EVOLUTION
The Human Predator

EXPLORATION
Journey to the Bottom of the Sea

NEUROSCIENCE
The Brain's Genetic Geography

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APRIL 2014

Cosmic Dawn

How the first stars ended the dark ages of the universe

SPECIAL REPORT
Medicine's RNA Revolution

IEEE Life Sciences Drives Innovation Across Multiple Domains

Advances in healthcare are increasingly dependent on applying knowledge from medicine, the exact sciences, the life sciences, computing and engineering. Commercial solutions to healthcare challenges must tap several domains of expertise just to emerge from the lab, let alone reach the market and succeed. Healthcare is truly multidisciplinary.

Whether you are a physician, researcher, educator, scientist or an engineer, we invite you to discover the deep, interdisciplinary resources provided by the coalition for life sciences at the IEEE.

No other global organization offers the breadth and depth of varied resources found under the IEEE Life Sciences umbrella. Our membership is engaged in fundamental research and commercial applications in the life sciences – in educational outreach and the development of relevant standards. You'll meet your industry and academia colleagues in the pages of our award winning, peer-reviewed journals and at the conferences we hold worldwide.

The IEEE Life Sciences Portal is the industry repository for the foremost news, links to key journals, commentary, conference information, and videos. More than 3,000 experts in healthcare, government, academia, research and related associations subscribe to the IEEE Life Sciences Monthly eNewsletter for up-to-date life sciences insights. In addition, IEEE develops many of the key standards that ensure the interoperability, safety and affordability of devices and systems that enable life sciences research and are used in diagnostics and treatment in clinical settings. We thus offer a "one-stop shop" that can support your path to professional development and the market.

IEEE Life Sciences is the platform for a "meeting of the minds," enabling collaboration across domains which is the most effective path to innovation. IEEE holds conferences that attract participants from different communities, and combine the emerging challenges and innovations across all aspects of the life sciences. We engage with all principal disciplines within biomedical engineering, and with diverse areas ranging from medical imaging to information technology in biomedicine and nanobiotechnology.

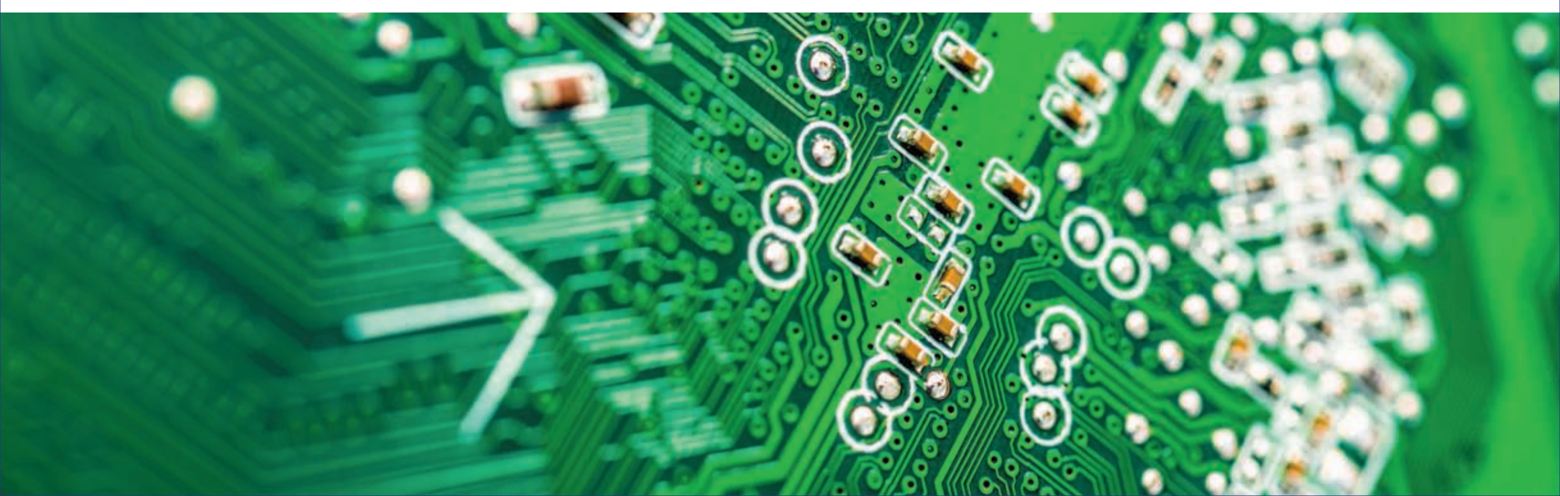
Virtually every current innovation in healthcare depends on a mix of technological expertise across an array of disciplines. Consider a few examples.

Nearly all technical systems for diagnosis and treatment of patients, from birth to the end-of-life, rely on sensors, actuators, algorithms, data networks and related computing innovations in data management, mining and security. The life sciences in fact may well become the most computer-intensive scientific field of the 21st century. A good example of the ensuing advantages is the use of data fusion in diagnostics. This is the integration of multiple data sources, combined to create a comprehensive view of diagnostic information – such as image fusion of MRI and CT scans or PET scans and CT scans. Fusion systems collect information from different sources and serve in decision-support frameworks that assist physicians. Robotic surgery, dependent on the disciplines of computing and engineering, is another example. It offers physicians an unprecedented degree of precision and dexterity. Advances in 3D printing promise to revolutionize the development of new replacement organs and limbs for the human body. Predictive toxicology is critical to the development of new medicines.

Recognizing the value of industry contributions to advance topics like these, the new IEEE Life Sciences Letters, a digital open access journal, is dedicated to the timely publication of high quality manuscripts that apply methods of quantitative analysis to biological problems at the molecular, cellular, organ, human and/or population levels. We invite you to publish your research in the new open access journal, which covers personalized medicine, pharmaceutical engineering, synthetic biology, and systems biology.

Supported by your contributions, IEEE Life Sciences provides a clear path to establish new standards, share best practices, publish new findings, and provide educational opportunities to further life sciences for the benefit of humanity.

Great ideas need support. Join us. Participate. Together, we can turn great ideas into reality.

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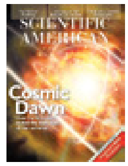
April 2014 Volume 310, Number 4

ON THE COVER



Shortly after the big bang, all was black. Primordial gas cooled and coalesced for hundreds of millions of years, enshrouding the universe in darkness. When the giant first stars eventually did appear, their light was quickly snuffed out by this fog of gas. Astronomers are only now piecing together the 13-billion-year-old mystery of how the fog lifted. Image by Kenn Brown, Mondolithic Studios.

FOOD STYLING BY KAREN EVANS

Photograph by Plamen Petkov

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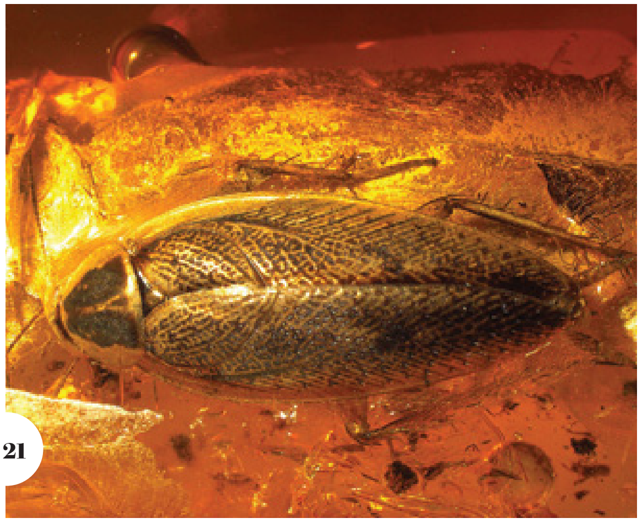

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ON THE WEB

The Path to a Clean Energy Future

The U.S. Advanced Research Projects Agency–Energy is seeking the next generation of alternative energy technology. Find out about the progress in biofuels, hybrid solar power and energy-efficient designs being contemplated and tested. *Go to www.ScientificAmerican.com/apr2014/energy*

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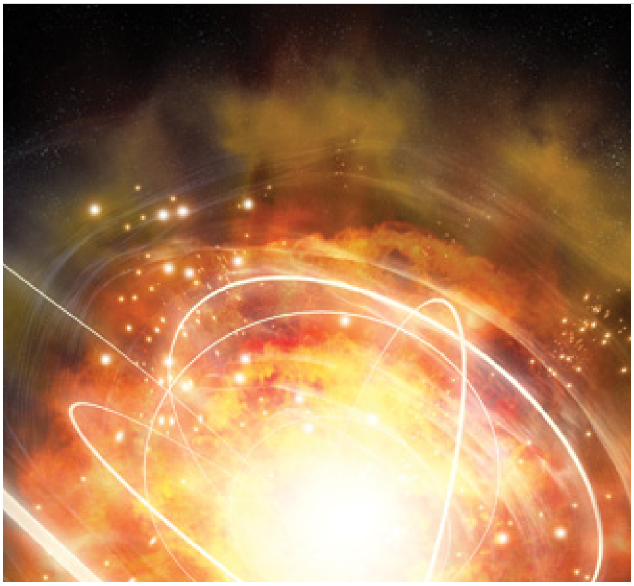


Mariette DiChristina is editor in chief of *Scientific American.* Follow her on Twitter @mdichristina

Out of Darkness

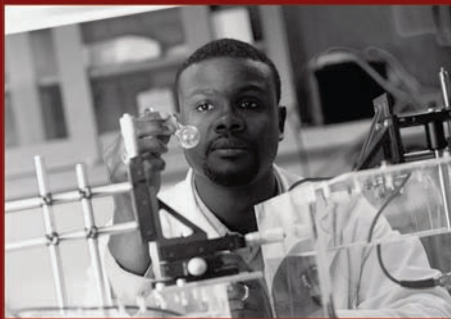
"ABOUT 13.8 BILLION YEARS AGO, JUST 400,000 YEARS OR SO after the big bang, the universe abruptly went dark," writes science journalist Michael D. Lemonick in this issue's cover story, "The First Starlight," starting on page 38. So began the mysterious dark ages of the universe. What happened next has always intrigued me. How did that cosmic fog lift? How did the first stars flare and then coalesce into the galaxies we know today? Astronomers have been gathering clues by looking at some of the oldest objects in the universe.

