe that retained both its firmness and flavor for weeks after it was harvested. Known as Melorange, this cultivar is grown in Central America and shipped to Sam's Club and other select chain stores in the U.S. between December and April, when it is too cold to grow cantaloupes locally. I tried a slice of one this past March: it had a dense texture and a splutter of flavor and aroma so robust, it bordered on spicy. Unfortunately, the kind of traditional breeding responsible for the Melorange relies an awful lot on serendipity. It can take more than a decade to perfect a consistently impressive new cultivar. Breeders must cross-pollinate plants over and over, hoping that some of the offspring will inherit the right characteristics. And they generally have to wait for the plants to grow and produce ripe fruit to find out. Much of what they reap is way off the mark and entirely unusable.

Genetics has recently offered an alternative path. At Monsanto, which acquired De Ruiter in 2008, Jeff Mills and his colleagues are able to predict the quality of a cantaloupe plant's eventual fruit before they ever put a single seed in the ground. First, Mills and his team pinpointed the melon genes underlying Melorange's unique combination of flavor and firmness. They can look for these genetic "markers" in cantaloupe seeds with help from a group of cooperative and largely autonomous robots.

I saw many of these machines in action when I visited Monsanto's molecular breeding laboratory at its vegetable research and development headquarters in Woodland, Calif., last November. A seed chipper shaves off a sliver of a seed for DNA analysis, leaving the rest of the kernel unharmed and suitable for sowing in a greenhouse or field. Another robot extracts the DNA from that tiny bit of seed and adds the necessary molecules and enzymes to chemically glue fluorescent tags to the relevant genes, if they are there. Yet another machine amplifies the number of these glowing tags to measure the light they emit and determine whether a gene is present.

Such techniques, known as marker-assisted breeding, are not brand-new, but they have enabled unprecedented feats of produce perfectionism in the past 10 years because genetic sequencing has become so much faster and cheaper. Monsanto's seed chippers can run 24 hours a day, and the entire system can deliver results to breeders within two weeks. In the past 10 years breeders at both private companies and universities have managed to create a cornucopia of more flavorful, colorful, shapely and nutritious fruits and vegetables, some of which are already available at grocery stores and farmers' markets. In addition to increasingly appetizing melons, the bounty includes broccoli that brims with even more nutrients than usual, truly succulent strawberries, and tomatoes that please both the eye and tongue.

"The impact of genomics on plant breeding is almost beyond my comprehension," says Shelley Jansky, a potato breeder who works for both the U.S. Department of Agriculture and the University of Wisconsin–Madison. "I had a grad student here five

IN BRIEF

Creating crops that were large and prodigious enough to meet the demands of industrial agriculture resulted in supermarket fruits and vegetables that often lack flavor and nutrition compared with older varieties.

Instead of improving such crops with genetic engineering, which would add controversial GMOs to the produce aisle, scientists are turning to the technique of marker-assisted breeding, which combines traditional plant breeding with ever speedier DNA analysis.

In the past plant breeders at public universities would have donated such improved crops to farmers. Now they are forced to license the seeds to a handful of large private companies that many people think have gained too much power.

STYLING FOR TOMATO AND CANTALOUPE BY BIRTE VON KAMPEN

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years ago who spent three years trying to identify DNA sequences associated with disease resistance. After hundreds of hours in the lab, he ended up with 18 genetic markers. Now I have grad students who can get 8,000 markers for each of 200 individual plants within a matter of weeks."

All this talk of DNA analysis sounds suspiciously like genetic engineering—the gene-editing technique that creates genetically modified organisms (GMOs). But it is not. It is a completely non-GMO technology. In fact, that is one of the main reasons it is so attractive to researchers and seed companies such as Monsanto.

SOWING CHANGE

PEOPLE HAVE BEEN CHANGING PLANTS to suit their purposes for at least 9,000 years. Just about every fruit and vegetable we eat is a domesticated species that we have transformed through decades of artificial selection and breeding: saving seeds only from plants with the most desirable characteristics and deliberately mating one plant with another to create novel combinations of traits. In this way, our ancestors turned a scrawny grass named teosinte into tall, plump-eared corn and molded a single species of wild cabbage into broccoli, Brussels sprouts, cauliflower and kale.

By the 1980s scientists had devised a much more exacting way of changing a plant's DNA: genetic engineering, which involves adding, removing or otherwise directly altering genes in a plant using lab tools. GMOs first appeared on the market in the U.S. in the 1990s. Although more than 70 percent of processed foods in the U.S. contain ingredients made from GMO corn, soybeans and canola, very few of the fresh vegetables and fruits sold in supermarkets have been genetically engineered. Exceptions include virus-resistant papaya, plum and squash, as well as pest-resistant sweet corn.

One reason that so few fresh fruits and veggies are GMOs is that, on the whole, they are far less profitable and less widely grown than the country's biggest crops: corn, soybeans, hay, wheat, cotton, sorghum and rice. When it comes to fruits, veggies and other so-called specialty crops, seed companies are not as motivated to deal with the burdensome and costly safety tests and federal regulatory procedures required to approve a GMO for sale.

The other big hurdle to GMO fruits and vegetables is public opposition. Universities and seed companies know that introducing new GMOs to the produce aisle today could ignite a furor among the segment of the U.S. population opposed to what they believe are "Frankenfoods." Most shoppers remain oblivious to the few genetically engineered fruits and veggies already in stores because they are usually not labeled as such.

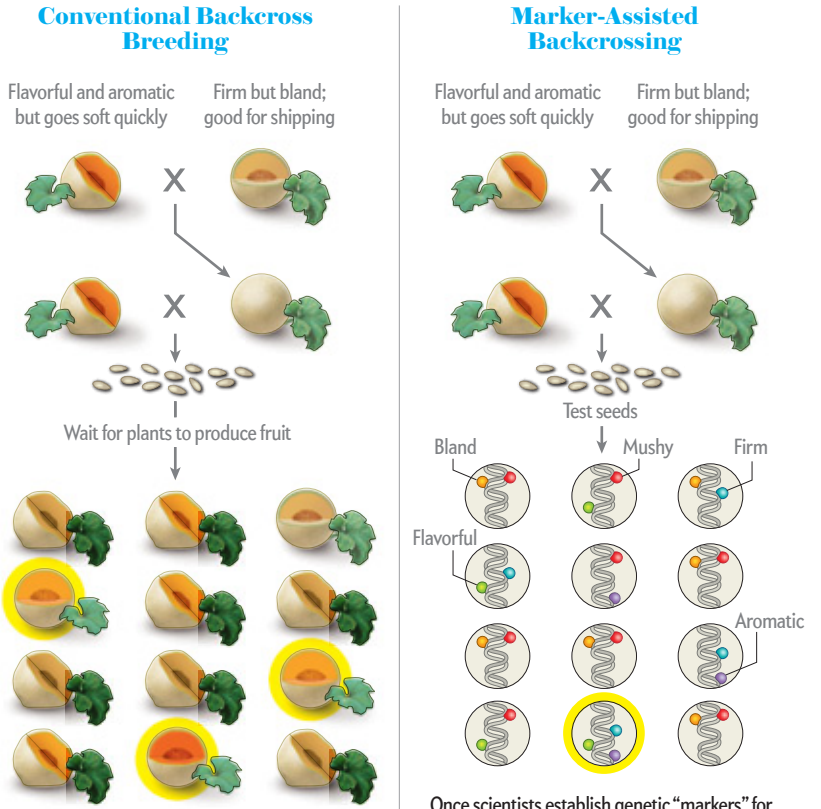
In the past decade marker-assisted breeding has become an increasingly viable way to improve fruits and vegetables while circumventing this controversy, especially as genetic technologies have improved and scientists have continued to sequence the genomes of more and more crop plants. In particular, the marriage of traditional breeding and DNA analysis is helping breeders turn their attention toward qualities of food that are important to consumers. "Asking what the consumer wants sounds really obvious, but it's not," says Harry Klee, a tomato breeder at the University of Florida. Instead, he says, you almost always see breeders prioritizing the needs of farmers or food distributors.

A perfect example is the classic supermarket tomato. For decades experts have regarded the balance of acids and sugars in a tomato as the primary factor that determines whether we enjoy its taste. In general, people like tomatoes on the sweet side.

BASICS

Marker-Assisted Breeding

To improve a single crop, plant breeders usually have to play botanical matchmaker for many years, laboriously weeding out unwanted traits without losing desirable ones. Identifying the genes underlying those traits opens up the possibility of a much more efficient and precise process known as marker-assisted breeding.



Breeders typically have to wait a full season for experimental crops to mature before they can assess the quality of the produce and select the top contenders for continued breeding (*yellow highlighting*).

Once scientists establish genetic "markers" for different traits—such as flavor and firmness—they can analyze DNA extracted from seeds or the leaves of young plants and reveal ideal candidates (*yellow highlighting*) for breeding experiments long before harvesttime.

Graphic by Jen Christiansen

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But most breeders have not been chiefly concerned with flavor. With large-scale commercial growers in mind, breeders have instead favored tomato plants producing lots of smooth, hardy fruit that remain plump on the often long journey to the grocery. The more tomatoes a plant makes, however, the fewer sugars it can give to each one. Typical supermarket tomatoes may look pretty, but they do not have enough sugar to satisfy our taste buds.

Klee is determined to rescue the industrial tomato from its current gustatory doldrums. Through a series of large taste tests, he has evaluated nearly 200 varieties of heirloom tomatoes—older cultivars preserved by small groups of farmers and gardeners and sold at some grocery stores and farmers' markets. Heirlooms are known for their vibrant colors and fantastic flavor, but their skin easily cracks and scars, they go soft quickly, and they come from plants that do not make enough fruit to meet the demands of large commercial farmers.

In his research, Klee has learned that many heirlooms are tastier than standard tomatoes not because they have more sugar but because they are chock-full of a much more complex component of flavor: pungent chemicals known as volatile organic compounds that waft off plants and into our nostrils (think: freshly cut grass or the alluring smell of citrus). In a 2012 study Klee and his colleagues discovered that people actually enjoy a tomato with moderate levels of sugar if it contains enough of an aromatic compound named geranial. Klee suspects that geranial and other volatiles not only give a tomato its scent but also magnify the fruit's innate sweetness. In follow-up studies, he created tomatoes that lacked geranial and other fragrant molecules. People did not like them. If a tomato had average to high sugar levels but no volatiles, volunteers did not perceive it as sweet.

Lately Klee has been trying to make hybrid plants that give growers and consumers the best of both tomato worlds, old and new. In the past three years he and his colleagues have mated the most delicious heirlooms they could find with modern conventional tomatoes to create crossbreeds that yield well, are firm and smooth-skinned, and taste great. Klee routinely stocks up on cheap electric toothbrushes, which he and his team use to gently but thoroughly rattle tomato flowers, gathering the pollen that falls off in test tubes so they can play matchmaker. All the while, the breeders have been using hole punches to collect bits of leaves and analyze the plants' DNA, looking for genetic patterns that correspond to high levels of volatiles, for instance, or flawless skin. "Genetic analysis has definitely informed crossing decisions," Klee says. "Our work has really accelerated in the last couple of years, with the emergence of the tomato genome sequence."

The University of Florida recently released two of these hybrids—Garden Gem and Garden Treasure—that it would like to license to a seed company for mass distribution. Although the hybrids do not yield quite as much as commercial tomatoes, they produce more than three times the number of fruit as their heirloom parents, they have tremendous flavor and they can survive a good deal of shipping. Klee's colleague Vance Whitaker is making good progress on a related project to enhance the pungency of supermarket strawberries, which have also gained size and durability at the expense of taste.

Another notable victim of distribution difficulties, along with cantaloupes and tomatoes, is broccoli. About 75 percent of broccoli harvested in the U.S. is grown in California. Broccoli adores cool weather and flourishes in the Salinas Valley's occasional fog blankets. When forced to endure hot, sticky summers in the Northeast, the vegetable produces gnarly heads with buds of mismatched sizes. Each of the small buds that together make up broccoli's treetop dome is a flower that has not yet blossomed. Thomas Björkman of Cornell University and his colleagues recently discovered that during a critical period of its development, broccoli tracks how many hours of cool temperatures it enjoys and produces a uniform flowering head only if the tally is high enough. That is why broccoli grown on the East Coast might end up with an unattractive mix of nice, plump flower buds and dinky, almost imperceptible ones.

Three and a half years ago Björkman, Mark Farnham of the USDA and their many collaborators decided to breed a new kind of broccoli that would thrive in the eastern part of the country. In

SCIENTIFIC AMERICAN ONLINE Explore modern breeding techniques for creating new foods at ScientificAmerican.com/jul2014/veggies-interactive

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their lab's growth chamber Björkman and his team have been subjecting broccoli to East Coast levels of heat and humidity, keeping seeds only from the plants that grow the most attractive flowering heads under these conditions. Although they have a lot of work ahead of them, they have already bred broccoli that can deal with a few more weeks of summer heat than the cultivars currently grown in the East. Meanwhile the researchers are searching the genomes of the various plants they grow, looking for genes that explain why some broccoli fares better than others. Finding them could shave years off the journey toward their ideal plant.

Breeding broccoli that stays beautiful in the heat is not just an exercise in aesthetics—it is also about getting tastier and more nutritious broccoli to farmers' markets and grocery stores. Fresh broccoli consumed the same day it has been harvested is different from typical supermarket fare, Björkman says—it is tender, with a mellow vegetative flavor, a hint of honeysuckle and no sharp aftertaste. Trucking broccoli from California to other parts of the country requires storing the vegetable on ice in the dark for days. With no light, photosynthesis halts, which means that cells stop making sugars. Rapidly dropping temperatures rupture cell walls, irrevocably weakening the plant's structure and diminishing its firmness. When the broccoli is thawed, various enzymes and molecules that escaped their cells bump into one another and trigger a sequence of chemical reactions, some of which degrade both nutritional and flavorful compounds. Giving farmers in the East broccoli they can grow and sell locally solves all these problems.

In a separate effort to boost the nutritional value of broccoli, Richard Mithen of the Institute of Food Research in England and his colleagues used marker-assisted breeding to raise levels of glucoraphanin, a compound that some evidence indicates may help fight bacteria and cancer. They have since licensed the resulting broccoli, called Beneforté, to Monsanto; you can find the florets at some Whole Foods Market and Stater Bros. stores.

SEEDING INNOVATION

TO GET THE GRANT that kicked off their initiative, Björkman and Farnham had to assure the USDA that seed companies were genuinely interested in this potential new regional market for broccoli by securing funding from the private sector. Monsanto, Syngenta and Bejo Seeds are contributing even though they are competitors. In theory, both seed companies and university researchers can benefit from such collaborations. During the research and development phase, they all share information and exchange seeds. Eventually, however, it is time for negotiations. As is the case for Klee and his tasty tomatoes, Björkman hopes that once he and his colleagues get closer to their beauteous broccoli, a private company will license those seeds and produce them on a massive scale for commercial growers. Björkman and his team do not have the capital to do so themselves. Looking for genetic markers in individual plants may be getting cheaper all the time, but generating enormous quantities of seed and marketing it to farmers is still costly.

Some plant breeders worry that because giant seed companies have far more financial and technological resources than smaller firms and universities, true innovation will wither. "There's been a rather large decline in public sector breeding programs as the technology has transferred into the private sector," says Irwin Goldman of the University of Wisconsin–Madison, who recently debuted flame-orange table beets with concentric gold stripes. "Some people argue that this transfer is a success for this country, but public breeding will do things that the private sector won't do—things that take too long or are too high risk."