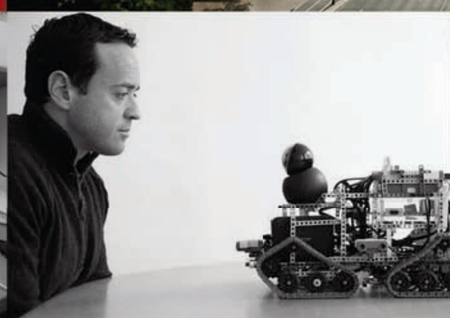
On our own, watery planet, we have suffered from an inability to thoroughly penetrate a different kind of darkness: the world below the waves. It is often now said that we know the bottom of the ocean less well than we do the surfaces of the moon and Mars—which anybody can enjoy via Google maps.

Today technology and privately funded ventures are combining to engage in the first systematic exploration of the deepest ocean trenches. In April, as science writer Mark Schrope details in "Journey to the Bottom of the Sea," a new submersible will descend to the bottom of the Kermadec Trench, at 10,000 meters, to collect video of the landscape and its strange creatures. It will sample the water and its sediments. Of course, robotic explorers are likely to play an even more prominent role, at least in the next few years. But one thing is clear: we will finally begin to get a truer picture of the dark depths of our own planet. Dive to page 60.

We're also shining a light on aspects of our own inner workings. RNA, less chemically stable than our DNA genetic-information repositories, was routinely overlooked as a mere cellular housekeeper, write staff editors Christine Gorman and Dina Fine Maron in "The RNA Revolution," a special report starting on page 52. It turns out, however, that RNA has "an astonishing degree of control over the behavior of DNA and proteins," as they describe—enough to spawn a multibillion-dollar therapeutics stampede in venture capital and research initiatives. As with most explorations by science that push the boundaries of human knowledge, we all stand to benefit. SA

Kenn Brown Mondolithic Studios (glowing cosmos), Illustration by Nick Higgins (DiChristina)

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December 2013

“We need to get these ‘reformers,’ who have never had a class of 38 students, out of education.”

ART ARONSEN *VACAVILLE, CALIF.*

YOUR BRAIN ON GOOGLE

“How Google Is Changing Your Brain,” by Daniel M. Wegner and Adrian F. Ward, discusses studies indicating that the Internet has changed the way humans have traditionally allocated remembering certain facts to others and our sense of self.

I worry that the Internet-induced high “cognitive self-esteem”—the sense of being smart or good at remembering—the authors report might discourage students from taking the care to patiently learn about profound concepts. Try looking up “topological group” or “chord progression.” Some of the most interesting subjects can’t be understood with the touch of a button.

LANCE WALTNER
Colorado Springs, Colo.

Wegner and Ward mention, as evidence of a profound psychological change created by the Internet, an experiment in which subjects remembered facts they typed into a computer much worse if they were told that the computer had saved them. But the same would have happened if subjects had written facts on paper, and then some were told that the paper had been filed and others that it had been burned.

GUY OTTEWELL
Dorset, England

The authors ignored a big difference between asking friends and family for information versus looking it up online: you don’t usually need to worry that the former have been paid to deceive you using sophisticated marketing or propaganda.

R. ALLEN GILLIAM
Winter Park, Fla.

DO CETACEANS SPREAD FUNGI?

In “Fungi on the March,” Jennifer Frazer discusses the unexpected spread of the airborne, lung-infecting fungus *Cryptococcus gattii* in Canada and the Pacific Northwest, where it was previously unknown.

C. gattii is described as infecting porpoises as well as people and other animals. How better to aerosolize and spread a pulmonary infection than for a sick and dying porpoise to spray fungus from its blowhole just offshore? And if *C. gattii* infects one cetacean, could it also be infecting others?

JIM SAKLAD
Baldwin, Md.

FRAZER REPLIES: According to veterinary pathologist Stephen Raverty of the Animal Health Center at British Columbia’s Ministry of Agriculture, based on extrapolation from terrestrial animals and from one case involving dolphins, it is unlikely that C. gattii *is spread from one infected animal to another, just as humans cannot spread the disease to each other. Scientists suspect this may be because “wet” forms of the yeast in animals may not be infective. So far* C. gattii *has been found to infect Dall’s porpoises, harbor porpoises and Pacific white-sided dolphins. Samples taken from killer whales roaming between northern Vancouver Island in British Columbia and the Puget Sound have not shown evidence of* C. gattii.

U.S. SCIENCE EDUCATION

In “Brain Exports” [Forum], Harold O. Levy expresses alarm at the percentage of graduate and undergraduate degrees in science and engineering awarded to foreign students in the U.S. He states that “the U.S. public education system … does not produce enough high school graduates who are qualified for college work.”

The number of U.S. students taking Advanced Placement exams has increased every year since their inception, and the majority of students have been passing them. Last year more than two million students took almost four million AP exams. The pass rate was generally around 60 percent. It seems that enough students are qualified to pursue higher education in science and technology but choose not to do so.

GEORGE SCHUTTINGER
Mountain View, Calif.

As a chemistry teacher in high school, I have watched the standards and testing increase while the breadth of the subjects narrows because we teach only what is on the test. Our school district has not even taught science in elementary schools for years because it is not tested. The more No Child Left Behind intruded into the school system, the less of a priority depth of understanding became. We need to get these “reformers,” who have never had a class of 38 students, out of education.

Furthermore, our students do not understand that education is a valuable commodity. If you want better schools, make education priority one at the dinner table.

ART ARONSEN
Vacaville, Calif.

More Americans don’t get Ph.D.s in engineering because it makes no economic sense. An engineer with a bachelor’s can give up, say, one year’s earnings to get a master’s and expect to make that back in three to four years from the higher salary. An engineer giving up three to five years’ earnings from a master’s to get a Ph.D. can expect to make the lost income back sometime between 20 years and never.

RICHARD J. WEADER II
via e-mail

INSECT FACIAL RECOGNITION

In “Good with Faces,” Elizabeth A. Tibbetts and Adrian G. Dyer describe their work showing that insects such as paper wasps and honeybees are able to recognize individual faces of others in their species.

Do these insects show a difference between the sexes in this ability?

Dennis Weber
Kalamazoo, Mich.

TIBBETTS AND DYER REPLY: There are likely to be sex differences in insect-face learning, although careful experimentation will be needed. Insects often vary within and between species in perceptually difficult tasks such as color discrimination. Bees and wasps are particularly likely to have cognitive differences across the sexes because the social lives of males and females are so distinct. We are planning experiments to address this question.

SECULARISM AND SOCIETY

In "Is God Dying?" [Skeptic], Michael Shermer's argument that religion is declining is short on hard and social science. Shermer gives one point from a supposedly longitudinal study but asserts time trend results. Likewise, he surmises that because religions help the poor, richer nations become less religious, yet he pronounces the U.S. über-religious. By the way, nonreligious societies have a pretty bad track record (Soviets, North Koreans, Nazis, etc.).

J. P. Harrison
Atlanta

SHERMER REPLIES: The U.S. has long been an outlier in religiosity among developed democracies, showing substantially higher rates. Recent surveys show that we may now be shifting to be more in line with comparable countries. As for the last point: National socialism was not an atheistic regime, and its exterminationist policies were clearly motivated by hegemonic politics and racial hygiene, not religion. The Soviet Union and the North Korean regime (not to mention the People's Republic of China) were and are officially atheistic, but nothing they did or are doing had or has religious motives.

ERRATA

"The Stuff of Dreams," by Gerbrand Ceder and Kristin Persson [World Changing Ideas], incorrectly spelled the name of Stefano Curtarolo of Duke University.

"Ugly Science Pays Off," by Rachel Feltman [Advances], refers to screwworms as worms. Screwworms are flies.

LETTERS TO THE EDITOR

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Letters may be edited for length and clarity. We regret that we cannot answer each one. Post a comment on any article at ScientificAmerican.com/apr2014

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Opinion and analysis from *Scientific American*'s Board of Editors

Preserve the Endangered Species Act

The most successful environmental legislation ever enacted faces new threats from Congress

A century ago an iconic, keystone species—the gray wolf—all but vanished from the continental U.S. Its loss was no accident. Rather it was the result of an eradication campaign mounted by ranchers and the government to protect livestock. Hunters shot, trapped or poisoned the wolves and received a bounty for each kill. Not even the national parks, such as Yellowstone, offered safe haven. Within decades the apex predator was nearly gone, a decline that triggered a cascade of changes down the food chain.

Today, however, in the 28,000-square-mile wilderness of the Greater Yellowstone Ecosystem, 400 gray wolves roam free. The Yellowstone wolves are among the 6,000 or so gray wolves that now inhabit the lower 48 states thanks to the Endangered Species Act (ESA). The act was signed into law in 1973 to protect endangered and threatened plants and animals, as well as the habitats critical to their survival. The ESA has prevented the extinction of 99 percent of the 2,000 listed species. It is widely considered the strongest piece of conservation legislation ever implemented in the U.S. and perhaps the world.

Yet for years the ESA has endured attacks from politicians who charge that it is economically damaging and ineffectual. Opponents argue that environmental groups use the legislation to file frivolous lawsuits aimed at blocking development. Moreover, they contend that the ESA fails to aid species' recovery. As evidence, they note that only 1 percent of the species that have landed on the protected list have recovered to the point where they could be delisted.