Jack Juvik, who directs the plant-breeding center at the University of Illinois at Urbana-Champaign and first got into breeding in the 1970s, remembers when big companies were not nearly as dominant as they are today. "When I first started, there were a lot of smaller companies selling a lot of seeds, but they have all been basically bought out or driven out of the market by the mega companies. That has changed the whole texture of the industry," Juvik says. "Instead of having people at public institutions developing finished varieties, most of us design germplasm [seeds and cultivars] for big companies to work with. These large companies have the resources to do some good testing and make some really good varieties, but they end up controlling most of the germplasm and technology used to make it."

Goldman and his University of Wisconsin–Madison colleague Jack Kloppenburg belong to a group of 20 breeders and farmers from around the country who are interested in creating the equivalent of open-source software for seeds—nonpatentable varieties that anyone can use. There is no precedent for such an arrangement in the 21st-century commercial seedscape, though. One potentially expensive option is for plant breeders to hire lawyers and obtain standard patents or copyrights on their seeds with the intent of letting just about anyone use them (excluding mammoth private companies, of course). Alternatively, they could try to create a kind of open-source license that allows people to use seeds only if they, too, agree to freely share them and anything they make with them. Goldman has also proposed a compromise in which breeders license some seeds to the private sector to make a profit but give others away.

Klee wonders whether a certain degree of conciliation is the best way forward. "The reality is that we in academia cannot compete with the Monsantos or other big seed companies," he says. "Breeders at universities are pushed out of big crops and into niche crops. In my department, we have a peach breeder, a blueberry breeder and a strawberry breeder. I know a lot of people at Monsanto who have dropped these kinds of crops that are marginal for them." Such dichotomy, he hopes, can be complementary, with the public and private sector relying on each other for distinct specialties.

Ultimately what Klee cares most about is the same prospect tantalizing more and more plant breeders: bridging the gulf between what growers need to make a living and what consumers want on their plates. "Marker-assisted breeding makes it possible to go back and fix things like flavor and texture," Klee says. "In the end, it's really very simple: let's give people stuff they like." SA

MORE TO EXPLORE

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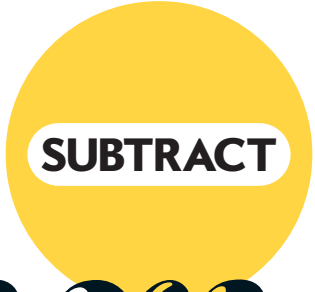
NEUROSCIENCE

Neurons



Anxiety

The adult brain generates neurons every day. These cells help us to distinguish one memory from another—a finding that could lead to novel treatments for anxiety disorders

By Mazen A. Kheirbek and René Hen

IN BRIEF

To keep memories from becoming jumbled, the brain must encode the distinct features of events and situations in a way that allows them to be distinguished from one another—a process called pattern separation. **Pattern separation** enables us to distinguish dangerous situations from similar ones that pose no risk. People with defects in this ability may be prone to anxiety disorders.

The process occurs in one of the two regions of the brain that generate neurons throughout life. These fledgling cells seem to be critical to pattern separation. **Interventions** that specifically boost the ranks of rookie neurons could provide new ways to regulate mood and possibly treat conditions such as post-traumatic stress disorder.

Illustration by Thomas Fuchs

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Mazen A. Kheirbek is assistant professor of clinical neurobiology in psychiatry at Columbia University and a research scientist at the New York State Psychiatric Institute.

René Hen is professor of psychiatry, neuroscience and pharmacology at Columbia and director of the division of integrative neuroscience in the department of psychiatry at the New York State Psychiatric Institute. The authors have worked together to explore the role that the dentate gyrus—and its newborn neurons—plays in memory and mood since Kheirbek joined Hen's laboratory as a postdoctoral student in 2009.

FOR CENTURIES THE NOTION THAT THE ADULT BRAIN COULD NOT MAKE NEW NEURONS stood as a central tenet of neurobiology. Even Santiago Ramón y Cajal—the Barcelona-based histologist who essentially invented modern neuroscience at the end of the 19th century—declared such neural renewal impossible. After decades of careful observation and painstaking illustration of the microscopic architecture of nerve cells and their connections, Ramón y Cajal concluded that in the adult brain, "the nerve paths are something fixed, ended, and immutable; everything may die, nothing may be regenerated."

So, when Joseph Altman, then at the Massachusetts Institute of Technology, published a series of papers in the 1960s showing that new neurons cropped up in the brains of adult guinea pigs, he was largely ignored. This disregard was perhaps not surprising, because from a logical standpoint, adding new neurons into a fully developed brain would be a recipe for disaster. After all, if the brain stores information in specific webs of neural connections, it would seem that randomly inserting inexperienced cells into these preexisting networks could cripple our ability to properly encode and recover information and thus garble our memories.

But logic is no match for experimental results, and in the 1990s the data began to roll in. Looking carefully at the brains of adult rodents, monkeys and even humans, investigators turned up evidence that new neurons continue to appear throughout life in two brain regions—one involved in smell and the other, the hippocampus, involved in learning, memory and emotion.

Since then, researchers have wondered what, exactly, these newborn neurons do. Although the role that neophyte neurons play in the olfactory system is still somewhat obscure, the hippocampus has begun to serve up its secrets. Work by our research group and others suggests that fledgling cells may be involved in helping to record memories in a way that distinguishes them as unique, preventing them from blurring, one into the next. This realization could lead to novel approaches to treating a variety of anxiety disorders, including post-traumatic stress disorder (PTSD), because people who suffer from such conditions have trouble telling the difference between situations that merit fear and those that are innocuous.

TRICKS OF MEMORY

AT ITS HEART, memory involves recalling as well as recording. Most often it is the former process—by which a vivid, detailed memory can be summoned by a single sight, smell or taste—that inspires wonder. The flavor of a cake dunked in a cup of tea instantly transported the narrator of Marcel Proust's *Remembrance of Things Past* (*À la recherche du temps perdu*) back to the Sunday mornings of his childhood:

> *Once I had recognized the taste of the crumb of madeleine soaked in the decoction of lime-blossom which my aunt used to give me … immediately the old gray house upon the street, where her room was, rose up like a stage set to attach itself to the little pavilion opening on to the garden…; in that moment … the whole of Combray and of its surroundings … sprang into being, town and gardens alike, all from my cup of tea.*

The ability of sensory cues to invoke the recollection of a previous experience—a process called pattern completion—is one of the most important functions of the brain's hippocampus. Yet before a memory can be retrieved, it must be laid down properly. Recording the details of an event in a way that allows us to distinguish one from another—pattern separation—is the other basic job of the hippocampus. Thanks to this ability, which appears to be linked to the production of new neurons, we can (in most cases) remember where we parked the car this morning, as opposed to where we left it yesterday or last week.

Such discrimination is essential not only for keeping memories organized but also for guiding our behavior—for example, allowing us to head toward where we last remember seeing the car. Unlike pattern completion, which seems to occur primarily in a region of the hippocampus called CA3, pattern separation takes place in a wedge of cells called the dentate gyrus.

The two of us decided to explore the role that new neurons play in distinguishing memories in part because these rookie

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cells are known to arise in that exact wedge. Inside this part of the hippocampus, neural stem cells—the parental cells that churn out new neurons—are packed into a thin layer of cells called the subgranular zone. Newborn cells then migrate out of this neural nursery into the rest of the dentate gyrus, where they become integrated into existing neural circuits. In mice, newborn cells can account for up to 10 percent of the neurons in the dentate gyrus. And a recent study using a form of carbon dating to estimate cells' "birth dates" showed that humans continue to produce fresh neurons in the hippocampus at a steady rate well into old age, adding about 1,400 every day.

SEPARATION ANXIETY

TO TEST WHETHER NEW NEURONS participate in pattern separation, in 2009 we began to study the question in mice. First, we either eliminated young, immature neurons by shutting neurogenesis down or boosted their numbers by promoting the cells' survival. Then we asked whether these manipulations affected the ability of the test animals to differentiate among similar situations.

Like many behavioral investigators, we made use of a type of conditioning developed by Russian physiologist Ivan Pavlov in the early 1900s. Pavlov found that if he rang a bell as he fed his dogs, the animals would come to associate the sound with the food—and begin to salivate on hearing the ding. Over the past 100 years this simple form of learning has been widely exploited to test the neural basis of memory.

In our experiments, instead of ringing a dinner bell to herald the appearance of food, we trained mice to anticipate receiving a mild foot shock when they were removed from their home cage and placed in an unfamiliar box. After a few exposures, an animal learns to associate that new environment with the shock, so that each time it is placed in this enclosure, it will freeze in fear.

Studies of the antidepressant Prozac lend support to the notion that a deficit in new neuron production can fuel anxiety disorders.

Next, to test the ability of the mice to engage in pattern separation, we placed them in a box that was very similar to the first one—but not exactly the same. If the "shock box" were square with silver walls, blue lighting and a distinct smell of anise, the lookalike box might be the same shape and color but carry a scent of banana or lemon. At first the animals are afraid. Yet when no shock is forthcoming, they soon learn to tell the two situations apart—standing immobile in the shock box but relaxing when they visit the version that is a little different.

If the production of new neurons were critical to pattern separation, we reasoned, eliminating neurogenesis in an animal's dentate gyrus would make it difficult to distinguish the two situations. And that is what we saw. Animals lacking new neurons remain overly skittish, reacting with alarm in both environments, even after repeated trips to the harmless box proceed without incident. Without the ability to perform pattern separation, the animals generalize their fear of the original location—allowing their anxiety to spread to any place that resembles the site of the unpleasant experience.

Conversely, we can experimentally boost the number of new neurons in the mouse dentate gyrus by eliminating a gene that would otherwise encourage any unneeded young cells to die. The resulting mice, which have a beefier dentate gyrus, are better able to distinguish between the shock box and its lookalike, becoming comfortable more quickly in the enclosure that has proved safe. These observations confirm that newborn neurons play a part in encoding and distinguishing among memories that are related but distinct.

Other laboratories have obtained similar results. Investigators led by Fred H. Gage of the Salk Institute for Biological Studies, whose work helped ignite the explosion of research on neurogenesis in the 1990s, and by Timothy Bussey of the University of Cambridge have shown that eliminating new neurons in the brains of adult mice impairs their ability to discriminate among closely spaced objects—as assessed by their ability to choose the correct arm in a maze or to touch the correct image with their nose on a computerized screen. Bussey's lab has further demonstrated that enhancing neurogenesis improves animals' performance in the touch-screen test. Also, using a conditioning protocol similar to the one we have employed, M.I.T.'s Susumu Tonegawa and his colleagues have confirmed that mice lacking new neurons demonstrate an inability to discriminate between safety and danger.

WHEN LESS IS MORE

STUDIES EXAMINING the effects of interrupting or enhancing neuron generation have not been conducted in human volunteers. But if neurogenesis were important to pattern separation in people, one would expect to find that disruptions in the process would be tied to some detectable disturbance in the activity of the dentate gyrus, where new neurons are born and reside. Indeed, such a connection has been seen in human subjects. Using functional MRI to track neural activity, Michael Yassa of Johns Hopkins University and Craig Stark of the University of California, Irvine, demonstrated that individuals who show an impaired ability to differentiate among similar items display elevated activity in the dentate gyrus.

Although the finding of hyperactivity, rather than reduced function, sounds counterintuitive, it may actually make sense. If every situation evoked widespread stimulation of neurons in the dentate gyrus—activating, say, 95 neurons in a population of 100—the associated memories would blur together, and none would be distinct. Instead the dentate gyrus accentuates the differences between one event and the next by selectively activating discrete, nonoverlapping subsets of neurons. So today's parking space sparks activity in, say, five neurons out of 100 in

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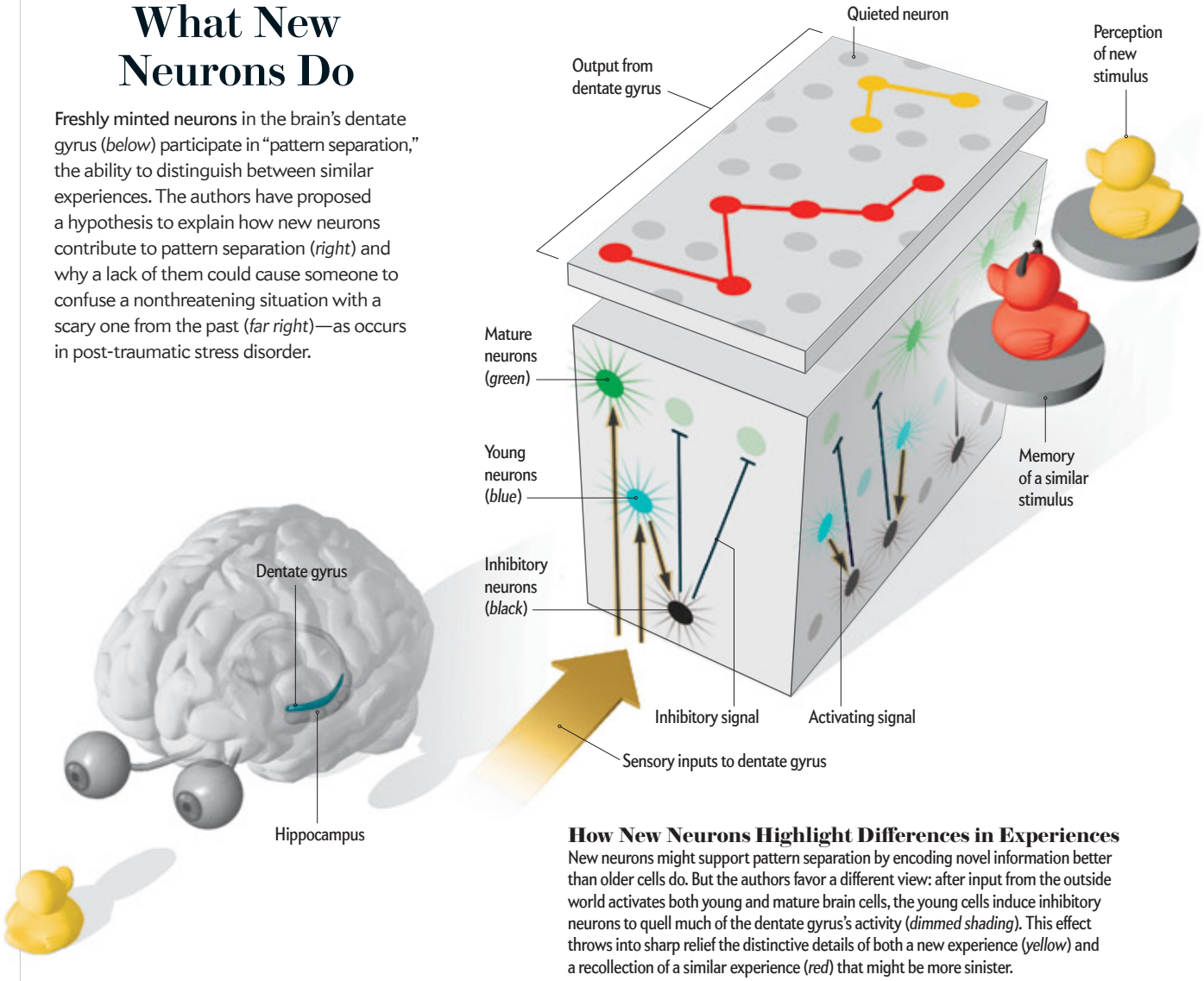
PROPOSED MECHANISM

What New Neurons Do

Freshly minted neurons in the brain's dentate gyrus (*below*) participate in "pattern separation," the ability to distinguish between similar experiences. The authors have proposed a hypothesis to explain how new neurons contribute to pattern separation (*right*) and why a lack of them could cause someone to confuse a nonthreatening situation with a scary one from the past (*far right*)—as occurs in post-traumatic stress disorder.



How New Neurons Highlight Differences in Experiences
New neurons might support pattern separation by encoding novel information better than older cells do. But the authors favor a different view: after input from the outside world activates both young and mature brain cells, the young cells induce inhibitory neurons to quell much of the dentate gyrus's activity (*dimmed shading*). This effect throws into sharp relief the distinctive details of both a new experience (*yellow*) and a recollection of a similar experience (*red*) that might be more sinister.

the dentate gyrus, whereas yesterday's parking location fired up a different set of five.

We have begun to speculate that new neurons may promote pattern separation by reining in the overall activity of the dentate gyrus. As newborn cells mature, they appear to interact preferentially with inhibitory neurons. When these inhibitory cells are excited, they dampen the activity of other neurons in the dentate gyrus. This connection between newborn neurons and suppression of the dentate gyrus is borne out in studies of mice in which neurogenesis has been eliminated. These mice, which lack newborn neurons, show elevated spontaneous activity in the dentate gyrus, suggesting that new neurons bear responsibility for keeping the overall neural activity in check.

If neurogenesis is, in fact, involved in pattern separation in humans, the finding could offer insights into the cause of anxiety disorders such as PTSD. Psychologists have long suspected that an overgeneralization of memory contributes to anxiety disorders, which are marked by an exaggerated, sometimes crippling fear response, even when the environment holds no immediate threat. Such inappropriate generalization could be the result of a diminished ability to distinguish between a past trauma and an innocuous situation that shares some similarity with the traumatic event—for example, a picnic that is interrupted by an unexpected loud noise. Individuals with a normal capacity for pattern separation might flinch at the sudden boom but quickly realize that the park is not a war zone and continue with their lunch. A veteran with an impaired ability to carry out pattern separation, on the other hand, may be unable to separate the sound of a car backfiring from the memory of the battlefield—a mistake that could precipitate a full-blown panic attack.

Experiments have lent support to the proposed connection between impaired pattern separation and anxiety disorders in

SCIENTIFIC AMERICAN ONLINE Hear Kheirbek discuss new neurons at ScientificAmerican.com/jul2014/brain

Illustration by Tami Tolpa

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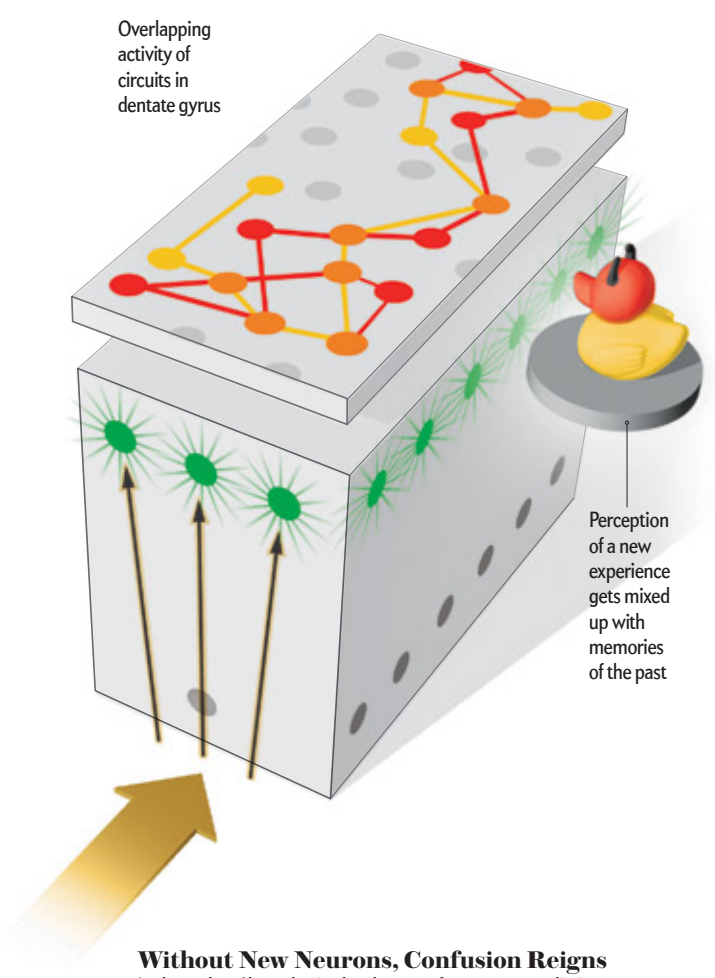

Without New Neurons, Confusion Reigns
In the authors' hypothesis, the absence of new neurons eliminates the cells' inhibitory effects in the dentate gyrus. Thus, more cells fire in response to new inputs and to the memories they evoke. As a result, the neural representations of the events may overlap excessively, thus causing the perception of the two events to merge inappropriately.

humans. Shmuel Lissek of the University of Minnesota and his colleagues have shown, for instance, that people afflicted by panic disorders have a tendency to become startled when viewing an object similar to one that has been associated with a mild shock to the wrist.

Studies of the antidepressant Prozac offer further support for the notion that a deficit in new neuron production can fuel anxiety disorders. Prozac relieves anxiety in both animals and people. Mice treated with the drug are much less nervous and more adventurous when placed in a novel environment, and this drug-induced boost in boldness, we find, is totally dependent on new neurons. Treatments that staunch the birth of new neurons abolish Prozac's antianxiety effects—work we published in *Science* in 2003.

Since then, one of us (Hen) has shown that neurogenesis is also required for Prozac to relieve depressive behaviors in adult macaques—a study that was performed in collaboration with his colleagues at Columbia University. We are also beginning to explore the role of new neurons directly in people. By examining brains that were donated postmortem, we have so far determined that treatment with antidepressants increases the number of neural stem cells—those that produce new neurons—in the dentate gyrus of patients who have major depressive disorder. Whether neurogenesis is necessary for these drugs to effectively treat depression and anxiety in people remains to be seen.

EASING THE PAIN

GIVEN THE GROWING APPRECIATION of the role that the dentate gyrus—and its newborn neurons—plays in pattern separation and potentially in the ability of antidepressants to quell anxiety, we suspect that many people who grapple with depression, PTSD and the cognitive decline that comes with aging could benefit from interventions aimed at boosting neurogenesis in the adult brain. One method that has already proved to encourage neurogenesis in adult animals is exercise. In fact, Gage's discovery that access to a running wheel boosted the numbers of neurons in the adult mouse brain is what rekindled interest in neurogenesis in the late 1990s. Physical activity and antidepressants such as Prozac, however, probably also influence behavior and neural activity in ways unrelated to their effects on neurogenesis—for example, promoting strengthened and more numerous neuronal interconnections.

A more targeted approach to enhancing the production of new neurons might help to specifically reverse the deficits in pattern separation that we think precipitates panic in some cases of PTSD or other anxiety disorders. A recent screen for chemicals capable of boosting neurogenesis in the dentate gyrus of adult mice turned up a promising candidate, called P7C3, which promotes the survival of newborn neurons. Coupled with our own studies showing a reduction of anxiety in mice when we inhibited the death of new neurons, such work makes us hopeful that advances in pharmacological approaches to encourage neurogenesis could help those suffering from anxiety.

Although Ramón y Cajal never imagined that the adult brain could generate new neurons, he could envision the therapeutic potential of such neuronal rejuvenation. As he noted in his 1914 book *Degeneration and Regeneration of the Nervous System,* "It is for science of the future to change, if possible, this harsh decree." SA

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SUSTAINABILITY

Bottoms Up

Treated sewage could be the safest, most environmentally sound source of tap water yet—if we can get over the yuck factor

By Olive Heffernan

ON A SUNNY DAY IN DECEMBER, I VISIT A SHINY, STERILE WATER-PROCESSING facility nestled in the hills of northern San Diego. Sheltered by an ugly cream-colored roof but lacking walls, the workings of this oversize chemist's laboratory glisten in the warm winter sun. Visible from every angle are row on row of silver tubes and canisters of various shapes and sizes and great gray metal vats of concealed liquid. As my tour of the small plant comes to a close, I am presented with a challenge: to identify, by sight, the contents of three large glass bottles, spaced evenly on a table before me and filled with clear fluids. The first bottle seems to have a slight yellow hue. The second is colorless. The third has the brilliance of a well-cut diamond.

Photograph by Sam Kaplan

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I complete my task with ease, identifying the contents, in order, as regular tap water, recycled wastewater from a conventional treatment plant and highly purified toilet bowl water, produced on-site. I am surprised not just by my overwhelming urge to drink the treated sewage but also that I cannot. "We're not allowed to taste it or to have visitors taste it," says a serious Marsi A. Steirer, my guide and deputy director of the City of San Diego Public Utilities Department, which runs the plant.

That could soon change. A six-year pilot project overseen by Steirer and completed in 2013 at this Advanced Water Purification Facility, or AWPF, showed that purified sewage from residential buildings is not only cleaner than existing drinking water, it can be produced at less cost than other options for creating freshwater, such as desalination. For San Diego, the process could be revolutionary, if and when state regulators sanction it.

San Diego imports as much as 90 percent of its water from the Colorado River to the east and the Sacramento–San Joaquin River Delta to the north. But both those sources are running dry. The price of imported water will double in the next decade. By converting effluent, San Diego could meet 40 percent of its daily water demands. And it would put an end to the city dumping poorly treated wastewater into the ocean.

But let's face it, not everyone wants a mouthful of treated sewage. This "yuck factor" quashed an attempt in the late 1990s to start a similar scheme in San Diego, and a poll in 2004 found that 63 percent of residents still opposed the idea of reuse. Numerous proposals in Australia have met the same fate, vetoed by vocal civic groups. Laurence Jones, who had founded one Australian group, Citizens Against Drinking Sewage, questions whether sewage sourced from hospitals, industry, homes and slaughterhouses can ever be fully cleaned. "What we know is that the sewage effluent is 100 percent contaminated," he says.

Attitudes in San Diego have undergone an amazing turnaround, however, as drought has worsened and coastal neighborhoods have grown. Now nearly three quarters of the population are in favor of treated toilet water, but with one stipulation: that after the effluent is cleaned, it will be sent back to a reservoir, where it can be highly diluted and then treated further before being piped to homes.

That process is known as indirect potable reuse. The people running the AWPF plant, currently a test site for this approach, hope to take an additional step: treat effluent to a high level of purity and send it straight to the tap—known as direct potable reuse. For many residents, though, that last step goes too far. "It just seems more palatable to put the water back into a reservoir," says Megan Baehrens, executive director of San Diego Coastkeeper, a nonprofit organization that played a key role in persuading the city to launch the project.

Which process wins will determine what California regulators will allow San Diego, and the rest of the state, to do. And if direct reuse is sanctioned here, where environmental regulations are notoriously rigid, experts say the process will soon spread to other drought-afflicted communities worldwide. "California tends to influence environmental decisions globally," says international water expert Shane Snyder of the University of Arizona, "and it will do the same with wastewater treatment."

Olive Heffernan is a freelance environment writer based in London and a former editor in chief of *Nature Climate Change*.

THE CLEANER THE BETTER

ALL EYES ARE INDEED on the San Diego pilot facility. Right now the plant produces one million gallons of water a day. Although the water is purified to drinking standards, it is sent to irrigate the nearby Torrey Pines Golf Course and a cemetery. Steirer wants to scale up to 10 times the current capacity in the next five to 10 years. The default plan is to release the treated water into the local San Vicente Reservoir to dilute it, after which the mix of treated and reservoir water would be sanitized and sent to homes. Plan B—if regulators allow it—will be the direct approach.

Regulation will not be enough, however, for either approach to gain the public's nod. The utility must get consumers past the yuck factor. Critically, it must convince people that the water is clean. More than 4,000 visitors have toured the plant, among them mothers, Girl Scouts, doctors and elected officials. Many of them question the safety of consuming what was once raw sewage. It is not a trivial concern. Every year 19 million Americans become sick, and 900 of them die, from viruses, bacteria and parasites in water that has undergone the routine treatment that most municipalities use.

One way to win hearts and minds is to make sure the resulting water is purer than current water supplies are. On the tour, visitors learn that purified effluent is, ironically, much cleaner than their tap water is now. That is because most of us are drinking "downstream"—the river or lake that supplies our tap water doubles as a disposal site for water coming from standard sewage treatment plants, which is not clean enough to drink. "Water in the Mississippi River has been used five times by the time it reaches New Orleans," explains George Tchobanoglous, an international water expert at the University of California, Davis. Yet people expect water that will come from effluent to be held to a much higher standard than regular municipal supplies are.

Steirer says the purified wastewater in San Diego is indeed "much cleaner" than water that comes from a typical drinking-water treatment plant. Furthermore, storing water for such a

IN BRIEF

Drinking water is getting scarce and expensive for communities worldwide. New multistep purification processes could help solve the problem by converting wastewater into clean tap water.

San Diego has developed a state-of-the-art purification system. If regulators allow it to send treated sewage directly to the tap, the operation could set the standard for many cities and countries.

The biggest hurdle, however, is persuading the public to overcome its reluctance to drink treated wastewater, even when it is proven to be cleaner than what residents drink today.

PAGE 68: STYLING BY LINDA KEIL *Halley Resources*

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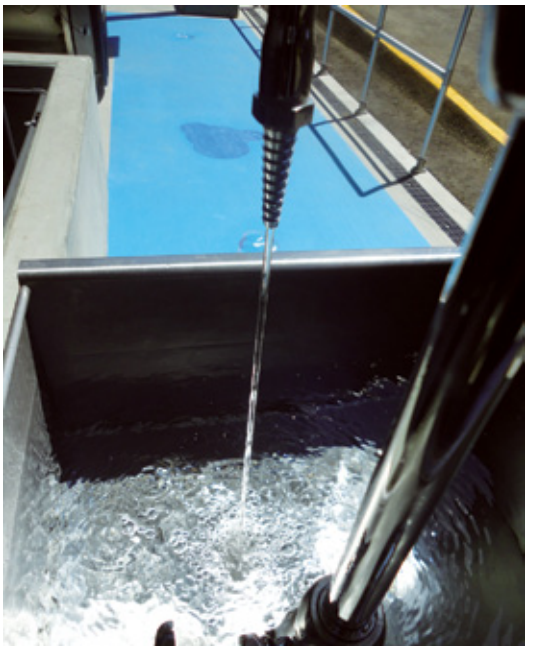

REVERSE OSMOSIS, done in long white cylinders (*above left*), removes salts and microscopic impurities from one million gallons of wastewater a day at the San Diego Advanced Water Purification Facility. The final product is almost as pure as distilled water.

plant in a reservoir or an aquifer carries its own risks, says David Sedlak, engineering professor at U.C. Berkeley. Ducks and other animals introduce filth into reservoirs, for example, and arsenic can leach from rocks into groundwater. "Some people argue we should cut that risk by going direct," he explains.

Traditional treatment for U.S. drinking water goes through two or three steps for removing suspended solids and is then disinfected using chlorine. Transforming fragrant sewage into pristine tap water requires different engineering. The AWPF plant takes sewage water treated by the North City Water Reclamation Plant and adds higher levels of cleansing to "purify" it.

The first step at the AWPF is microfiltration, which happens in large tubes that resemble giant drums of pasta [*see box on pages 72 and 73*]. Shane Trussell, president of Trussell Technologies and head of engineering at the project, tells me that each drum contains 9,000 of these pastalike fibers and that each fiber is dotted with microscopic pores 300 times as narrow as a human hair. As water is forced through the tubes, the fibers filter out viruses, bacteria, protozoa and suspended solids.

Next, the water is sent at high pressure through tubes with even smaller fibers, in a process known as reverse osmosis. This step removes any remaining dissolved particles, up to 10,000 times as small as even the tiniest bacteria, including chemicals, viruses and pharmaceuticals. For the final step, water at the AWPF goes to advanced oxidation, where it is mixed in huge vats with minute amounts of highly concentrated hydrogen peroxide and then exposed to ultraviolet light. This stage destroys any remnant contaminants, even at quantities of parts per trillion, a dose equivalent to a single drop in hundreds of Olympic swimming pools.