The latest assault comes in the form of the Endangered Species Management Self-Determination Act, a bill introduced by senators Rand Paul of Kentucky and Dean Heller of Nevada and Representative Mark Amodei of Nevada. The bill would, among other things, require state and congressional approval to add new species to the protected list—the U.S. Fish and Wildlife Service and the National Marine Fisheries Service do this now, based on the best scientific data available. It would also automatically delist species after five years and allow governors to decide if and how their states follow ESA regulations.

Senator Paul and others advocating for reform say that they want to improve the law to better serve imperiled species and local people. But their arguments are flawed. The reason why few species have recovered to the point where they can be delisted is not because the ESA is ineffective but because species take decades to rebound. In fact, 90 percent of the listed species are on track to meet their recovery goals.

In addition, lawsuits filed by environmental groups have led to many of the ESA's accomplishments. The ESA may require a development project to make modifications to address concerns about listed species, but the benefit of the ESA to ecosystems outweighs this inconvenience to developers. The changes critics are lobbying for, while undoubtedly appealing to groups such as farmers and loggers, would cripple the ESA.

Yet the flaws of this bill do not mean the ESA cannot be improved on. For example, Congress should help the private landowners who choose to act as stewards of their land. According to the Fish and Wildlife Service, about half of ESA-listed species have at least 80 percent of their habitat on private lands. Yet landowners have few incentives to preserve the habitats of threatened species. More financial and technical assistance needs to be made available to landowners who want to help protect the species on their property, as well as to people such as ranchers whose herds may be affected by the return of a species like the gray wolf.

Perhaps most important, conservation efforts must be updated to reflect what scientists now know about climate change and the threats it poses to wildlife. As temperatures rise, many more species will fall on hard times. Policy makers should thus increase ESA funding to allow more rigorous monitoring of wildlife and to protect more species.

Against the backdrop of budget cuts, setting aside more money to save animals and plants might seem like a luxury. Nothing could be further from the truth. Healthy ecosystems provide a wealth of essential services to humans—from purifying water to supplying food. We must preserve them for our own well-being and that of future generations. SA

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Illustration by Ross MacDonald

Commentary on science in the news from the experts

Kate Crawford is a principal researcher at Microsoft Research, a visiting professor at the Massachusetts Institute of Technology Center for Civic Media and a senior fellow at New York University's Information Law Institute.

Big Data Stalking

Data brokers cannot be trusted to regulate themselves

Many of us now expect our online activities to be recorded and analyzed, but we assume that the physical spaces we inhabit are different. The data-broker industry does not see it that way. To it, even the act of walking down the street is a legitimate data set to be captured, catalogued and exploited. This slippage between the digital and physical matters not only because of privacy concerns—it also raises serious questions about ethics and power.

The *Wall Street Journal* recently published an article about Turnstyle, a company that has placed hundreds of sensors throughout businesses in downtown Toronto to gather signals from smartphones as they search for open Wi-Fi networks. The signals are used to uniquely identify phones as they move from street to street, café to cinema, work to home. The owner of the phone need not connect to any Wi-Fi network to be tracked; the entire process occurs without the knowledge of most phone users. Turnstyle anonymizes the data and turns them into reports that it sells back to businesses to help them "understand the customer" and better tailor their offers.

Prominent voices in the public and private sectors are currently promoting boundless data collection as a way of minimizing threats and maximizing business opportunities. Yet this trend may have unpleasant consequences. Mike Seay, an OfficeMax customer, recently received a letter from the company that had the words "Daughter Killed in Car Crash" following his name. He had not shared this information with OfficeMax. The company stated that it was an error caused by a "mailing list rented through a third-party provider."

Clearly, this was a mistake, but it was a revealing one. Why was OfficeMax harvesting details about the death of someone's child in the first place? What limits, if any, will businesses set with our data if this was deemed fair game? OfficeMax has not explained why it bought the mailing list or how much personal data it contains, but we know that third-party data brokers sell all manner of information to businesses—including, as Pam Dixon, executive director of the World Privacy Forum, testified before the U.S. Senate last December, "police officers' home addresses, rape sufferers…, genetic disease sufferers," as well as suspected alcoholics and cancer and HIV/AIDS patients.

In the absence of regulation, there have been some attempts to generate an industry code of practice for location-technology companies. One proposal would have companies de-identify personal data, limit the amount of time they are retained, and prevent them from being used for employment, health care or insurance purposes. But the code would only require opt-out consent—that is, giving your details to a central Web site to indicate that you do not want to be tracked—when the information is "not personal."

The trouble is, almost everything is personal. "Any information that distinguishes one person from another can be used for re-identifying anonymous data," wrote computer scientists Arvind Narayanan, now at Princeton University, and Vitaly Shmatikov of the University of Texas at Austin in a 2010 article in *Communications of the ACM*. This includes anonymous reviews of products, search queries, anonymized cell-phone data and commercial transactions. The opt-out-via-our-Web-site model also compels customers to volunteer yet more information to marketers. And it is not clear that self-regulation will ever be sufficient. Most industry models of privacy assume that individuals should act like businesses, trading their information for the best price in a frictionless market where everyone understands how the technology works and the possible ramifications of sharing their data. But these models do not reflect the reality of the deeply unequal situation we now face. Those who wield the tools of data tracking and analytics have far more power than those who do not.

A narrow focus on individual responsibility is not enough: the problem is systemic. We are now faced with large-scale experiments on city streets in which people are in a state of forced participation, without any real ability to negotiate the terms and often without the knowledge that their data are being collected. SA

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Illustration by Skip Sterling

Dispatches from the frontiers of science, technology and medicine

THEORETICAL PHYSICS

The New Black Hole Battle

A decades-old paradox returns

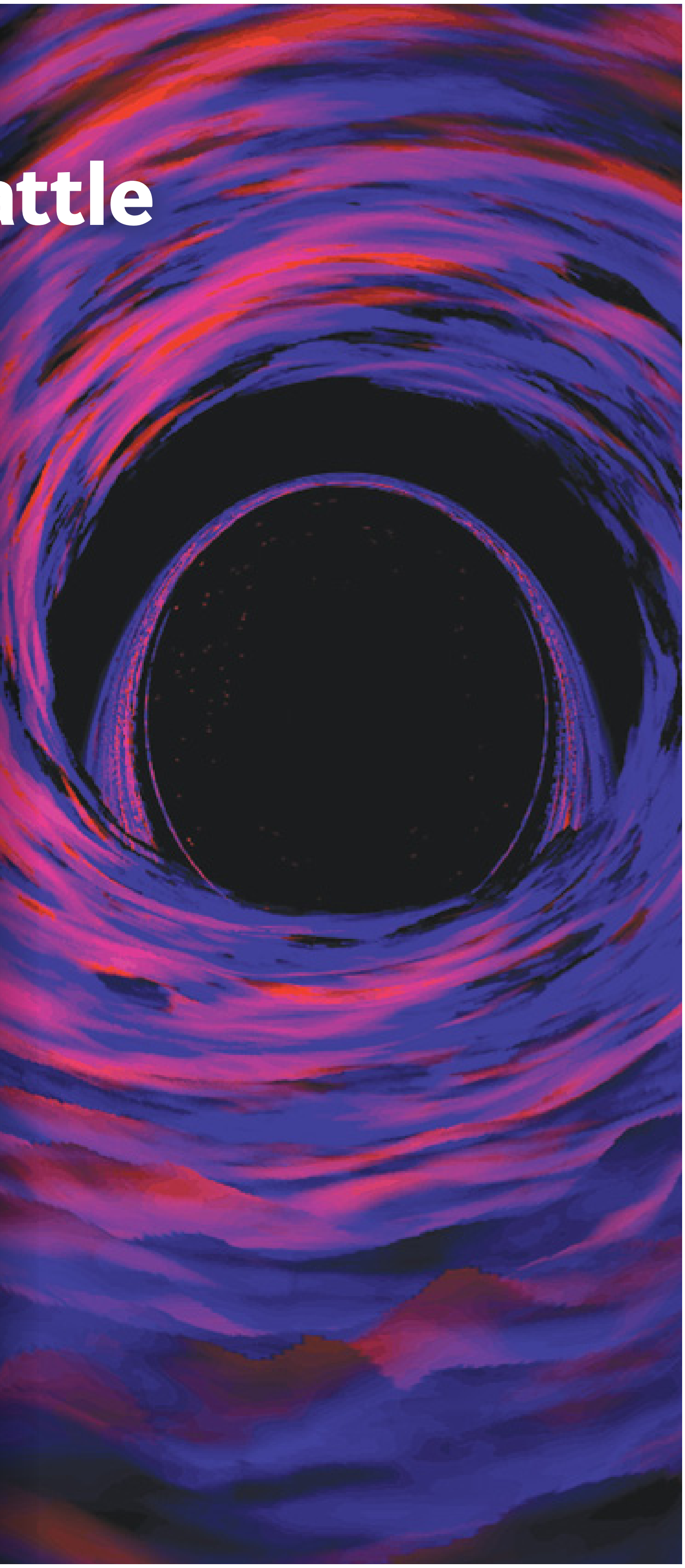
When Stephen Hawking was quoted earlier this year as saying that "there are no black holes," he wasn't really talking about black holes. At least not about black holes as you or I imagine them—astrophysical objects that suck in everything, even light. Those, everyone agrees, are just as black as ever.

Hawking's quip instead concerns black holes in a highly theoretical sense. Like many other theorists, Hawking has been trying to understand a paradox eating at the heart of physics. The issue—often referred to as the black hole firewall paradox—implies that physicists might have to abandon (or deeply modify) quantum mechanics or Einstein's general theory of relativity, or both.