Of the one million gallons of wastewater entering the plant daily, 80 percent makes it through to final approval—it is as pure as premium-grade bottled brands. It could be sent to the San Vicente Reservoir if the plant had a permit for indirect reuse. As it stands, the water goes into the state's purple pipes, seen alongside certain roads, which supply the region with recycled water for irrigation and industry. The remaining 20 percent is sent to the local sewage treatment facility for disposal. Some of the substances that regularly turn up in the purified water are caffeine, hand cleaner and artificial sweetener, but they are in such minute doses as to be harmless, Trussell says. The final product is also extremely low in salt—20 parts per million (ppm), compared with 600 ppm in the city's imported water.

This past April, Trussell and his band of engineers added yet another step to make the water clearer and cleaner still. The purified water would be exposed to ozone, which would raise the removal of microbes, for example, to 99.9999 percent. The water would then go through specialized filters meant to further reduce any organic content. If successful, this single addition could be enough to convince regulators that there is no need to send the treated water to a reservoir. "We can never say that we've removed every pathogen from the water," Trussell says. Yet the water quality would far exceed all state and federal drinking-water standards; in fact, the purified water that was produced before this latest add-on step already met or exceeded those standards.

PSYCHOLOGICAL ADVANTAGE

FACTS DO NOT necessarily win minds, however. Advocates of direct reuse need to overcome psychological resistance. Many people seem willing to consider indirect reuse partly because storing the water in a reservoir or aquifer provides an important psychological separation between sewage as the source and drinking water as the product.

Lessons about acceptance can be learned from several communities that have successfully implemented indirect water

COURTESY OF THE CITY OF SAN DIEGO

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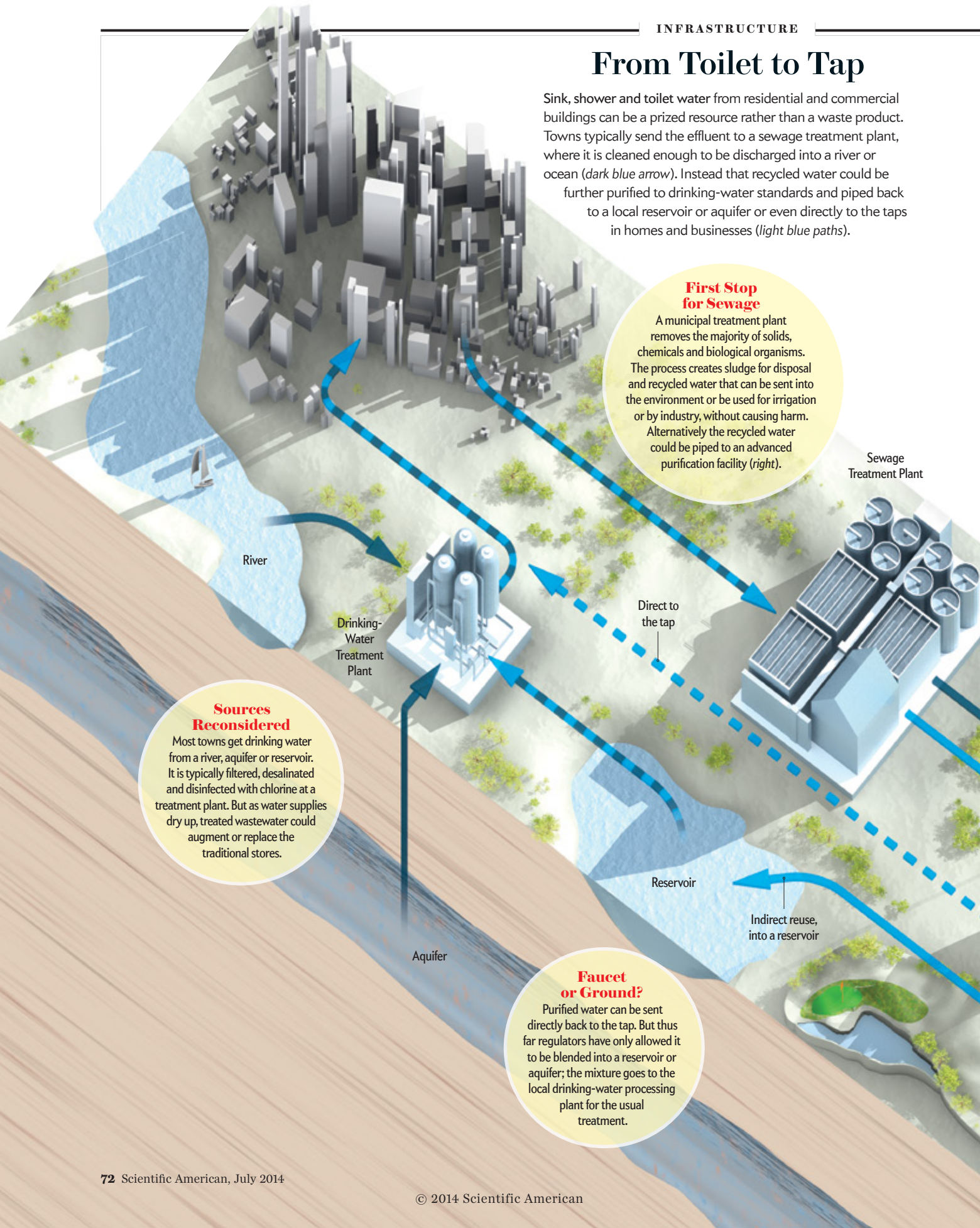
From Toilet to Tap

Sink, shower and toilet water from residential and commercial buildings can be a prized resource rather than a waste product. Towns typically send the effluent to a sewage treatment plant, where it is cleaned enough to be discharged into a river or ocean (*dark blue arrow*). Instead that recycled water could be further purified to drinking-water standards and piped back to a local reservoir or aquifer or even directly to the taps in homes and businesses (*light blue paths*).



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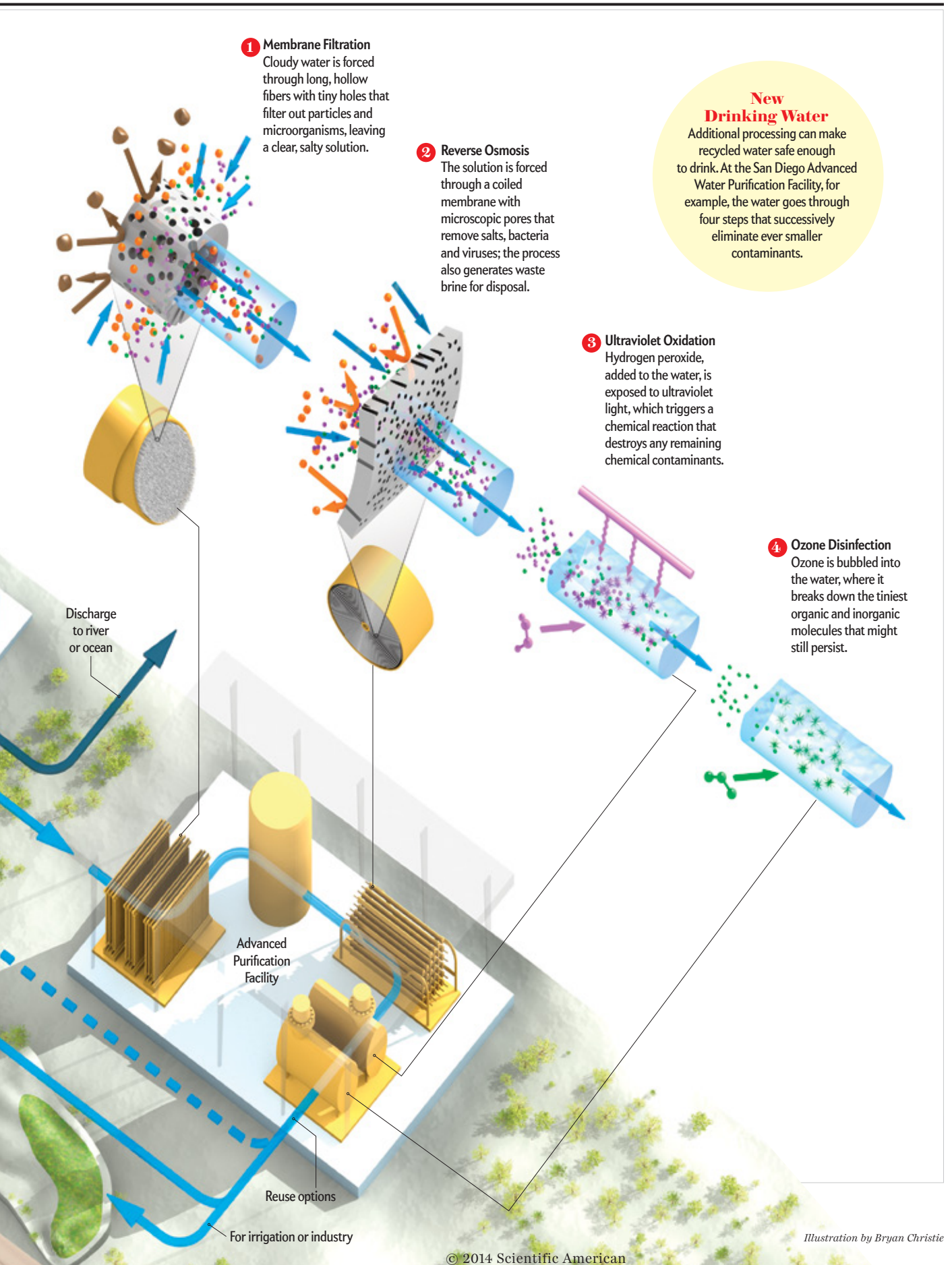

Illustration by Bryan Christie

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reuse. In the late 1990s Orange County, California, 90 miles north of San Diego, faced diminishing water supplies, escalating import costs and a growing population. By 2008 it boasted the world's largest facility for supplementing local groundwater with treated effluent for drinking, processing 70 million gallons of wastewater daily, equivalent to 20 percent of local demand. A few other municipalities in California also drink tap water that has been supplemented with treated effluent but to a lesser extent. An advanced $68-million wastewater treatment plant in San Jose, designed to supply Silicon Valley with eight million gallons of treated toilet water a day, was scheduled to start in June; it is clean enough to drink, but for now it will be used just to water farms and golf courses and for local industry.

At the outset—much like in San Diego—Orange County residents were skeptical; 70 percent opposed the plan. But by the time the plant came online, it had the backing of the entire community, thanks to a very effective public relations campaign. Ron Wildermuth, who led the effort, explains that staff members of the county's water district had seven years' worth of data on water quality before they even approached the community. They then spent another 10 years talking to everyone from rotary and garden clubs to local businesses, explaining the options and inviting them to taste the water.

The effort set the stage for what is now happening in San Diego. "The Orange County project showed that indirect potable reuse was both safe and feasible," Steirer says. "Without it, we wouldn't even be talking about the direct approach." San Diego has adapted much of Orange County's technology, too. It hopes for the direct approach in part because it has no natural groundwater basins to store the purified water. Many municipalities across the U.S. and the world are in a similar situation, so San Diego is the proving ground.

Experiences in Australia reveal how *not* to influence the public. Progress has been "disappointing," says water management expert Stuart Khan of the University of New South Wales in Sydney. Some provinces have banned the drinking of reclaimed water altogether, and water reuse schemes for cities such as Brisbane and Melbourne—which are prone to long, sporadic droughts—have imploded under public opposition. The mistake made by the government was pushing for public acceptance at exactly the wrong time, Khan believes. "We've learned the folly of waiting until things are desperate," he laments, meaning that people felt forced into accepting something with which they were uncomfortable.

It is best to start the conversation early, Khan says, adding that now may be an opportune time to try again in Australia because water supplies have rebounded somewhat, providing some time for discussion with the public. One facility is ripe for conversion. Commissioned in 2006 at the height of a drought period, the Western Corridor Recycled Water Project is a $2.3-billion system that was originally developed to supply recycled water for industry, agriculture and drinking. The plan was to send the water to the Wivenhoe Dam, the source of most tap water in and around Brisbane. The system gathers effluent from six wastewater treatment plants and sends it for advanced treatment at three cleansing plants.

As the system came online between 2008 and 2010, however, the drought ended, and plans to drink the water were shelved until storage supplies dropped to below 40 percent of capacity. The recycled water is now used only for local industrial processes. Khan is one of many Australian water experts arguing that one of the advanced treatment plants should be converted to a direct reuse facility, which could fulfill about 35 percent of Brisbane's water supply.

By converting wastewater into drinking water, San Diego will create a reliable, local supply, reduce waste dumped at sea and avoid huge treatment plant renovation costs.

If the Queensland government opts for this plan, it would create the largest direct potable reuse facility in the Southern Hemisphere. Convincing politicians and the public may be easier this time around, but they will need information in addition to time to consider the options—just like in Orange County.

Officials may be inspired by research published last year by the U.S.-based WateReuse Research Foundation. In a study, foundation researchers showed a group of Californians and Australians of mixed gender, age and education four scenarios for sourcing tap water. The first represented current practice and showed drinking water being sourced from a river that was also a disposal site for treated sewage. The second scenario showed cleansed sewage being further purified by a facility and then blended in a reservoir before being sent to a drinking-water plant for added treatment. In the third example, purified water was sent straight back to the river, where it mixed before being sent for treatment. In the final scenario—direct reuse—the purified water went straight to the city's homes, sidestepping the reservoir and the additional treatment plant. Study participants, irrespective of gender or education level, considered direct reuse as the safest option and the current practice as the least safe.

NECESSITY AS INVENTION

DEMONSTRATING AN UTTER LACK of alternative water sources is another way to sway the public. That is what succeeded in Namibia, the only place in the world that is supplying directly recycled water on a significant scale. Back in 1957, severe drought depleted the city of Windhoek's groundwater supply in just eight weeks. Located about 190 miles inland and 500 miles from the closest perennial river, the community was left with no other

SCIENTIFIC AMERICAN ONLINE More on how to save and cleanse drinking water at ScientificAmerican.com/jul2014/heffernan

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reliable water source. By 1968 the city had a fully operational direct reuse facility. Today 25 percent of Windhoek's tap water comes from processed sewage.

Windhoek faced fewer public challenges than San Diego does. For a start, "there was no activism back then," says Petrus du Pisani, who oversees the facility. "Citizens may have been a little wary, but they accepted the necessity of the decision." Back in the late 1960s, he notes "people had a lot of faith in science and officialdom." Still, the city informed locals and invited them to taste the water. "Now, for us," du Pisani says, "drinking recycled water is just accepted practice."

The system in Namibia would never fly elsewhere today, however. Although it uses multiple treatment steps, it does not include reverse osmosis, key to the San Diego project and others such as Orange County. Officials in Namibia say the water is safe and meets standards set by the World Health Organization.

Windhoek, located inland, could not easily dispose of the large volume of waste brine that reverse osmosis creates. And in the 1960s "there were fewer man-made chemicals" in the wastewater, du Pisani says. "Our main concerns were soaps and frothing agents." One downside of omitting this step is that the drinking water is high in total dissolved solids, which makes it taste salty.

Du Pisani says Windhoek will probably add small-scale reverse osmosis by 2020 to reduce saltiness. Drinking-water standards are changing rapidly throughout the world, even in Namibia, he adds, noting that Windhoek's approach is no longer the most appropriate. The volume of brine, as well as the large amount of energy needed for reverse osmosis, could make direct potable reuse too costly for other communities. Ironically, new treatments are being developed that could reduce the amount of brine, and waste in general, from the overall process. Indirect reuse and desalination can both use reverse osmosis, too. Direct reuse is thus often less energy-intensive than those options because they require additional pipelines and energy to push water through them.

As drought has taken hold in the U.S., several communities have been forced to confront a fate similar to Windhoek's. Big Spring, Tex., had seen little rainfall, year after year. Cloudcroft, N.M., a small mountain community that more than doubles in size on weekends and holidays, had been hauling water over considerable distances. In the past year both towns have begun to purify effluent to supplement their drinking water. Neither community boasts a suitable reservoir or aquifer for storing the treated water over the long term. Instead in Cloudcroft, the purified wastewater is blended with water taken from a local well or spring and stored temporarily in a holding tank before being treated again and piped to people's homes. In Big Spring, the cleansed wastewater is mixed with water from a distant, regional reservoir, and the mixture is treated. The approaches evade classification; some say they are direct reuse, and others call them indirect.

A TASTE FOR SUCCESS

SAN DIEGO IS NOT IN such dire straits yet, which causes some experts to say the city should consider alternative solutions. Although "a big fan of the concept," water authority and Pacific Institute president Peter Gleick thinks that direct reuse is still decades away from happening in California. "There's no sense of urgency to use reclaimed water," he says. Gleick argues that California should instead focus on conserving water, both in cities and, even more so, in agricultural operations, which use 80 percent of the state's water supply. But Baehrens thinks that San Diegans are already pretty mindful of how they use water: "We don't stay in the shower for long, and we only water our plants in the cool hours of early morning and evening." Part of the problem with water conservation, Steirer adds, is that it is usually voluntary and therefore hard to rely on for planning.

Being prepared with wastewater technology might be prudent. Singapore opened its first NEWater facility in 2000. It now has four of the plants, which are well known for producing the most purified effluent on the planet. Less than 5 percent or so of this water is used for drinking, and it is first blended with water in local reservoirs. The rest is used by industry. Should relations deteriorate with neighboring Malaysia, where 40 percent of its water comes from, however, Singapore could send more of the NEWater supply to the city's taps.

Some communities might worry that cleaning wastewater could be costly. Studies of San Diego indicate that indirect reuse processing at a facility that took in 15 million gallons a day would cost about $2,000 per acre-foot of clean water produced, roughly the same cost as water the city imports now. Studies of direct use processing plants that operate at the advanced level of AWPF show a cost of $700 to $1,200 per acre-foot. Operators of the Poseidon desalination plant now under construction in nearby Carlsbad, Calif., estimate a cost of $1,876 to $2,097 per acre-foot, although independent estimates for desalination in California are $2,000 to $3,000 or more.

Whether the AWPF plant is given a green light for direct or indirect reuse, it is a win for San Diego because it will be a reliable local supply of water, it will reduce waste dumped at sea and it will avoid the billions of dollars needed to upgrade the wastewater treatment plant. Until then, cleansed (but not purified) water will continue to run in the purple pipes that line the roads leading to industries. The pipes are marked clearly with signs that read, "Do not drink."

The city has an opportunity to lead the world in a major rethinking of how we see—and use—wastewater. "Water is a recoverable resource, not a source of waste," Tchobanoglous says. Once that is realized, "municipalities will become like private entrepreneurs and try to recover it." It could be a decade before California has laws on the books allowing direct reuse and before San Diego is able to send a premium-grade product directly to the tap. "We'd love to drink the water and for people to taste it," says Steirer, who looks forward to finally having a glass. SA

MORE TO EXPLORE

Direct Potable Reuse: A Path Forward. George Tchobanoglous et al. WateReuse Research Foundation and WateReuse California, 2011. Available as a PDF at http://aim.prepared-fp7.eu/viewer/doc.aspx?id=39

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Saving the Ogallala Aquifer. Jane Braxton Little; March 2009.

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BIOLOGY

BODY WORKS

Nobel Prize winners have published 245 articles in the pages of *Scientific American*. Here we present excerpts from stories in our archives that highlighted new insights into how the body functions. These selections are our tribute to the scientists who are convening in Germany this summer for the 64th Lindau Nobel Laureate Meeting, at which some 600 up-and-coming young researchers will exchange findings and ideas with 38 prizewinners in physiology or medicine.

Compiled by Ferris Jabr — Illustrations by Sam Falconer

IN BRIEF

This summer Nobel laureates in medicine or physiology are meeting with hundreds of promising young scientists on the island of Lindau in Germany. **To complement the gathering,** we present a selection of excerpts that are taken from archival *Scientific American* articles on biology authored by Nobel Prize winners. **The excerpts tour various parts** of the body, including muscles, the brain and the immune system.

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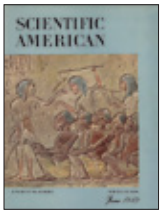
BIOCHEMISTRY

Physiology

By Edgar Douglas Adrian
PUBLISHED: September 1950
NOBEL: 1932

The aim of physiology is to describe the events that take place in the body and incidentally to help the doctor by doing so. But what events, and in what terms shall it describe them? About this there has been, during the past half-century, a change of view. Today it is generally agreed that although physiology is concerned with living processes, it must in the end bring its descriptions within the framework of physics and chemistry.

In the 19th century physiology could be less ambitious. There was so much to find out about the structure and large-scale activities of the various organs without attempting to measure the physical and chemical changes in them, for which there were, in any case, few methods of exact measurement available. That early phase is now over. The general organization of the body has been cleared of its more obvious problems. Physiologists have borrowed many new techniques from the exact sciences, and their interest is shifting in the direction of biophysics and biochemistry.



Muscle Research

By Albert Szent-Györgyi
PUBLISHED: June 1949
NOBEL: 1937

Muscle is a machine, and in any machine we must deal with two elements. One is the energy-yielding reaction, such as the expansion of steam in a steam engine, the burning of fuel in an internal combustion engine, or the flow of current in an electric motor. These elementary reactions can accomplish useful work only if they take place within a specific structure, be it a cylinder and a pistol or a coil and a rotor. So in a muscle we must also look for both the energy-yielding reaction and the meaningful structure.

The energy-yielding reaction is a chemical change which takes place among molecules, and its study belongs to the realm of biochemistry. The structure is the domain of the anatomist, working with his knife, microscope or electron microscope. Both paths of inquiry are most exciting. We can expect to find that the basic energy-yielding reaction is identical, at least in principle, in all living forms. Muscle research can thus take us to the very founda-

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tion of life. Its structure, although specialized, can likewise reveal the fundamental principles of biomolecular architecture. In this light muscle ceases to be a special problem. The study of its function merges with the study of all life, and for such study muscle is a wonderful and unique material.

NEUROSCIENCE

Brain Mechanisms of Vision

By David H. Hubel and Torsten N. Wiesel

PUBLISHED: September 1979
NOBEL: 1981

The cerebral cortex, a highly folded plate of neural tissue about two millimeters thick, is an outermost crust wrapped over the top of, and to some extent tucked under, the cerebral hemispheres. In this article we hope to sketch the present state of knowledge of one subdivision of the cortex: the primary visual cortex, the most elementary of the cortical regions concerned with vision.

We can best begin by tracing the visual path in a primate from the retina to the cortex. The output from each eye is conveyed to the brain by about a million nerve fibers bundled together in the optic nerve. These fibers are the axons of the ganglion cells of the retina. A large fraction of the optic-nerve fibers pass uninterrupted to two nests of cells deep in the brain called the lateral geniculate nuclei, where they make synapses. The lateral geniculate cells in turn send their axons directly to the primary visual cortex.

To examine the workings of this visual pathway our strategy since the late 1950s has been (in principle) simple. Beginning, say, with the fibers of the optic nerve, we record with microelectrodes from a single nerve fiber and try to find out how we can most effectively influence the firing by stimulating the retina with light. For this one can use patterns of light of every conceivable size, shape and color, bright on a dark background or the reverse, and stationary or moving. Working in this way, one finds that both a retinal ganglion cell and a geniculate cell respond best to a roughly circular spot of light of a particular size in a particular part of the visual field.

The first of the two major transformations accomplished by the visual cortex is the rearrangement of incoming information so that most of its cells respond not to spots of light but to specifically oriented line segments. There is a wide variety of cell types in the cortex, some simpler and some more complex in their response properties, and one soon gains an impression of a kind of hierarchy, with simpler cells feeding more complex ones. A typical cell responds only when light falls in a particular part of the visual world. The best response is obtained when a line that has just the right tilt is flashed in the region or, in some cells, is swept across the region. The most effective orientation varies from cell to cell and is usually defined sharply enough so that a change of 10 or 20 degrees clockwise or counterclockwise reduces the response markedly or abolishes it. (It is hard to convey the precision of this discrimination. If 10 to 20 degrees sounds like a wide range, one should remember that the angle between 12 o'clock and one o'clock is 30 degrees.)

There was a time, not so long ago, when one looked at the millions of neurons in the various layers of the cortex and wondered if anyone would ever have any idea of their function. For the visual cortex the answer seems now to be known in broad outline: Particular stimuli turn neurons on or off; groups of neurons do indeed perform particular transformations. It seems reasonable to think that if the secrets of a few regions such as this one can be unlocked, other regions will also in time give up their secrets.

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The Molecular Logic of Smell

By Richard Axel

PUBLISHED: October 1995
NOBEL: 2004

The basic anatomy of the nose and olfactory system has been understood for some time. In mammals, for example, the initial detection of odors takes place at the posterior of the nose, in the small region known as the olfactory epithelium. A scanning electron micrograph of the area reveals two interesting types of cells. In this region, millions of neurons, the signaling cells of sensory systems, provide a direct physical connection between the external world and the brain. From one end of each neuron, hairlike sensors called cilia extend outward and are in direct contact with the air. At the other end of the cell, a fiber known as an axon runs into the brain. In addition, the olfactory epithelium contains neuronal stem cells, which generate olfactory neurons throughout the life of the organism. Unlike most neurons, which die and are never replaced, the olfactory sensory neurons are continually regenerated.

When an animal inhales odorous molecules, these structures bind to specialized proteins, known as receptor proteins, that extend from the cilia. The binding of odors to these receptors initiates an electrical signal that travels along the axons to the olfactory bulb, which is located in the front of the brain, right behind the nose itself. The olfactory bulb serves as the first relay station for processing olfactory information in the brain; the bulb connects the nose with the olfactory cortex, which then projects to higher sensory centers in the cerebral cortex, the area of the brain that controls thoughts and behaviors. Somewhere in this arrangement lies an intricate logic that the brain uses to identify the odor detected in the nose, distinguish it from others, and trigger an emotional or behavioral response.

To probe the organization of the brain, my co-workers and I began where an odor is first physically perceived—at the odor recep-

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tor proteins. Instead of examining odor receptors directly, Linda Buck, then a postdoctoral fellow in my laboratory, and I set out to find the genes encoding odor receptors. Genes provide the template for proteins, the molecules that carry out the functions of cells.

Using the technique of gene cloning, we were able to isolate the genes encoding the odor receptors. This family of receptor genes exhibited several properties that suited it to its role in odor recognition. First, the genes encoded proteins that fall squarely within a previously described group of receptors that pass through the cell membrane of the neuron seven times; these receptors activate signaling proteins known as G proteins. Early studies by Doron Lancet of the Weizmann Institute of Science and Randall R. Reed of the Johns Hopkins School of Medicine have established that odor receptors, too, use G proteins to initiate the cascade of events resulting in the transmission of an electrical impulse along the olfactory sensory axon. Second, the genes encoding the odor receptor proteins are active only in olfactory neurons. Although nearly every cell of the body carries a copy of every gene, many genes are expressed only in specialized cells.

Finally, a broad range of odor receptor genes appears to mirror the striking range of odors. By examining DNA from a variety of mammals, including humans, we determined that around 1,000 genes encode 1,000 different odor receptors. (Each type of receptor is expressed in thousands of neurons.) Given that mammalian DNA probably contains around 100,000 genes, this finding indicates that 1 percent of all our genes are devoted to the detection of odors, making this the largest gene family thus far identified in mammals. The enormous amount of genetic information devoted to smell perhaps reflects the significance of this sensory system for the survival and reproduction of most mammalian species.

The Biological Basis of Learning and Individuality

By Eric R. Kandel and Robert D. Hawkins
PUBLISHED: September 1992
NOBEL: 2000 (Kandel)

Elementary aspects of the neuronal mechanisms important for several different types of learning can now be studied on the cellular and even on the molecular level. Researchers agree that [some] forms of learning and memory require a conscious record. These types of learning are commonly called declarative or explicit. Those forms of learning that do not utilize conscious participation are referred to as nondeclarative or implicit.

Explicit learning is fast and may take place after only one training trial. It often involves association of simultaneous stimuli and permits storage of information about a single event that happens in a particular time and place; it therefore affords a sense of familiarity about previous events. In contrast, implicit learning is slow and accumulates through repetition over many trials. It often involves association of sequential stimuli and permits storage of information about predictive relations between events. Implicit learning is expressed primarily by improved performance on certain tasks without the subject being able to describe just what has been learned, and it involves memory systems that do not draw on the contents of the general knowledge of the individual.

The existence of two distinct forms of learning has caused the reductionists among neurobiologists to ask whether there is a representation on the cellular level for each of these two types of learning process. Canadian psychologist Donald O. Hebb boldly suggested that associative learning could be produced by a simple cellular mechanism. He proposed that associations could be formed by coincident neural activity: "When an axon of cell A … excite[s] cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as one of the cells firing B, is increased." According to Hebb's learning rule, coincident activity in the presynaptic and postsynaptic neurons is critical for strengthening the connection between them (a so-called pre-post associative mechanism).

Ladislav Tauc and one of us (Kandel) proposed a second associative learning rule in 1963 while working at the Institute Marey in Paris on the nervous system of the marine snail *Aplysia*. They found that the synaptic connection between two neurons could be strengthened without activity of the postsynaptic cell when a third neuron acts on the presynaptic neuron. The third neuron, called a modulatory neuron, enhances transmitter release from the terminals of the presynaptic neuron. They suggested that this mechanism could take on associative properties if the electrical impulses known as action potentials in the presynaptic cell were coincident with action potentials in the modulatory neuron (a pre-modulatory associative mechanism).

Subsequently, we and our colleagues found experimental confirmation. We observed the pre-modulatory associative mechanism in *Aplysia,* where it contributes to classical conditioning, an implicit form of learning. Then, in 1986, Holger J. A. Wigström and Bengt E. W. Gustafsson, working at the University of Göteborg, found that the pre-post associative mechanism occurs in the hippocampus, where it is utilized in types of synaptic change that are important for spatial learning, an explicit form of learning.

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IMMUNOLOGY

The Immune System

By Niels Kaj Jerne

PUBLISHED: July 1973

NOBEL: 1984

The immune system is comparable in the complexity of its functions to the nervous system. Both systems are diffuse organs that are dispersed through most of the tissues of the body. In man the immune system weighs about two pounds. It consists of about a trillion cells called lymphocytes and about 100 million trillion molecules called antibodies that are produced and secreted by the lymphocytes. The special capability of the immune system is pattern recognition, and its assignment is to patrol the body and guard its identity.

The cells and molecules of the immune system reach most tissues through the bloodstream, entering the tissues by penetrating the walls of the capillaries. After moving about, they make their way to a return vascular system of their own, the lymphatic system. The tree of lymphatic vessels collects lymphocytes and antibodies, along with other cells and molecules and the interstitial fluid that bathes all the body's tissues, and pours its contents back into the bloodstream by joining the subclavian veins behind the collarbone.

Lymphocytes are found in high concentrations in the lymph nodes, way stations along the lymphatic vessels, and at the sites where they are manufactured and processed:

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the bone marrow, the thymus and the spleen. The immune system is subject to continuous decay and renewal. During the few moments it took you to read this far, your body produced 10 million new lymphocytes and a million billion new antibody molecules. This might not be so astonishing if all these antibody molecules were identical. They are not. Millions of different molecules are required to cope with the task of pattern recognition, just as millions of different keys are required to fit millions of different locks. The specific patterns that are recognized by antibody molecules are epitopes: patches on the surface of large molecules such as proteins, polysaccharides and nucleic acids. Molecules that display epitopes are called antigens. It is hardly possible to name a large molecule that is not an antigen.