The firewall problem is related to a paradox that Hawking first pointed out in the 1970s. It concerns this question: What happens to information that falls into a black hole? The rules of quantum mechanics require that information can never be lost. Even burning a book doesn't destroy the information inside—it just scrambles it up. But black holes *do* seem to destroy information, sucking it past the event horizon, a point of no return.

The black hole information paradox stumped physicists for two decades. It appeared to be solved in the late 1990s, when researchers figured out that information could leak out of a black hole in the form of Hawking radiation. Then, in 2012, physicists at the University of California, Santa Barbara, found flaws in the previous solutions. They concluded that an event horizon is not, as previously thought, an ordinary place. Instead it is a wall of fire that prevents Hawking radiation on the outside from remaining intertwined on a quantum level with material inside.

Hawking's latest work is an attempt to offer an alternative solution. He proposes that a black hole has an "apparent" horizon in addition to its event horizon. The two are nearly always identical. Information can rise from inside the black hole to the apparent horizon. At that point, quantum effects can blur the boundary between the "apparent" and "event" horizons, sometimes allowing information to escape. Hence, black holes would not be strictly black, provided you had hundreds of trillions of years to watch them. But ultimately, what Hawking's paper means is that there is something fundamental about black holes we still do not understand. —*Michael Moyer*



COURTESY OF J. SCHNITTMAN *NASA Goddard Space Flight Center*, J. KROLIK *Johns Hopkins University* AND S. NOBLE *Rochester Institute of Technology*

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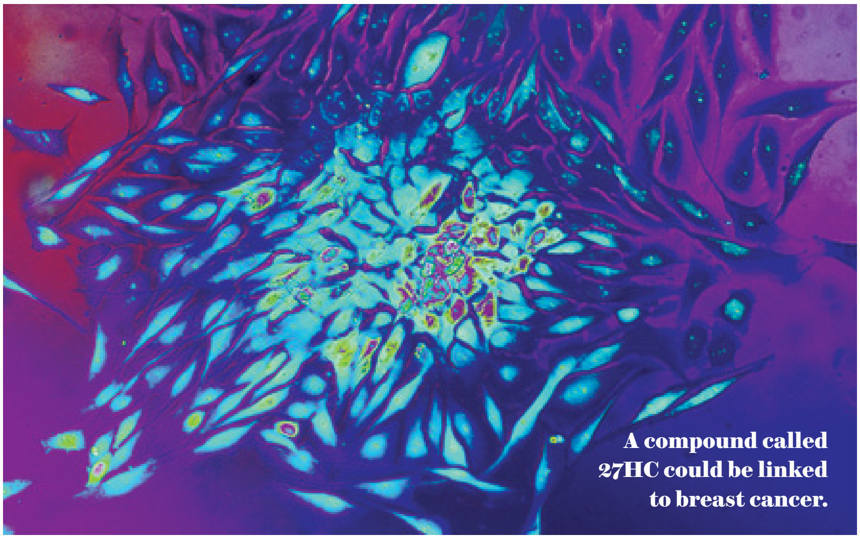

A compound called 27HC could be linked to breast cancer.

CECIL H. FOX *Science Source*

MEDICINE

Cancer Culprit?

A common product of cholesterol may fuel breast tumor growth

Scientists have long struggled to understand why women with heart disease risk factors are more likely to develop breast cancer. Now research suggests that high cholesterol may play an important role.

Estrogen drives the majority of breast cancers in women. The hormone binds to proteins known as receptors inside the tumor, helping it grow. So when Philip Shaul, a pediatrician and biologist at the University of Texas Southwestern Medical Center, and his colleagues learned that a common breakdown product of cholesterol also activates estrogen receptors, they thought they might be on to something. Teaming up with Duke University cancer biologist Donald McDonnell, they showed in 2008 that the cholesterol product, known as 27HC, spurs tumor growth in human breast cancer cells.

Building on their work, Shaul and McDonnell showed, in independent studies published in November 2013 in *Cell Reports* and *Science,* respectively, that 27HC drives cancer growth in mice harboring estrogen receptor–positive human breast tumors. Using samples from patients at his hospital, Shaul also found that 27HC levels were three times higher in the healthy breast tissue of women with breast cancer compared with that of cancer-free women; 27HC levels were 2.3 times higher still in tumor cells. Furthermore, cancer patients who had lower levels of an enzyme that breaks down 27HC in tumors were less likely to survive. When McDonnell's team fed mice high-cholesterol or high-fat diets, they were more likely than animals with normal diets to develop breast cancer, too. The two papers "bring 27HC to the 'limelight' of breast cancer research," says Sérgio Dias, a biologist at the Institute of Molecular Medicine in Lisbon.

It is still unclear, however, how blood cholesterol levels might affect breast cancer risk because Shaul found no consistent link between 27HC levels in human tumors and blood cholesterol levels. "But there may be subsets of women with high cholesterol at greater risk," he says.

The findings could have important treatment implications. They bolster the idea, backed already by one study, that cholesterol-lowering statin drugs may slow the progression of some breast cancers. And because between 30 and 65 percent of women with estrogen-fueled breast cancers do not respond to drugs that thwart estrogen production, the studies suggest that in some women "there's simply an entirely different driver of the cancer," Shaul says. —*Melinda Wenner Moyer*


WHEN SOMETHING NEEDS
TO BE DONE
YOU MAKE IT HAPPEN.

IMPORTANT FACTS

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

IMPORTANT SAFETY INFORMATION ABOUT VIAGRA

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

ABOUT ERECTILE DYSFUNCTION (ED)

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

ABOUT VIAGRA

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

VIAGRA does not cure ED.

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

VIAGRA is not a hormone or an aphrodisiac.

WHO IS VIAGRA FOR?

Who should take VIAGRA?

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

Who should NOT take VIAGRA?

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

BEFORE YOU START VIAGRA

Tell your doctor if you have or ever had:

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

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

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

POSSIBLE SIDE EFFECTS OF VIAGRA

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

The most common side effects are:

- Headache
- Feeling flushed
- Upset stomach

Less common side effects are:

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

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

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

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

HOW TO TAKE VIAGRA

Do:

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

Don't:

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

NEED MORE INFORMATION?

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

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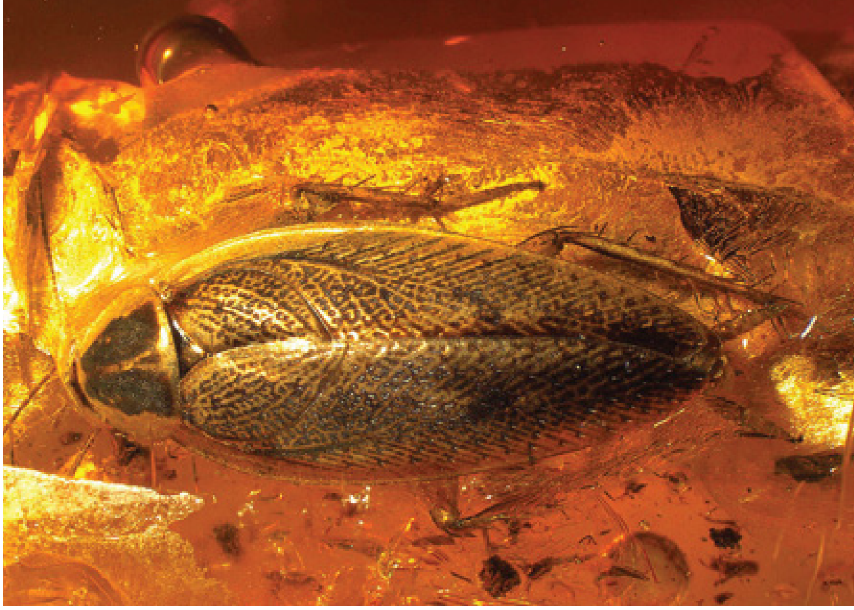


ENTOMOLOGY

Cockroach Homecoming

Once thought to be invasive, a bug reveals its American roots

In 1951 scientists thought they had found a new invader on American soil. *Ectobius,* a cockroach found throughout Europe and Africa, had begun turning up in homes in Massachusetts. Three decades later another *Ectobius* species, commonly known as the dusky cockroach, made an appearance in New Hampshire and then in Vermont. Eventually four *Ectobius* species were being tallied in the northeastern U.S.

But *Ectobius,* it turns out, is not really a stranger to North America at all. It has just returned home after an absence of 49 million years.

Entomologists got the mistaken impression that *Ectobius* was an Old World species back in 1856, when they found the first specimens in 44-million-year-old Baltic amber. That's how the matter sat for more than 150 years. Then, in 2010, Conrad Labandeira, a research scientist and curator of fossil arthropods at the Smithsonian National Museum of Natural History, invited Peter Vrsansky, a cockroach specialist at the Slovak Academy of Sciences, to examine some fossils that had been gathering dust for years in the Smithsonian Institution's collection. They had been taken from the Green River Formation in Colorado. "Lo and behold, [Vrsansky] said, 'This is *Ectobius*!'" Labandeira recalls.

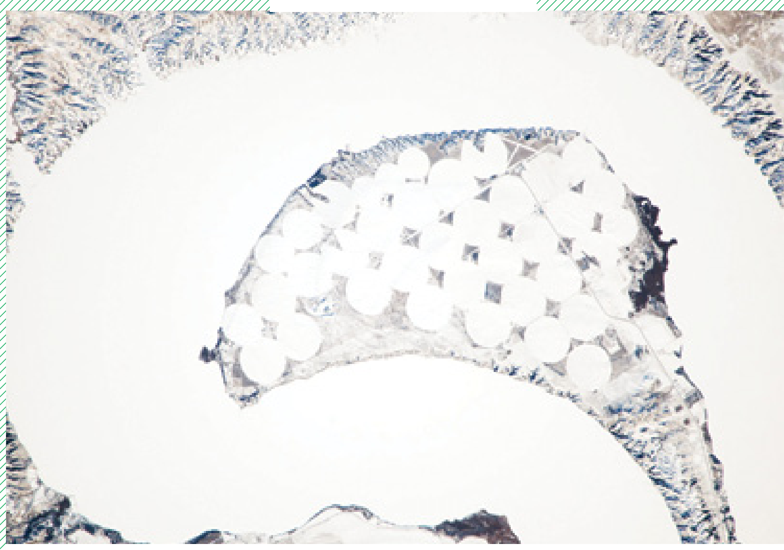
The 21 fossils had revealed four species of *Ectobius* dating back to the Eocene—predating the European specimens by some five million years. "It's amazing," Labandeira says, "how one little discovery can change the entire understanding of the history of this particular lineage of cockroaches."

Most likely, *Ectobius* went extinct in North America as a result of increasingly harsh conditions as the glaciers crept south. When that extinction occurred, exactly, is unknown, but before it happened, Labandeira says, some of the insects made a break for Europe, either traveling through Greenland or else scuttling across the Bering land bridge.

Recently announcing the news in the *Annals of the Entomological Society of America,* Labandeira and Vrsansky named one of the new cockroaches *Ectobius kohlsi*—a hat tip to the fossils' original discoverer, David Kohls, an amateur collector in Colorado who has amassed hundreds of thousands of fossil insects. The three other new *Ectobius* species, though preliminarily identified, did not possess enough detail for the researchers to name them.

"There are so many amazing, beautiful fossils, and so few people have had the chance to work on them," says Dena Smith, an associate professor of geological sciences at the University of Colorado Boulder. "I think there will be a lot more of this kind of exciting work to come." *—Rachel Nuwer*

WHAT IS IT?



On the frozen plains of central South Dakota, the Missouri River takes a dramatic turn known as a meander bend, creating the 130-kilometer-long Lake Sharpe. Meander bends form as fast-moving water erodes the outer bank and deposits sediment on the more placid inner bank. Eventually the Missouri River will cut through the skinny peninsula in the lower right of this image, creating a shorter path to the sea. In time, sediment deposition will sever Lake Sharpe from the river, forming what is called an oxbow lake—a freestanding, horseshoe-shaped body of water. *—Annie Sneed*

COURTESY OF PETER BARNA AND PETER VRSANSKY *(top)*; COURTESY OF NASA *(bottom)*

TECHNOLOGY

War Funding Inside?

Intel and other tech companies crack down on "conflict minerals"

It is hard to believe that our mundane social media banter could have an impact on the civil war that has been raging in the Democratic Republic of the Congo for more than a decade. The problem is not the content of these messages; it is the devices used to send them. Smartphones, tablets, PCs and other gadgets often have electronic components made from so-called conflict minerals—gold, tantalum, tin and tungsten—taken from specific mines in the D.R.C. that give a cut of their profits to armed groups.

Chipmaker Intel used the Consumer Electronic Association's International CES trade show in January to spotlight this problem and declare that its microprocessors are now free of conflict minerals. The company says it has taken steps to have its suppliers—in particular, the smelters that extract metals from mined ore—audited by third-party companies and to certify that they are not cooperating with extortion efforts that funnel money to local warlords.

The idea of conflict minerals was relatively obscure four years ago, when the Enough Project, a Washington, D.C.–based nongovernmental organization, brought the issue to Intel's attention. Intel's work has encouraged other companies to examine the sources of their products' raw materials, Enough Project senior policy analyst Sasha Lezhnev said at the International CES.

Tech companies do not use as much of these minerals as other industries, such as jewelry makers. Yet gold, tantalum, tungsten and tin play an important role in our gadgets. Like many device manufacturers, Intel relies on highly conductive gold in circuit cards, connectors and semiconductor packaging. The company uses tantalum in some of its capacitors and in the "sputtering" deposition process used to make its semiconductors. Tungsten also plays a limited role in the semiconductor fabrication process. Tin, meanwhile, is a key component in the silver-tin solder that attaches electronic components to their circuit boards.

Soon all companies will have to scrutinize their supply chains. In August 2012 the Securities and Exchange Commission began requiring firms to annually disclose the sources of the gold, tin, tungsten and tantalum used in their products. The U.S. Chamber of Commerce and the National Association of Manufacturers have filed a lawsuit against the SEC in response to its new rules, but companies will still have to get their first disclosure reports to the agency by May 31. —*Larry Greenemeier*

BY THE NUMBERS

5 billion

Number of years the JILA strontium atomic clock, developed by researchers at the National Institute of Standards and Technology and the University of Colorado Boulder, could tick away without gaining or losing one second.

COURTESY OF RESOLVE (*top*); SOURCE: NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (*bottom*)

DRUGS

Fuzzy Discovery

Researchers find potential cures on the backs of sloths

Treatments for human diseases often come from unexpected places. Several years ago microbiologist Sarah Higginbotham was talking with an ecologist colleague about how she looks for bioactive organisms—those that produce substances that inhibit the growth of other organisms. "When I told him I look for places where lots of organisms live together, he said, 'Sloths sound perfect,'" she says.

Sloths are microbial jackpots because they move so slowly and infrequently and because their fur contains microscopic grooves that create a perfect breeding ground for algae, fungi, bacteria, cockroaches and caterpillars.

Interest piqued, Higginbotham, during

a temporary research stay at the Smithsonian Tropical Research Institute in Panama, obtained hair samples from nine three-toed sloths—the famously sedentary, tree-dwelling mammals from Central and South America. From the samples, she identified 28 different fungal strains, several of which might represent new species. (Chemical testing could help determine whether they are in fact new species.) Higginbotham, now at Queen's University Belfast, and her colleagues published a paper in *PLOS ONE* confirming bioactivity in some of their fungal strains against the parasites that cause malaria and Chagas' disease, a breast cancer cell line and several types of harmful bacteria. In all, they discovered two dozen drug leads hiding in the fur of sloths. —*Rachel Nuwer*

Illustrations by Thomas Fuchs

COURTESY OF EVA DE MAS CASTROVERDE

BIOLOGY

Love Him or Eat Him?

Some female wolf spiders prioritize food over sex

Spider courtship is a risky business. In some species, females routinely decide that they would rather eat a male than mate with him, and researchers have struggled for decades to understand why. A recent experiment with a type of Spanish wolf spider suggests that the reason may depend on the spider's personality.

A virgin spider cannot be sure how many chances she will have to mate. Every male could be her last, and if she eats all of them, she will never reproduce. Why would a spider take this risk? One possibility is that females are choosy, holding out for large, healthy males with good genes and devouring the rest. Another possibility is the aggressive spillover hypothesis, which suggests that some females have strong predatory instincts that spill over into aggression toward potential mates. These females might eat males even when they would be better off mating with them.

To learn more about cannibalistic spiders, researchers at the Experimental Station of Arid Zones in Spain and their colleagues caught 80 juvenile females of the species *Lycosa hispanica*—a type of wolf spider—and fed them as much as they wanted while they matured. Some females put on weight more quickly than others. "Since all females had similar prey availability, we estimated that female growth rate would be the result of female voraciousness," says Rubén Rabaneda-Bueno, the study's lead author.

After each female molted to adulthood, the researchers placed a male in her enclosure. Females that ate their suitors were offered additional chances with new males. Most of the cannibal females were choosy. They ate males that were in poor condition and mated with males that were of high quality. "But we found that there were a few females that would consistently get a male and kill it and get another male and kill it—so they were really aggressive," says Jordi Moya-Laraño, the study's senior author.

The most aggressive females killed big, healthy males as often as they killed scrawny ones. The same females also had the highest growth rates, indicating that they were the most aggressive toward prey. "In this study, a female personality trait—her voracity toward prey—was correlated with her aggressiveness toward males," Rabaneda-Bueno says. "Our results provide evidence that different female personalities can lead to different outcomes in the interactions between males and females in a sexual cannibal."

—Nala Rogers

COMMENT AT ScientificAmerican.com/apr2014

ECOLOGY

Where Farmers and Birds Agree

Some species adapt well to no-till fields

As grassland has morphed into farmland across the American Midwest, wildlife diversity and abundance have declined. But for some birds things might not be so grim. Some grassland species appear to have adapted particularly well to no-till soybean fields, according to research published in March in the journal *Agriculture, Ecosystems, and Environment.*

Tilling is a process in which farmers remove weeds and loosen soil before seeding the ground, but no-till farming eschews that practice. Detritus from the previous season's harvest is left covering the ground, where it provides a nice foundation for nesting birds.

That birds were more likely to nest in no-till fields than in tilled ones was not terribly surprising. Rather it was "the extent that birds used no-till [fields], the species of birds we found nesting, and their nest success relative to what we consider quality habitat," says Kelly R. VanBeek, who conducted the study for a master's thesis at the University of Illinois at Urbana-Champaign.

James Herkert, director of the Office of Resource Conservation at the Illinois Department of Natural Resources, was also surprised by the species diversity in no-till fields, including several "that are of conservation interest such as eastern meadowlark, dickcissel [and] upland sandpiper." American robin nests were the most common found in both field types, which was also unexpected because robins tend to prefer nesting in trees and shrubs. It "shows just how adaptable they are," he says.

Nest loss was high in both types of fields, though. The birds whose nests were destroyed by machinery would have been spared if planting were delayed until June 1. But in the past 10 years farmers have planted, on average, 66 percent of soybeans by May 30, in part because soybeans have better yields if planted earlier.

The conflicting needs of farmers and wildlife "make finding win-win solutions challenging," Herkert says. Still, the researchers suggest that rather than buying small tracts of land to set aside as wildlife reserves, conservationists should work with farmers to implement more ecologically sustainable strategies, such as no-till farming.