The immune system and the nervous system are unique among the organs of the body in their ability to respond adequately to an enormous variety of signals. Both systems display dichotomies: their cells can both receive and transmit signals, and the signals can be either excitatory or inhibitory.

The nerve cells, or neurons, are in fixed positions in the brain, the spinal cord and the ganglia, and their long processes, the axons, connect them to form a network. The ability of the axon of one neuron to form synapses with the correct set of other neurons must require something akin to epitope recognition. Lymphocytes are 100 times more numerous than nerve cells and, unlike nerve cells, they move about freely. They too interact, however, either by direct encounters or through the antibody molecules they release. These elements can recognize as well as be recognized, and in so doing they too form a network. As in the case of the nervous system, the modulation of the network by foreign signals represents its adaptation to the outside world. Both systems thereby learn from experience and build up a memory, a memory that is sustained by reinforcement but cannot be transmitted to the next generation. These striking analogies in the expression of the two systems may result from similarities in the sets of genes that encode their structure and that control their development and function.

Skin Transplants

By Peter B. Medawar
PUBLISHED: April 1957
NOBEL PRIZE: 1960

Plainly the reaction against a graft is an immunological one; i.e., a reaction of the same general kind as that provoked in the body by foreign proteins, foreign red blood cells, or bacteria. This is easily demonstrated by experiments. After a mouse has received and rejected a transplant from another mouse, it will destroy a second graft from the same donor more than twice as rapidly, and in a way which shows that it has been immunologically forearmed. This heightened sensitivity is conferred upon a mouse even when it merely receives an injection of lymph node cells from a mouse that has rejected a graft.

In most immunological reactions the body employs antibodies as the destroying agent—e.g., in attacking foreign proteins, germs and so on. Antibodies are formed in response to a homograft (a transplant between different animals of the same species), but there are reasons to doubt that these are normally the instruments of the reaction against such a graft. Paradoxically enough, a high concentration of circulating antibodies seems if anything to weaken the reaction: it allows the graft to enjoy a certain extra lease of life.

The actual agents of attack on the graft seem to be not antibodies but cells produced by the lymph glands. Some skillfully designed experiments by G. H. Algire, J. M. Weaver and R. T. Prehn at the National Cancer Institute certainly do point in that direction.

In one experiment they enclosed a homograft in a porous capsule before planting it in a mouse which had been sensitized by an earlier homograft from the same donor. When the pores of the capsule were large enough to let cells through, the mouse destroyed the graft. But when the experimenters used membranes with pores so fine that they kept out cells and let through only fluid, the graft survived.

The hypothesis that the action against a graft is carried out by cells explains why grafts in the cornea are mercifully exempted from attack. The cornea has no blood vessels; consequently blood-borne cells cannot reach the graft.

In the brain, on the other hand, the converse of this situation obtains: the brain lacks a lymphatic drainage system, so that any antigens released by a graft there may not be able to travel to centers where they can stir up an immunological response. This probably explains why homografts can often be transplanted successfully into the brain. SA

MORE TO EXPLORE

Lindau Nobel Laureate Meetings: www.lindau-nobel.org

FROM OUR ARCHIVES

A Nobel Celebration. Ferris Jabr; June 2011.
Nobel Pursuits. John Matson and Ferris Jabr; July 2012.
A Nobel Gathering. Ferris Jabr; July 2013.

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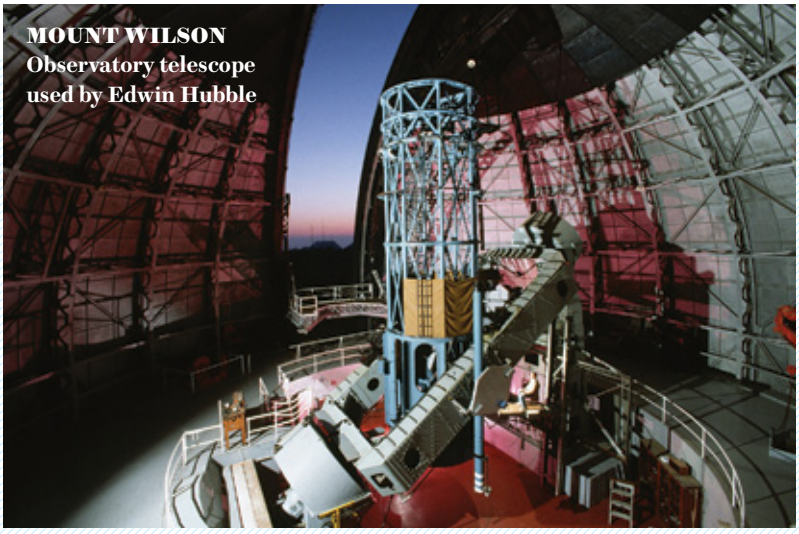
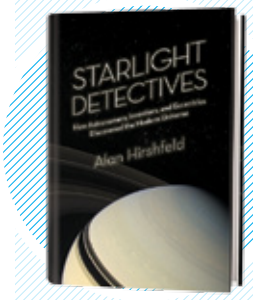


MOUNT WILSON
Observatory telescope used by Edwin Hubble

ROGER RESSMEYER *Corbis*

Starlight Detectives: How Astronomers, Inventors, and Eccentrics Discovered the Modern Universe

by Alan Hirshfeld. Bellevue Literary Press, 2014 ($19.95)



The fundamental tool of astronomy used to be the human eye. It is now the combination of the telescope and the camera, which together have allowed a deeper view of the heavens than earlier generations could have conceived of. Astrophysicist Hirshfeld chronicles the radical changes in our conception of the cosmos that have accompanied the advent of modern astronomy over the past century and a half, "a remarkable and complex period in the development of humanity's oldest science," he writes. Hirshfeld tells the tale by describing an eclectic selection of the trailblazers of astronomy during this time, from amateurs who poured their personal time and savings into the study of the stars to professional astronomers such as Edwin Hubble, who, in the early 20th century, used the biggest and best telescopes the world had ever seen.

The Chemistry of Alchemy: From Dragon's Blood to Donkey Dung, How Chemistry Was Forged

by Cathy Cobb, Monty Fetterolf and Harold Goldwhite. Prometheus Books, 2014 ($24.95)

Often dismissed as delusional dreamers, many ancient alchemists were good scientists, too. In their quest to turn base materials into gold, they managed to discover acids, alkalis, alcohols and salts. Chemists Cobb, Fetterolf and Goldwhite explain the real science behind many alchemists' practices and tell the stories of some of the more colorful practitioners. To understand what made these searchers tick, the authors re-created their experiments: "We wanted to know what made them think they could make gold, and what kept them at their kettles failure after failure." Through their exhilarating experiments to make tin "cry" (a noise produced by tiny crystalline structures) or turn dull copper pennies into shiny brass, the authors glimpsed some of the answers to that question. The book includes instructions for at-home alchemy.

The End: The Human Experience of Death

by Bianca Nogrady. Random House Australia, 2014 ($19.95)

Although everyone dies, no one alive fully knows what the experience is like. Nogrady, a journalist, describes what science says about the goings-on in the mind and body at death and investigates phenomena that lack good explanations, such as seeing a light at the end of a tunnel. She also examines the politics of death, such as the debate over euthanasia, as well as personal accounts of people who have had near-death experiences or have watched a loved one die. Nogrady's book offers a comprehensive reflection on everything we know—and what we can only guess—about the end.

—Annie Sneed

Zoom: How Everything Moves, from Atoms and Galaxies to Blizzards and Bees

by Bob Berman. Little, Brown, 2014 ($27)

Science writer Berman invites readers to consider movement in all its mundane and fascinating forms: the temperature state of absolute zero, wherein atoms nearly stop moving; water circling down a toilet drain; hurricane-force winds; the mind-boggling speed of our universe's expansion; and more. Part scientific and historical exploration, part travelogue, Berman's story reminds us of this inescapable law of nature: "Nothing in the universe is stationary," he writes. "Absolutely everything moves."

—A.S.

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Meet the Beauty in the Beast

Discover this spectacular 6½-carat green treasure from Mount St. Helens!

For almost a hundred years it lay dormant. Silently building strength. At 10,000 feet high, it was truly a sleeping giant. Until May 18, 1980, when the beast awoke with violent force and revealed its greatest secret. Mount St. Helens erupted, sending up a 80,000-foot column of ash and smoke. From that chaos, something beautiful emerged… our spectacular ***Helenite Necklace***.

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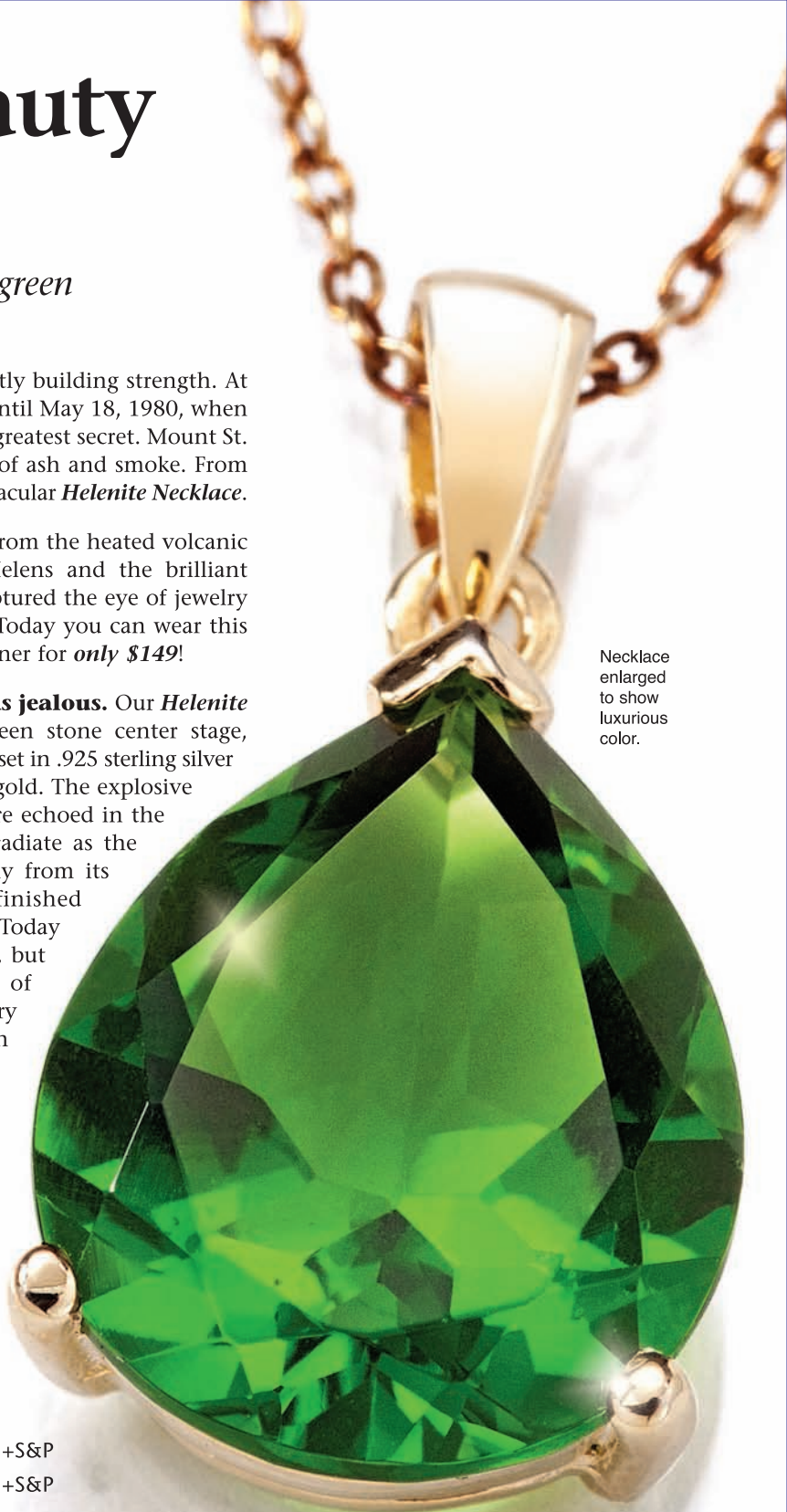

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Michael Shermer is publisher of *Skeptic* magazine (www.skeptic.com). His next book is *The Moral Arc*. Follow him on Twitter @michaelshermer

The Myth of Income Inequality

The American dream is not dead yet

One of the best-selling books of 2014 is *Capital in the Twenty-First Century* by French economist Thomas Piketty, a 696-page doorstop tome on economic history. Why is a data-heavy treatise from the "dismal science" so appealing? Because it is about income inequality and immobility, which in a December 2013 speech President Barack Obama called "the defining challenge of our time," concluding that it poses "a fundamental threat to the American dream." But does it? Maybe not.

The rich *are* getting richer, as Brookings Institution economist Gary Burtless found by analyzing tax data from the Congressional Budget Office for after-tax income trends from 1979 through 2010 (including government assistance). The top-fifth income earners in the U.S. increased their share of the national income from 43 percent in 1979 to 48 percent in 2010, and the top 1 percent increased their share of the pie from 8 percent in 1979 to 13 percent in 2010. But note what has not happened: the rest have not gotten poorer. They've gotten richer: the income of the other quintiles increased by 49, 37, 36 and 45 percent, respectively.

The pie metaphor is deceptive because a pie is of a fixed size such that if your slice is larger, then someone else's is smaller. But economies grow, and the pie gets larger such that you and I can both get a larger slice compared with the slices we got from last year's pie, even if your slice increase is relatively larger than mine. A report released by the Federal Reserve in early 2014, for example, noted that the overall wealth of Americans hit the highest level ever, with the net worth of U.S. households rising 14 percent in 2013, which is an increase of almost $10 trillion to an almost unimaginable $80.7 trillion, the most ever recorded by the Fed. Of course, on a planet with finite resources such an expansion cannot continue indefinitely, but historically capital and wealth production shifts as industries change from, say, farming and agriculture to coal and steel to information and services.

What about income mobility, which President Obama also identified as a problem? Writing in the *National Tax Journal,* economists Gerald Auten and Geoffrey Gee analyzed individual income tax returns between 1987–1996 and 1996–2005 and found that for individuals age 25 and up, "over half of taxpayers moved to a different income quintile and that roughly half of taxpayers who began in the bottom income quintile moved up to a higher income group by the end of each period" and that "those with the very highest incomes in the base year were more likely [than those in other quintiles] to drop to a lower income group." In fact, they found that "60 percent of those in the top 1 percent in the beginning year of each period had dropped to a lower centile by the 10th year. Fewer than one fourth of the individuals in the top 1/100th percent in 1996 remained in that group in 2005." In a follow-up study that included income data through 2010, the economists found that "approximately half of taxpayers in the first and fifth quintile remained in the same quintile 20 years later. About one-fourth of those in the bottom moved up one quintile, while 4.6 percent moved to the top quintile."

One reason for the controversy is that people overestimate differences between the rich and poor. In a 2013 study published in *Psychological Science* entitled "Better Off Than We Know," St. Louis University psychologist John R. Chambers and his colleagues found that most people estimate that the richest 20 percent make 31 times more than the poorest 20 percent (it is 15.5 times), and they believe that the average annual income of the richest 20 percent of Americans is $2 million, whereas in fact it is $169,000, a perceptual difference of nearly 12 times. "Almost all of our study participants," the authors concluded, "grossly underestimated Americans' average household incomes and overestimated the level of income inequality."