—Jason G. Goldman

ENERGY

Solar Times Two

A hybrid approach combines the benefits of photovoltaic and solar-thermal technologies into a device the size of a fingernail

COURTESY OF FELICE FRANKEL *Massachusetts Institute of Technology*

The two most common ways of generating power from the sun both have their drawbacks. Photovoltaic cells, which absorb photons from sunlight and convert them to electricity, operate with only 20 percent efficiency. That is because they can use only photons within a certain range of wavelengths to excite electrons. Solar-thermal systems, which turn sunlight into heat and then into electricity, are more efficient than photovoltaics—because they can use the entire solar spectrum, they can reach efficiencies of 30 percent—but they are impossible to scale down to rooftop size. The usual solar-thermal setup involves vast mirror arrays that concentrate sunlight, heating liquid that eventually powers an electricity-generating turbine.

To overcome the limitations of the two approaches, researchers at the Massachusetts Institute of Technology have created a device that combines elements of both, which they described in a February study in *Nature Nanotechnology*. (*Scientific American* is part of Nature Publishing Group.)

Their fingernail-size invention is known as a solar-thermophotovoltaic device. The first thing it does is produce heat from sunlight. Carbon nanotubes—extremely efficient absorbers of sunlight, which convert nearly the entire solar spectrum into heat—take care of that step. The heat then flows into a photonic crystal, which is composed of layers of silicon and silicon dioxide. Once the photonic crystal reaches approximately 1,000 degrees Celsius, it begins to glow, emitting mostly photons of a wavelength well matched to the photovoltaic cell below. When those photons strike the photovoltaic cell, they generate electricity.

The process of transforming light into heat and then back into light—and, finally, into electricity—is not simple. So far the thermophotovoltaic device has achieved only 3 percent efficiency. But "this is just a starting point," says senior author Evelyn Wang. The key will be making it work on a larger scale. "If we can scale up, then we can get over 20 percent efficiencies," Wang says. *—Geoffrey Giller*

Black Knight Transformer could become the army's first flying car.

WARFARE

When Cars Fly

Military "Transformer" vehicles move closer to takeoff

The idea of a car taking off like a helicopter sounds like science fiction. But four years after the Pentagon funded its vision for a "Transformer" military flying machine, the project has found solid footing. Two prototype designs, one by aerospace and defense giant Lockheed Martin and one by aerospace start-up Advanced Tactics, offer possible paths for the automated flying car to become a reality on future battlefields ruled by robots.

A flying car or similar vehicle could be useful in inserting U.S. Navy SEALs into enemy territory, evacuating wounded soldiers from urban locations inaccessible to helicopters or resupplying spread-out military units. The U.S. Defense Advanced Research Projects Agency also wanted a vehicle that an ordinary soldier could operate without pilot training—a crucial specification that highlights the need for an autonomous "brain" similar to those that may one day operate battlefield drones and robots.

DARPA recently gave the go-ahead for Lockheed Martin to build and fly a Transformer prototype, now known as the Aerial Reconfigurable Embedded System (ARES), by mid-2015. ARES is not, strictly speaking, a flying car: it is an unmanned vertical-takeoff-and-landing drone capable of picking up a light ground vehicle such as a dune buggy. This approach makes it possible for ARES to also carry cargo and medical evacuation pods, as well as sensors for battlefield surveillance and reconnaissance. ARES also comes with ducted fans rather than a helicopter's open-rotor design, so it can fly faster than a helicopter and operate without exposing soldiers to rotating blades.

A different prototype developed independently of the DARPA effort by Advanced Tactics, an aerospace start-up in El Segundo, Calif., is more of a recognizable flying car. The Black Knight Transformer is designed to fly up to 150 miles per hour, with a range of almost 290 miles. Its flying capability comes from eight small, open rotors that can be stowed close to the vehicle's body when it is driving on the ground. The vehicle can also ramp up to 70 mph, with the automotive suspension and drivetrain of an off-road truck, and it packs a payload capacity of more than 1,000 pounds (or five passengers).

Advanced Tactics envisions its Transformers having the brains to fly medical evacuation and cargo resupply missions on their own—humans would drive the vehicles only on the ground. It conducted driving tests with a Black Knight Transformer prototype in December 2013 and scheduled a test flight for early this year.

Even if flying cars don't pan out, the push for smarter software in autonomous flying vehicles is worthwhile, says Paul Scharre, project director for the 20YY Warfare Initiative at the Center for a New American Security. Flying car software capable of taking off, flying and landing on its own would pave the way for smarter drone and robot swarms operating under the direction of a few human soldiers. Or it could allow the U.S. military to turn manned helicopters and other vehicles into unmanned robots ready to enter the danger zone. *—Jeremy Hsu*

BY THE NUMBERS

2,000 (+/−45)

Strontium atoms in the JILA atomic clock.

COURTESY OF ADVANCED TACTICS, INC. (*top*); SOURCE: NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (*bottom*)

COMMENT AT ScientificAmerican.com/apr2014

For people with a higher risk of stroke due to Atrial Fibrillation (AFib) not caused by a heart valve problem

I focused on finding something better than warfarin.

NOW I TAKE ELIQUIS® (apixaban) FOR 3 GOOD REASONS:

1 ELIQUIS reduced the risk of stroke better than warfarin.

2 ELIQUIS had less major bleeding than warfarin.

3 Unlike warfarin, there's no routine blood testing.

ELIQUIS and other blood thinners increase the risk of bleeding which can be serious, and rarely may lead to death.

Ask your doctor if ELIQUIS is right for you.

ELIQUIS is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation, a type of irregular heartbeat, not caused by a heart valve problem.

IMPORTANT SAFETY INFORMATION:

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

- **ELIQUIS can cause bleeding which can be serious,** and rarely may lead to death.

- **You may have a higher risk of bleeding if you take ELIQUIS and** take other medicines that increase your risk of bleeding, such as aspirin, NSAIDs, warfarin (COUMADIN®), heparin, SSRIs or SNRIs, and other blood thinners. **Tell your doctor about all medicines, vitamins and supplements you take.** While taking ELIQUIS, you may bruise more easily and it may take longer than usual for any bleeding to stop.

- Get medical help right away if you have any of these signs or symptoms of bleeding:
  - unexpected bleeding, or bleeding that lasts a long time, such as unusual bleeding from the gums; nosebleeds that happen often, or menstrual or vaginal bleeding that is heavier than normal
  - bleeding that is severe or you cannot control
  - red, pink, or brown urine; red or black stools (looks like tar)
  - coughing up or vomiting blood or vomit that looks like coffee grounds
  - unexpected pain, swelling, or joint pain; headaches, feeling dizzy or weak

- **ELIQUIS is not for patients with artificial heart valves.**

- **Before you take ELIQUIS,** tell your doctor if you have: kidney or liver problems, any other medical condition, or ever had bleeding problems.

Tell your doctor if you are pregnant or breastfeeding, or plan to become pregnant or breastfeed.

- **Do not take ELIQUIS if you** currently have certain types of abnormal bleeding or have had a serious allergic reaction to ELIQUIS. A reaction to ELIQUIS can cause hives, rash, itching, and possibly trouble breathing. Get medical help right away if you have sudden chest pain or chest tightness, have sudden swelling of your face or tongue, have trouble breathing, wheezing, or feeling dizzy or faint.

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

Please see additional Important Product Information on the adjacent page.

Individual results may vary.

Visit ELIQUIS.COM
or call 1-855-ELIQUIS

Eliquis®
(apixaban) tablets 5mg

IMPORTANT

FACTS

Eliquis® (apixaban) tablets ℞ ONLY

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

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

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

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

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

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

While taking ELIQUIS:

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

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

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

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

What is ELIQUIS?

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

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

Who should not take ELIQUIS?

Do not take ELIQUIS if you:

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

What should I tell my doctor before taking ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

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

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

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

How should I take ELIQUIS (apixaban)?

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

What are the possible side effects of ELIQUIS?

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

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

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

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

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

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

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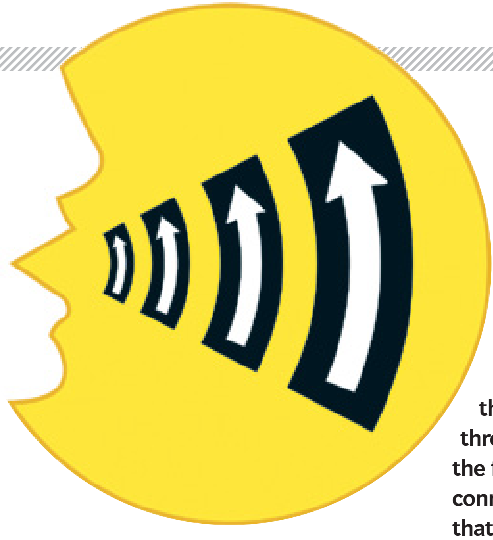

ACOUSTICS

One-Way Street for Sound

Engineers achieve the difficult task of transmitting acoustic waves in only one direction

One-way mirrors and one-way streets both permit flow in just one direction, but it is difficult to create something that permits sound or other waves to ripple in one direction and not the opposite. This is because of a fundamental property known as time-reversal symmetry. It usually makes no difference from what direction a sound is created—if you hear, you can be heard.

In January electrical engineer Andrea Alù and his colleagues at the University of Texas at Austin published results on a device that could make one-way sound transmission practical. Called an acoustic circulator, the device is analogous to isolators used in telecommunications and radar, which restrict the flow of microwaves and radio waves to one direction. In an isolator, electromagnetic waves pass through a material that has a magnetic field applied to it. Traveling through this magnetically altered material breaks the time-reversal symmetry of the wave.

To mimic the effect with sound, Alù and his colleagues installed three tiny fans in a resonant metal ring; the fans blow air (the medium that transmits sound in the device) through the ring at a speed matched to the frequency of the sound. The ring is connected to three equally spaced ports that can carry sound waves in and out of the ring. When the fans are off, sound from one port will flow to both other ports with equal strength. But when the fans are turned on, the airflow interrupts the time-reversal symmetry of the sound waves passing through it. The result: nearly all sound ripples to one receiving port and not the others, in a direction counter to the airflow.

Using off-the-shelf components, the Texas investigators' acoustic oscillator suppressed the amount of sound traveling in the undesired direction by 10,000. The findings were detailed in the January 31 issue of *Science*. "They used a very clever idea to make something that had never been made before," says electrical engineer Steven Cummer of Duke University, who did not take part in this research. Cummer notes that this device works only for very specific sound frequencies and that future work might focus on controlling wider ranges of frequencies.

Alù and his associates are now also pursuing a device for one-way sound transmission that has no moving parts. The finding could lead to new kinds of soundproofing, noise control and sonar. In addition, further studies could lead to new methods for manipulating light and radio waves, Alù says. —*Charles Q. Choi*

BY THE NUMBERS

430 trillion

Number of times the strontium atoms in the JILA atomic clock tick each second. The "ticks" occur as strontium atoms transition between energy states. Scientists measure this frequency both to keep time and to determine the clock's stability.

SOURCE: NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY

HEALTH

Antibiotic Overkill

A new approach may help curb unnecessary prescriptions

Antibiotics kill bacteria, not the viruses that cause the common cold and the flu. Yet doctors frequently overprescribe them—out of habit or to satisfy patients' demands—fueling antibiotic resistance.

The U.S. Centers for Disease Control and Prevention reports that up to 50 percent of antibiotic prescriptions in the U.S. are unnecessary or not optimally effective as prescribed.

One new approach may help curb the drugs' overuse. A recent randomized controlled study reported that having clinicians sign a letter pledging to "avoid prescribing antibiotics when they are likely to do more harm than good" reduced inappropriate antibiotic use during flu season. Pledged physicians reduced prescribed antibiotics by about one third compared with unpledged ones. The findings appeared online January 27 in *JAMA Internal Medicine.*

In the study, seven clinicians—doctors or nurse-practitioners—signed a poster-size commitment to follow prescription guidelines. The letter, which was displayed in exam rooms, also explained that antibiotics cannot cure colds but do cause side effects and contribute to drug resistance. Seven other clinicians served as controls and did not sign a letter or alter their normal practices.

Providers who signed the commitment letter reduced unnecessary prescriptions by about one fifth during the intervention period, whereas those who did not sign a poster increased their inappropriate prescribing rates by about one fifth. Still, even the poster-signing clinicians appear to have provided antibiotics to patients who did not need them roughly one third of the time.

Previous studies have looked at the effects of posting guideline reminders, but they did not include signed commitment letters and did not report the same level of success. "Our hypothesis is that this commitment device is a key difference between our intervention and past work," asserts lead author Daniella Meeker, a scientist at Rand Corporation who focuses on health and behavioral economics.

The study does not settle the matter. The findings need to be replicated with a larger group of physicians. Yet if the approach triggers similar responses in other settings, the authors say it could theoretically eliminate 2.6 million unnecessary prescriptions and save $70.4 million in drug costs nationwide. *—Dina Fine Maron*

GETTY IMAGES

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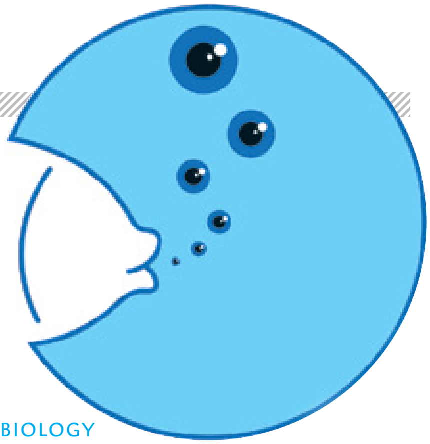

BIOLOGY

Evolution's Little Helper

A protein may have eased a fish's transition from rivers to caves

In the classic view of evolution, organisms undergo random genetic mutations, and nature selects for the most beneficial ones. A recent study in *Science* adds a twist to that theory: variability already present in a population's genome may remain hidden in times of plenty but come unmasked in stressful situations, ready to help with adaptation.

At the theory's core is a protein called HSP90. It binds to other proteins to keep them properly folded. Work over the past few decades by Susan Lindquist, a professor of biology at the Massachusetts Institute of Technology and a co-author of the *Science* paper, has established that when HSP90 is distracted from that task, as might occur in a stressful new environment, traits that were once uniform suddenly show lots of variation.

The thought is that when HSP90 holds proteins in a certain shape, it compensates for minute variations that have crept into them over generations. When stress diverts HSP90, the proteins' alternative forms are released, triggering the wider variety in traits. Natural selection can then act on those new traits, spurring adaptation.

The study's lead author, Harvard Medical School's Nicolas Rohner, tested the idea on the Mexican tetra, a river-dwelling fish. In the distant past, populations of Mexican tetra ended up in underwater caves, a new environment to which the fish adapted by losing their eyesight.

Rohner and his colleagues raised surface fish in water treated with an HSP90 blocker. Those fish, they found, had greater variations in eye and eye-socket sizes. Stressing surface fish with water chemically similar to cave water also yielded offspring with a greater than normal variety of eye sizes.

Although the findings do not prove that HSP90-masked variation helped the fish change their eyes, they lend the idea plausibility. Exactly how stress on HSP90 induces variation is still mysterious, but it is a topic of active research. —*Veronique Greenwood*

Carina Storrs is a freelance science and health writer whose work has appeared in *Popular Science, The Scientist* and Health.com, among other publications.

Hidden Dangers of Going Under

Anesthesia may have lingering side effects on the brain, even years after an operation

Two and a half years ago Susan Baker spent three hours under general anesthesia as surgeons fused several vertebrae in her spine. Everything went smoothly, and for the first six hours after her operation, Baker, then an 81-year-old professor at the Johns Hopkins Bloomberg School of Public Health, was recovering well. That night, however, she hallucinated a fire raging through the hospital toward her room. Petrified, she repeatedly buzzed the nurses' station, pleading for help. The next day she was back to her usual self. "It was the most terrifying experience I have ever had," she says.

Baker's waking nightmare was a symptom of postoperative delirium, a state of serious confusion and memory loss that sometimes follows anesthesia. In addition to hallucinations, delirious patients may forget why they are in the hospital, have trouble responding to questions and speak in nonsensical sentences. Such bewilderment—which is far more severe than the temporary mental fog one might expect after any major operation that requires general anesthesia—usually resolves after a day or two.

Although physicians have known about the possibility of such confusion since at least the 1980s, they had decided, based on the then available evidence, that the drugs used to anesthetize a patient in the first place were unlikely to be responsible. Instead, they concluded, the condition occurred more often because of the stress of surgery, which might in turn unmask an underlying brain defect or the early stages of dementia. Studies in the past four years have cast doubt on that assumption, however, and suggest that a high enough dose of anesthesia can in fact raise the risk of delirium after surgery. Recent studies also indicate that the condition may be more pernicious than previously realized: even if the confusion dissipates, attention and memory can languish for months and, in some cases, years.

IN TOO DEEP

ANESTHESIA COMES IN THREE MAIN TYPES. Local anesthesia, the mildest form, merely numbs a very small area, such as a single tooth. Regional anesthesia desensitizes a large section of someone's body by injecting drugs into the spine that block nerve signals to the brain. Often a patient getting regional anesthesia also takes a relatively small dose of a powerful sedative drug, such as propofol—not enough to put them under but enough to alter brain activity in a way that makes the person less aware and responsive.

General anesthesia relies on a cocktail of drugs that renders patients completely unconscious, prevents them from moving and blocks any memories of the surgery. Although anesthetic drugs have been around since 1846, many questions remain as to how exactly they work. To date, the strongest evidence suggests that the drugs are effective in part because they bind to and incapacitate several different proteins on the surface of neurons that are essential for regulating sleep, attention, learning and memory. In addition, it seems that interrupting the usual activity of neurons may disrupt communication between far-flung regions of the brain, which somehow triggers unconsciousness.

When postoperative delirium was first recognized, researchers wondered whether certain anesthetic drugs—but not others—deserved the blame. Yet studies comparing specific drugs and rates of delirium in patients after surgery have always been scant and inconclusive. "No particular anesthetic has been exonerated in patients," says Roderic G. Eckenhoff, a professor of anesthesiology at the University of Pennsylvania. But "we can't say yet that there is an anesthetic that patients should not get."

One reason scientists struggled to say whether sedative drugs were at fault was the difficulty of separating them from other major hospital stresses, such as surgery itself. Indeed, many of the things that make being hospitalized so unpleasant—poor sleep, restricted movement and a regimen of medicines—can also cause confusion, forgetfulness and even delusions.

In spite of these difficulties, researchers hit on two other factors that increased the chances a patient would become dra-

Illustration by Ashley Mackenzie

matically confused after an operation: being older than about 70 and having preexisting mental deficits, such as regularly forgetting appointments or severe dementia. Delirium is also more common after major surgeries—which can last at least a few hours and require patients to stay one night or longer in the hospital. Among patients above age 60 about 50 percent become seriously disoriented after heart bypass or valve replacement surgery, according to one study, yet the same is true for only 15 percent or so of patients in the same age range who have elective hip joint surgery—a shorter and less risky procedure.

Research over the past several years has revived anesthesia as a potential culprit in delirium: instead of focusing on the type of anesthetic drug, scientists are now concerned about the amount of overall anesthesia. Researchers suspect that the more anesthesia someone receives—and, consequently, the deeper someone slips into unconsciousness—the greater the risk of delirium. In one study, for example, Frederick E. Sieber of the Johns Hopkins University School of Medicine and his colleagues gave 57 elderly hip surgery patients enough propofol to achieve regional anesthesia and another 57 patients enough propofol to induce general anesthesia. Eleven of the lightly anesthetized patients became delirious after the operation, compared with 23 of the patients under general anesthesia.