So both income inequality and social mobility, though not as ideal as we would like them to be in the land of equal opportunity, are not as large and immobile as most of us perceive them. SA

SCIENTIFIC AMERICAN ONLINE
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Illustration by Izhar Cohen

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Chicago Doctor Invents Affordable Hearing Aid
Outperforms Many Higher Priced Hearing Aids

Reported by J. Page

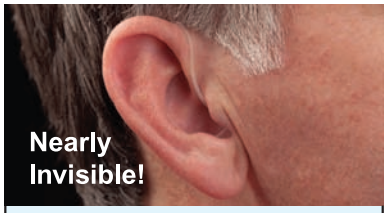
Chicago: Board-certified physician Dr. S. Cherukuri has done it once again with his newest invention of a medical grade **ALL DIGITAL affordable hearing aid.**

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

New Digital Hearing Aid Outperforms Expensive Competitors

This sleek, lightweight, fully programmed hearing aid is the outgrowth of the digital revolution that is changing our world. While demand for "all things digital" caused most prices to plunge (consider DVD players and computers, which originally sold for thousands of dollars and today can be purchased for less then $100), yet the cost of a digital medical hearing aid remained out of reach.

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



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- ✓ **Advanced noise reduction to make speech clearer**
- ✓ **Feedback Cancellation eliminates whistling**
- ✓ **Wide dynamic range compression makes soft sounds audible and loud sounds comfortable**
- ✓ **Telecoil setting for use with compatible phones, and looped environments like churches**
- ✓ **3 programs and volume dial to accommodate most common types of hearing loss even in challenging listening environments**

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

Affordable Digital Technology

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

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

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

Can a hearing aid delay or prevent dementia?

A study by Johns Hopkins and National Institute on Aging researchers suggests older individuals with hearing loss are significantly more likely to develop dementia over time than those who retain their hearing. They suggest that an intervention—such as a hearing aid—could delay or prevent dementia by improving hearing!

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"I have used many expensive hearing aids, some over $5,000. The Airs have greatly improved my enjoyment of life" —Som Y., Michigan

"I would definitely recommend them to my patients with hearing loss" —Amy S., Audiologist, Munster, Indiana

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The ongoing search for fundamental farces

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

Wrong Number

Do you promise to tell the truth on however many phones you carry?

Call it the case of the justices versus modern times.

Just prior to this column going to press, the Supreme Court heard arguments in *United States v. Wurie (and Mr. Wurie's cell phone)*. The case centers on whether the Fourth Amendment protects against warrantless searches of a cell phone possessed by a guy who is already under arrest.

I don't know how *United States v. Wurie* is going to be decided, but I'm betting on a 5–4 decision that basically grants the police the right to examine the contents of your cell phone and possibly your stomach and small intestine. Meanwhile, at the Web site Techdirt, blogger Parker Higgins pointed out a telling bit of the back and forth during the oral arguments between the justices and a lawyer for Wurie concerning how regular people in America use cell phones.

Chief Justice John Roberts was intrigued that Wurie was apparently carrying two cell phones: "The police have told us [that drug dealers] typically use cell phones to arrange the deals and the transfers, and this guy is caught with two cell phones. Why would he have two cell phones?" Wurie's lawyer, Judith Mizner, explained, presumably patiently, "Many people have multiple cell phones."

An intrigued Roberts asked Mizner to back up her claim regarding the commonality of multiple cell phones: "Really? What is your authority for the statement that many people have multiple cell phones on their person?" Mizner, apparently reacting as if she were asked how she could be so sure that many Americans drive to work, said, "Just observation." At which point Justice Antonin Scalia popped in with: "You've observed different people from the people that I've observed."

Maybe the justices' robes have no pockets, which could limit their ability to carry cell phones. Yet as Higgins points out in his blog, it's a good bet that "at least half of the lawyers in the Supreme Court Bar brought two cell phones with them to the courthouse that day." My brother is a lawyer who has been admitted to the Bar of the Supreme Court, and he had to buy cargo pants so he'd have enough pockets for all his cell phones.

In fact, and I hope that this does not immediately make me a criminal suspect, I have two cell phones. I bought a Samsung Galaxy a couple of years ago, and last year Scientific American issued iPhones to all its editors. So I use the Galaxy for all my usual smartphone activities, such as e-mail, Web browsing and texting, and I use the iPhone for my drug deals. By which, of course, I mean refilling my prescriptions at Walgreens. Because that drug chain has a really good iPhone app: you just scan your medication bar code, and an hour later you've got Nasonex up your nose.

So Justice Scalia either truly travels in circles where people have zero or one cell phone, or people in his presence are not dumping the contents of their pockets for his perusal. Or he's not observing accurately. Or some combination of those three possibilities. Scalia also compared a cell phone to a pack of cigarettes, in that police should be able to just open it and look inside. There is a certain logic to that view if what they're looking for is a microprocessor or an accelerometer rather than one's banking information, personal correspondence, unfinished screenplay, U.S. Constitution app and extensive collection of selfies.

I know lawyers who proudly proclaim that it was their forebears who created the Constitution of the United States that George Washington swore to uphold in 1789, when doctors were practicing the bloodletting that likely hastened Washington's death a decade later. Physicians and their colleagues in biomedical research have come a long way since then, having, for example, sequenced the entire human genome. They engage in the occasional bloodletting only when it can be efficacious against hemochromatosis. But Supreme Court justices fully engaged in the 21st century may be in a 5–4 minority. SA

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Illustration by Matt Collins

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The coin features Generals Robert E. Lee and Stonewall Jackson on horseback, exactly as they appear on the Stone Mountain Memorial near Atlanta, Georgia. The memorial was designed by famed sculptor Gutzon Borglum, whose next masterpiece would be the magnificent Mount Rushmore.

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July 1964

Picturephone

"By this month it should be possible for a New Yorker, a Chicagoan or a Washingtonian to communicate with someone in one of the other cities by televised telephoning. The device he would use is called a Picturephone and is described by the American Telephone and Telegraph Company, which developed it, as 'the first dialable visual telephone system with an acceptable picture that has been brought within the range of economic feasibility.' A desktop unit includes a camera and a screen that is 4 ⅜ inches wide and 5 ¾ inches high. AT&T says it cannot hope to provide the service to homes or offices at present, one reason being that the transmission of a picture requires a bandwidth that would accommodate 125 voice-only telephones."

Toolmaking Chimps

"Jane Goodall of the University of Cambridge has reported in *Nature* her observations of toolmaking and tool-using among wild chimpanzees over a three-year period in a Tanganyika reserve. The most frequently observed behavior involved the chimpanzees' making probes out of twigs six inches to a foot long by stripping off leaves with their hands or lips. The probes were then pushed into holes in termite nests. When a probe was withdrawn, a few termites that had seized it were eaten. Immature animals frequently watched their elders at work and imitated their actions. She concludes that the chimpanzee population of the reserve is transmitting a series of primitive cultural traditions from one generation to the next."

July 1914

How Mighty Is the Pen?

"A peaceful competition of peoples is taking place this year, for the benefit of civilization and the profit of mankind. The International Exposition of Book Trade and the Graphic Arts at Leipzig, Germany, may fitly be called a symposium of human education; it unfolds before our eyes the history of culture, man's own history, giving an insight into the intellectual evolution of nations, the rise from darkness, superstition, and ignorance to light and joy, education, knowledge, and understanding."

AUTOMOTIVE CRAFTSMANSHIP: Workers in a French firm build up car bodies from wood and wire netting as a base for plaster, 1914

Electric Hand Dryer

"Agitation for the suppression of the roller or common towel for public use has swept over the entire country, as it is considered a menace to public health. The common towel was succeeded by the paper towel. Now the last word in economical and sanitary innovations is the 'air towel' used in the large public lavatory in the District Building at Washington, D.C. This 'air towel,' or electric hand dryer, is the invention of John M. Ward [patent no. US1108285], superintendent of the District Building. The device consists of a blower that forces air through an electric heating element to ducts and deflectors suitably placed."

Crafting Cars

"A French firm of car manufacturers makes its car bodies by a novel process of plastering, or maybe we should say modeling; for it requires more skill than that of the common plasterer. The framework of the car is made of wood, and on this wire netting is tacked, as shown in our illustration. Then the modeler begins operations with palette and trowel, daubing the wire netting with the plastic material. After the coating has set, it may be dressed down with a plane and sandpaper, just like wood. It is claimed for the new process that a very light and durable body is obtained."

July 1864

Mummy Wheat

"There is a popular belief, according to which wheat found in the ancient sepulchres of Egypt will not only germinate after the lapse of three thousand years, but produce ears of extraordinary size and beauty. The question is undecided; but Antonio Figari-Bey's paper, addressed to the Egyptian Institute at Alexandria, appears much in favor of a negative solution. One kind of wheat which Figari-Bey employed for his experiments had been found in Upper Egypt, at the bottom of a tomb at Medinet-Aboo. The form of the grains had not changed, but their color, both without and within, had become reddish, as if they had been exposed to smoke. On being sown in moist ground, on the ninth day their decomposition was complete. No trace of any germination could be discovered."

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1

Centennial of a Calamity

One hundred years ago *Scientific American* documented the First World War as it engulfed soldiers, civilians and industries

By Daniel C. Schlenoff

THE POLITICAL CRISIS IN EUROPE THAT FOLLOWED THE ASSASSINATION OF Archduke Franz Ferdinand and his wife, Sophie, on June 28, 1914, in Sarajevo received no notice in the pages of *Scientific American*. When Germany declared war on Russia and France and then invaded Belgium on August 4, the magazine weighed in: "It is very difficult for the American to realize that the great European war, which has been dreaded for a generation, is actually taking place. The calamity is so appalling that it seems to stretch beyond the reach of the imagination" [August 15, 1914].

Thereafter, the then weekly *Scientific American* covered the First World War as a vast, world-changing event in which science, technology and massive industrial output played key roles. The American Civil War (1861–1865) saw the first successful use of the machine gun and the submarine, but both sides manufactured fewer than 100 machine guns (including about 20 Gatlings) and 20 submarines. In World War I more than one million machine guns were churned out. Artillery became the king of the battlefield, with up to a billion artillery shells fired during the war. The countermove from the science of defense was to dig deeper into the dirt. One modern calculation says it took 329 shells to wound an opponent sheltering in a trench, four times that to kill him.

The emergence of trench warfare produced a deadlock on the Western Front. C. S. Forester in his 1936 novel *The General* rather unkindly compared the generals in charge with savages trying to rip a screw out of a piece of wood by using larger and larger levers. The problem with the analogy is that both sides in the war were desperately trying to find a way of turning the screw. Science provided one way out of the deadlock.

The Germans deployed toxic chlorine gas on a large scale in April 1915; we noted J.B.S. Haldane's assessment of the technique as "brutally barbarous" [June 12, 1915]. Airplanes were a new invention, and for four years we tracked their improvements as scouts, artillery spotters, fighters and bombers. The first tanks sent into battle—36 of them at Flers-Courcelette in France in 1916—were slow and mechanically unreliable. They inflicted so much damage on the German defenses, though, that 1,000 more were quickly ordered. Continuing reports on the new weapons were strictly controlled: "Strange tales are coming to us from the battlefields of northern France. We would almost believe that our old friend Baron Münchausen had come to life" [September 30, 1916].

For most of the "great European war," we decried "Europe's mad carnage" [Sep-

SCIENTIFIC AMERICAN, VOL. CXIX, NO. 24, DECEMBER 14, 1918 (1)

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Daniel C. Schlenoff edits the 50, 100 and 150 Years Ago column.

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CLASSIC COVER IMAGES: A British heavy tank attacks a German trench in this somewhat fanciful painting (*1, opposite page*), a veterinary ambulance tends to injured horses (*2*), a submarine lurks in open water (*3*), "Liberty trucks in the Liberty war" give an impression of the volume of equipment and supplies coming from the U.S. (*4*), and a French civilian starts up an air-raid siren to warn of enemy bombers (*5*).

tember 23, 1916]. On May 7, 1915, wartime sentiment began to change for America. The RMS *Lusitania,* a civilian liner (unarmed but carrying some military cargo), was torpedoed off the coast of Ireland with the loss of 1,198 lives, including 128 Americans. Our editorial thundered, "Has this ceased to be a war of army against army and degenerated into a war against civilians and women and children?" [May 15, 1915]. The *Scientific American* issues of 1916 and 1917 show that U-boat warfare created a palpable fear in this country; it was certainly one reason the U.S. declared war on Germany on April 6, 1917.

America in 1917 had a tiny army but a lot of factories. The pace of war production quickly became frenetic. One report noted a U.S. Shipping Board motto: "Don't apologize, don't explain; let 'em holler, GET IT DONE!" [April 6, 1918]. In this new "total war," even food became a weapon: "It is a military necessity that each acre produce the maximum of human food" [August 10, 1918].

By 1918 American troops and supplies were pouring in for the Allies. The Hundred Days Offensive drove the Germans out of France, and the Central Powers collapsed. The armistice ending the war took effect on the 11th day of the 11th month at the 11th hour: November 11, 1918, at 11 A.M.

Even as the war wound down, the next horror to visit humankind had made an appearance. The October 19, 1918, *Scientific American Supplement* carried a report from the July meeting of the Munich Medical Union noting a new pandemic they called "Spanish Influenza." Within two years 50 million people had died of the disease, overshadowing the loss of the 10 million war dead.

The Victory Medal handed out to American, French, British and Allied soldiers bears the phrase: "The Great War for Civilization." Yet the awful irony is that the children of "the war to end all wars" went on to fight and die in much larger numbers in the Second World War 20 years later—yet another calamity that eclipsed the First World War. SA

World War I Archives Available

From 1914 through 1918, *Scientific American* devoted up to a quarter of its editorial space to topics related to the war. We have assembled many of these articles into digital packages organized by topic and have also drawn on our archival material to produce Web slide shows, eBooks and other offerings. Find links to the full collection at **ScientificAmerican.com/wwi**

SCIENTIFIC AMERICAN, VOL. CXVII, NO. 15; OCTOBER 13, 1917 (2); *SCIENTIFIC AMERICAN*, VOL. CXIII, NO. 6; AUGUST 7, 1915 (3); *SCIENTIFIC AMERICAN*, VOL. CXVIII, NO. 1; JANUARY 5, 1918 (4); *SCIENTIFIC AMERICAN*, VOL. CXIX, NO. 6; AUGUST 10, 1918 (5)

SCIENTIFIC AMERICAN ONLINE See an extended version of this article at ScientificAmerican.com/jul2014/great-war-centennial

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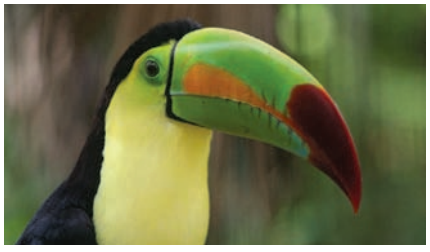

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Lightning

Speaker: Joseph R. Dwyer, Ph.D.

The Mysteries of Lightning

While lightning is one of the most widely recognized natural phenomena, it remains poorly understood. Learn what we do and don't know about lightning, including the recent discovery that lightning emits bursts of x-rays and gamma-rays. By measuring these high-energy emissions, researchers are gaining a better understanding of this fascinating phenomenon.

Ball Lightning

Ball lightning has been reported by eyewitnesses as a grapefruit-sized glowing sphere as bright as a 60-watt light bulb, often seen along with thunderstorms. Yet little is known about ball lightning, and it has never been replicated in the lab. We'll discuss amazing reports of ball lightning and some of the latest explanations.

Sprites, Pixies, and Other Atmospheric Phenomena

Although we spend our entire lives inside our atmosphere, there are surprisingly many things that we don't know about the air right over our heads. Learn about strange discharge phenomena dubbed sprites, elves, trolls, pixies, and gnomes, and other amazing atmospheric curiosities.

Lightning Safety

Lightning strikes our planet about 4 million times every day, causing billions of dollars in property damage and killing or injuring many people each year. Despite the dangers, many people don't know how to be safe during thunderstorms. Learn about the harmful effects of lightning, along with lightning protection and safety.

The Maya

Speaker: Joel Palka, Ph.D.

Archaeological Highlights of Maya Civilization

From over a century of excavations in Mexico and Central America, we understand when Maya society formed, how their cities flourished in the tropical forests, and how they lived their daily lives, yet some mysteries of the Maya remain. We'll overview this fascinating civilization and some of the questions we still have.

Maya Hieroglyphic Writing for Everyone

Maya hieroglyphs present exciting details on ancient Maya life including religion, politics, trade, and the organization of society. We'll cover the deciphering of Maya writing, the structure of the texts, and basic knowledge of Maya culture through their hieroglyphs.

Native Maya Perspectives of the Sea

For many of us the sea represents beauty and wonder, but how did indigenous Maya people

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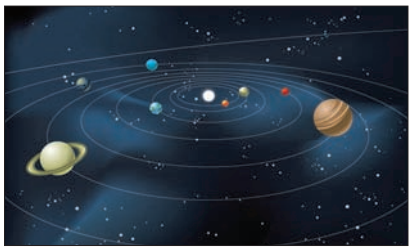
view the sea? We'll focus on Maya culture and the sea as seen in painted pottery, monumental sculpture, and colonial-era narratives.

Maya Pilgrimage to Ritual Landscapes

Recent archaeological and anthropological findings have shed new light on ancient Maya travel, religion, and views of the landscape. Islands, mountains, caves, and lakes made up sacred places to them. This session looks at the latest interpretations of ancient Maya pilgrimage, their ritual landscapes, and how these were central to Maya society.



Our Solar System

Speaker: Adriana C. Ocampo, Ph.D.

Cosmic Collision: The Search for the Dinosaur Killer

Around 65 million years ago a massive space rock hit Central America, setting off a biospheric disaster that wiped out the dinosaurs. Take a voyage back in time, via Belize and neighboring Mexico, to explore the impact site of the ancient asteroid that drastically altered the balance of life on Earth.

Our Neighborhood in the Solar System

In this extraordinary time for planetary science we are beginning to understand planetary formation processes that were wholly unknown to us just a short time ago. Guided by the latest scientific insights, we'll discuss how planets form, why asteroids and comets are important, and whether habitable environments exist beyond Earth.

Exploring our Solar System

NASA's robots have now taken us out to 180 astronomical units (AU), or about 180 times the distance from Earth to the Sun. We'll delve into some of their fascinating discoveries, such as the similarities and differences between the gas giant planets and the key role Jupiter plays for Earth.

Neuroscience

Speaker: Lary C. Walker, Ph.D.

Life and its Discontents

Disease is an inescapable fact of life, but our very existence is shaped by our relationship with potential disease agents. We'll explore the biological origins of disease to understand why the brain is vulnerable to a distinctive constellation of disorders as we age.

Scratching Sheep, Mad Cows, and Laughing Death

Follow the incredible scientific odyssey that began in the 18th century with a mysterious disease of sheep and, in the 20th century, bore two Nobel Prizes. Learn about the prion, an infectious protein and possibly the most controversial molecule in the history of medicine.

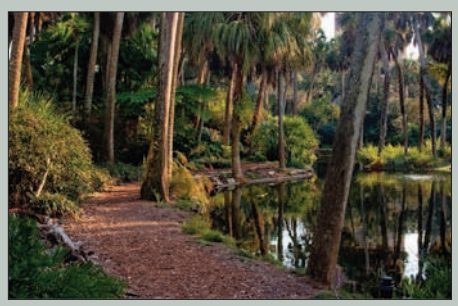
Why Old Brains Falter

One of the most feared diseases of old age is Alzheimer's disease, the most frequent cause of dementia. Learn how the brain changes in normal aging and in Alzheimer's disease, how Alzheimer's emerges and spreads within the brain, and why it is so difficult to stop.

Alzheimer's Therapies: Hype and Hope

No current treatment can stop the relentless progression of Alzheimer's disease. We'll explore the history of rational therapeutic approaches to Alzheimer's and take a frank look at the benefits and shortcomings of existing treatments. Finally, we'll consider how our growing knowledge of brain aging offers hope that an effective therapy is possible.

SCIENTIFIC AMERICAN Travel HIGHLIGHTS OUTER SPACE AND OPEN SPACE IN FLORIDA



BOK TOWER GARDENS: Sunday, March 22, 11am – 4pm

KENNEDY SPACE CENTER (KSC): Monday, March 23, 8am – 7:30pm

Continue the Bright Horizons fun with a two-day exploration of two very different central Florida gems: Bok Tower Gardens and Kennedy Space Center.

Bok Tower Gardens — a National Historic Landmark botanical garden and bird sanctuary — is an opportunity to relax amidst subtropical landscape gardens which help preserve 64 rare Central and North Florida plant species. We'll also hear the Garden's 60-bell carillon play.

Reconnect with the spirit and substance of space exploration on our visit to Kennedy Space Center. Guided by tour specialists, explore the world's largest launch facility.

First stop: Launch Control Center. Journey inside the firing room where the last 21 shuttle launches were controlled. Pass by the computer consoles at which engineers constantly monitored the launch controls. See the launch countdown clock and large video monitors on the walls. Enter the bubble room with its wall of interior windows through which the management team viewed all of the proceedings below. Re-live the last shuttle launch, Atlantis mission STS-135 (see takeoff photo, below), while watching the launch footage in the room where the launch became part of history.

Get the right stuff at lunch as we meet a veteran member of NASA's Astronaut Corps, have a hot buffet lunch, and participate in a 30-minute interactive Q&A during "Lunch with an Astronaut."

Onward to the Space Shuttle Atlantis, along with the interactive exhibits that bring to life the complex story of the shuttle and the thousands of people who created and maintained it.

Join us for a memorable look at KSC's role in the endeavor of exploration.

Price: $899 per person, based on double occupancy; $1,399 for a single. Kennedy Space Center launch facilities are transitioning to commercial missions and are under construction. Therefore the structures and vantage points we experience and the entire sequence of our day are subject to change. Regardless of our tour route, we will have an excellent tour of KSC!

For more info please email Concierge@InsightCruises.com or visit ScientificAmerican.com/travel

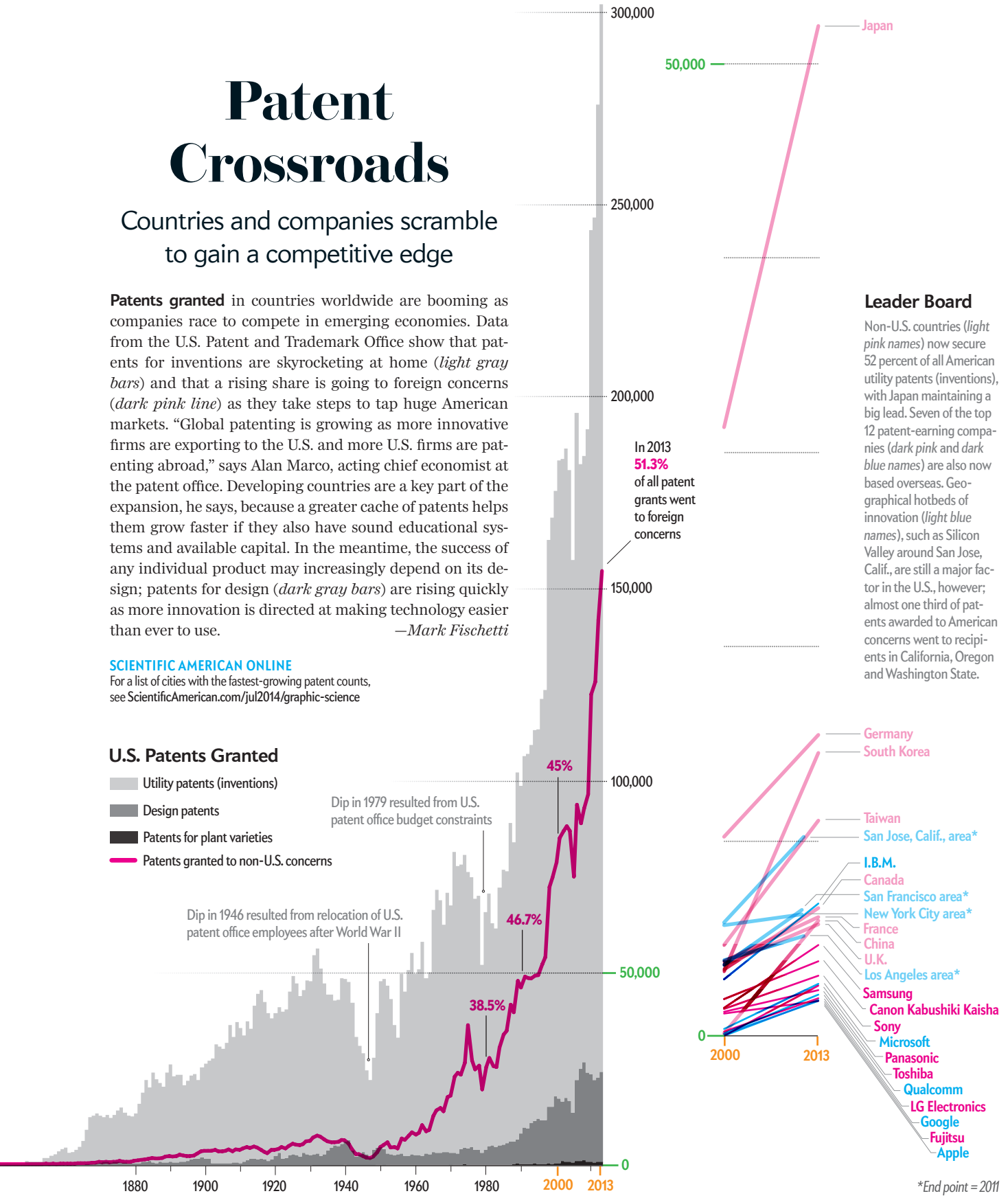
Patent Crossroads

Countries and companies scramble to gain a competitive edge

Patents granted in countries worldwide are booming as companies race to compete in emerging economies. Data from the U.S. Patent and Trademark Office show that patents for inventions are skyrocketing at home (*light gray bars*) and that a rising share is going to foreign concerns (*dark pink line*) as they take steps to tap huge American markets. "Global patenting is growing as more innovative firms are exporting to the U.S. and more U.S. firms are patenting abroad," says Alan Marco, acting chief economist at the patent office. Developing countries are a key part of the expansion, he says, because a greater cache of patents helps them grow faster if they also have sound educational systems and available capital. In the meantime, the success of any individual product may increasingly depend on its design; patents for design (*dark gray bars*) are rising quickly as more innovation is directed at making technology easier than ever to use.

—Mark Fischetti

SCIENTIFIC AMERICAN ONLINE
For a list of cities with the fastest-growing patent counts, see ScientificAmerican.com/jul2014/graphic-science



Leader Board

Non-U.S. countries (*light pink names*) now secure 52 percent of all American utility patents (inventions), with Japan maintaining a big lead. Seven of the top 12 patent-earning companies (*dark pink* and *dark blue names*) are also now based overseas. Geographical hotbeds of innovation (*light blue names*), such as Silicon Valley around San Jose, Calif., are still a major factor in the U.S., however; almost one third of patents awarded to American concerns went to recipients in California, Oregon and Washington State.

*End point = 2011

SOURCE: U.S. PATENT AND TRADEMARK OFFICE

Graphic by Jen Christiansen

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A compelling look at one of the most pressing issues of our time...

Heart disease and related non-communicable diseases were once considered a problem that only wealthy, industrialized nations faced. Together, they now rank as the leading cause of death across the globe.

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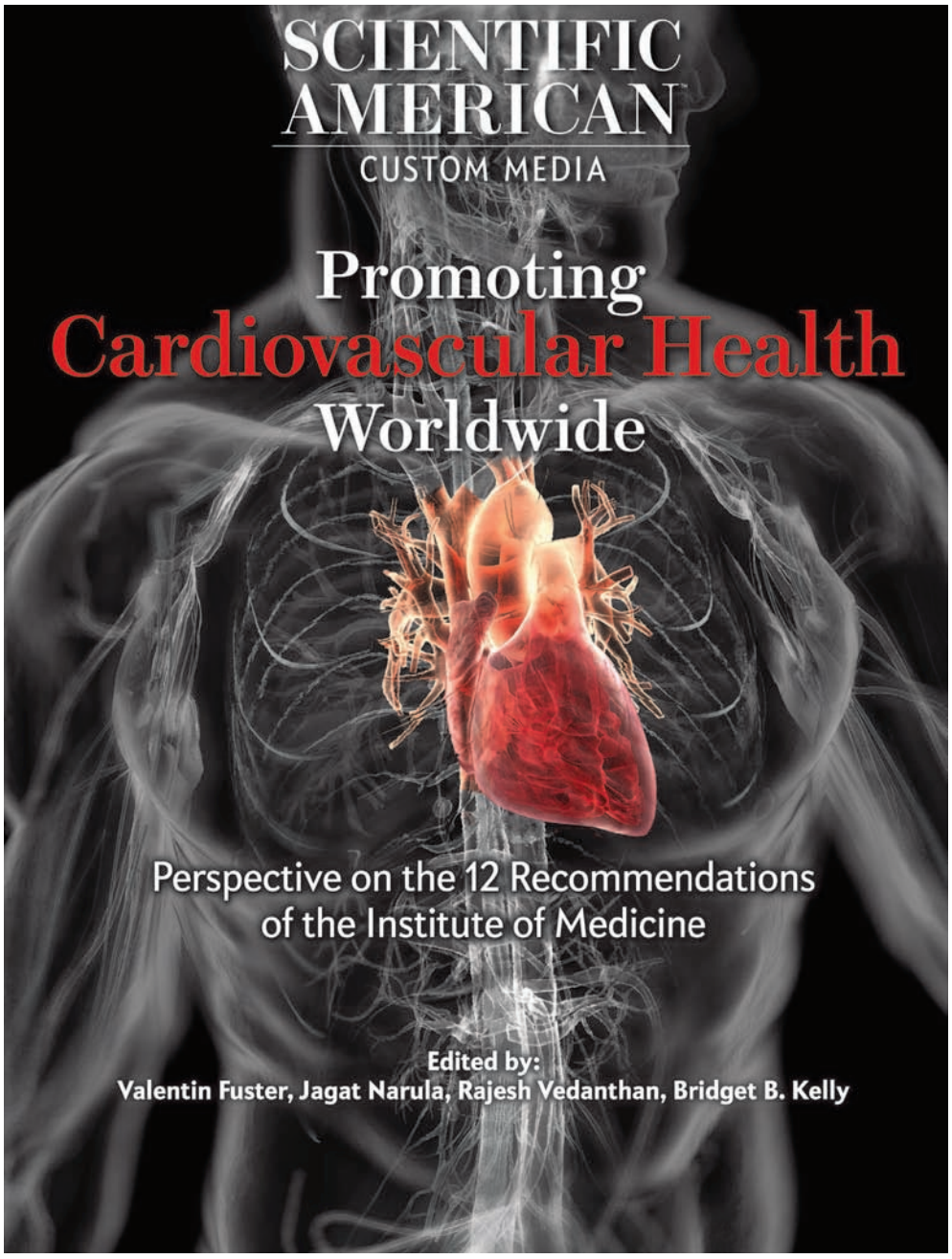

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[1]Lichtenberg FR. NBER Working Paper No. 18235. Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000-2009. Available at http://www.nber.org/papers/w18235. Accessed May 2014.

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