A related study offers a clue as to why previous research failed to see a difference in rates of delirium between patients receiving general and regional anesthesia. Sieber tracked 15 patients aged 65 years and older who were all undergoing surgery to repair fractured hips. The team gave the patients regional anesthesia consisting of propofol and an anesthetic that disabled nerves in the spinal cord. Based on standard practice, the team monitored blood pressure and heart rate as a proxy for depth of anesthesia to determine the appropriate dose. Meanwhile a computer, which the team could not see, also determined the depth of anesthesia based on a more direct but less commonly used measurement: electrical activity in the patients' brain, as gauged by electrodes attached to their forehead. The fewer electrical impulses crackling through their brains, the deeper the anesthesia. Eighty-seven percent of patients' brain activity dipped low enough to qualify as general anesthesia during at least part of the surgery.

"I was flabbergasted," Sieber says. Because of this study and similar findings, he suspects that it is common for patients getting regional anesthesia to receive so much sedative drug that they are actually in a state of general anesthesia.

LASTING EFFECTS

DEEP ANESTHESIA has also been linked to subtler but longer-lasting cognitive problems. In a 2013 study, doctors at a Hong Kong hospital monitored the brain activity of 462 patients undergoing major surgery, keeping the electrical activity as high as possible while still inducing general anesthesia. For another 459 patients receiving general anesthesia, the doctors monitored only blood pressure and heart rate. Patients received either propofol or one of several anesthetic gases. The morning after surgery, 16 percent of patients who had received light anesthesia displayed confusion, compared with 24 percent of the routine care group. Likewise, 15 percent of patients who received typical anesthesia had postoperative mental setbacks that lingered for at least three months—they performed poorly on word-recall tests, for example—but only 10 percent of those in the light anesthesia group had such difficulties.

In some cases, these mental handicaps persist longer than a few months. Jane Saczynski, an assistant professor of medicine at the University of Massachusetts Medical School, and her colleagues tracked the mental abilities of patients 60 years and older in the Boston area for up to one year after heart bypass or valve surgery. Based on tests of memory and attention in which patients repeated phrases and named everyday objects, those who did not develop any delirium generally regained their presurgery mental capabilities within a month, whereas patients with postoperative delirium took between six months and a full year to recuperate. Patients whose mental fog lasted more than three days after surgery had still not regained their full acumen a year after the operation.

Although researchers remain uncertain about how anesthetic drugs might usher in a state of postoperative delirium, they have some ideas. The drugs may have an easier time overwhelming neurons in older adults because the proteins that anesthetic drugs are thought to target on the surface of neurons become less abundant with age. Some experts have suggested that in elderly patients, the brain may also have a harder time refashioning the connections between different regions that could break down during anesthesia.

PRELIMINARY PROTECTIONS

AS RESEARCHERS CONTINUE TO LOOK for more precise answers about postoperative delirium, clinicians are adopting a number of strategies to minimize risk. Doctors at John Hopkins and other hospital settings now constantly talk with elderly patients during regional anesthesia, making sure they can respond to their name. Sieber thinks this practice could be at least as effective a gauge of the depth of anesthesia as brain activity and could be superior to blood pressure and heart rate measurements.

Other precautions include making sure patients are well hydrated and nourished before surgery, which likely improves blood flow to the brain. After surgery, experts recommend orienting patients to their hospital stay by encouraging family and friends to visit, getting them up and out of bed during the day, encouraging a good night's sleep, and discontinuing any medications that could further alter brain activity. Although it remains unclear exactly how these interventions help, physical and mental activities stimulate communication between nerve cells, which could reestablish vital connections between brain regions.

For her part, Susan Baker has always made an effort to be as active as possible and to spend time with loved ones following the various surgeries in her life, just because it has seemed like a good way to spur recovery. But when she had to have another procedure after her delirious episode, she took a couple of extra precautions—asking her son to stay in her hospital room that night, for example. And before her operation, she made a special request: to keep the anesthesia as light as possible. SA

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

The Great Net Debate

Who gets to control what's passing through those pipes?

Good evening, ladies and gentlemen, and welcome to "Intractable Tech Battles!" Today—net neutrality! Yes, net neutrality: it's in the news, it's just been in the courts and, sooner or later, it will affect you! It's my pleasure to introduce Pro, who's in favor of net neutrality, and Con, who's against it.

Pogue: Now, Pro, whose side do you represent?
Pro: Why, nearly every proconsumer organization on earth, including the Consumers Union and Common Cause. Also, the creators of the Internet (including Vinton Cerf) and the Web (including Tim Berners-Lee). And every true believer in free speech, innovation and the American way.
Pogue: And you, Con?
Con: I represent the companies that bring America its Internet, including Verizon, Comcast, AT&T and Time Warner.
Pogue: Okay, Pro, let's start simple: What is this "network neutrality"?
Pro: It's the idea that all Internet data should be equal. That the Comcasts and Verizons of the world can provide the pipes but should have no say in what passes through them. The Internet providers shouldn't be allowed to charge different companies more or less for their data or to slow down, or block, access to Web sites and services they don't like.
Pogue: Isn't that the way the Internet has always been?
Pro: Yes. Neutrality has been a core democratizing principle of the Internet since the day it was born. Internet service should be like phone service: the phone company can't make the connection worse if they don't approve of the person you're calling.
Con: But times have changed. Today Netflix and YouTube videos clog our pipes with enormous amounts of data. Or consider the BitTorrent crowd, which uses our lines to download insane exabytes of software, movies and music—illegally. Or how about Google and Skype? They've created services that let people make phone calls—for free—on networks that we spent billions to build. Why shouldn't all those services pay their share?
Pro: Because net neutrality protects innovation. If big companies such as Netflix and Google could pay to get special treatment—faster speeds, more bandwidth—little start-ups would be at a disadvantage.
Con: Net neutrality is *stifling* innovation! If we could charge higher fees to the biggest bandwidth hogs, we could afford to build advanced fiber networks that permit all kinds of new Internet services.
Pro: But what about freedom of speech? Without net neutrality, Comcast could give priority to video from TV networks it owns—such as NBC—and slow down the signals from its rivals.
Con: We wouldn't do that. Pinky swear. Verizon said that giving "unblocked access to lawful Web sites … will not change."
Pro: Oh no? Then why was Verizon the company that led the charge to strike down net neutrality in court?
Con: Ah, you mean the District of Columbia Circuit Court of Appeals decision in January. Yes, the court already struck down the Federal Communications Commission's 2010 net neutrality rules—proving that I've been right all along.
Pro: You were never right. The FCC lost that one on a technicality. And the American public will ultimately be the losers.
Con: You call that a technicality? It was the FCC itself that originally classified us Internet providers as an "information service," which isn't susceptible to much regulation, instead of a "telecommunications service," which is. It's the FCC's fault.
Pro: On that point, you are correct. The FCC chair who voted for that initial *mis*classification is now the chief lobbyist for the telecom companies. It was a fox-in-the-henhouse situation—one that the current chair, if he has any backbone, will quickly reverse, despite his own background lobbying for big telecoms.
Pogue: And I'm afraid that's all the time we have. Join us next time! If your Internet provider allows it. SA

SCIENTIFIC AMERICAN ONLINE
Battle history of the net neutrality war: ScientificAmerican.com/apr2014/pogue

Illustration by Scott Brundage

Not long after the big bang's flash, all light left

FIRST STARS in the universe were unimaginably large—perhaps a million times the mass of our sun. They would have helped clear the fog enshrouding the early universe before dying in supernova explosions, seen here in an artist's impression.

ASTRONOMY

the first starlight

the cosmos. Astronomers are now solving the mystery of its return

By Michael D. Lemonick

Michael D. Lemonick is a writer at Climate Central, a nonprofit news site, and author of *Mirror Earth: The Search for Our Planet's Twin* (Walker Books, 2012). For 21 years he was a science writer for *Time* magazine.

ABOUT 13.8 BILLION YEARS AGO, just 400,000 years or so after the big bang, the universe abruptly went dark.

Before that time, the entire visible universe was a hot, seething, roiling plasma—a dense cloud of protons, neutrons and electrons. If anyone had been there to see it, the universe would have looked like a pea soup fog, but blindingly bright.

Around the 400,000-year mark, however, the expanding universe cooled enough for hydrogen atoms to form at last—an event known as recombination. The fog lifted, the universe continued to cool and everything quickly faded to black. After the unimaginable brilliance of the big bang and its immediate aftermath, the cosmos entered what astronomers call the dark ages of the universe.

And dark they were. For even when the first stars started to ignite, their light shone brightest in the ultraviolet portion of the spectrum—just the kind of light that the newly formed hydrogen gas tends to absorb. The universe traded its primordial hot, bright fog for one that was cool and dark.

Eventually this fog would lift, but how it did so is a question that has long baffled astronomers. Maybe it was accomplished by the first stars, whose intense light gradually but relentlessly broke the hydrogen apart in a process called reionization. Perhaps instead the energy for reionization came from the radiation that is generated by hot gas spiraling into giant black holes.

The key to figuring out how and when reionization took place, unsurprisingly, is finding the oldest objects in the universe and trying to tease out their nature and their origins. When did the first stars turn on, and what were they like? How did individual stars assemble themselves into galaxies, and how did those galaxies form the supermassive black holes that lie at the core of nearly all of them? At what point in this progression from stars to galaxies to black holes did reionization take place? And was the process gradual or abrupt?

Astrophysicists have been asking many of these questions since the 1960s. Only recently, however, have telescopes and computer models gotten powerful enough to offer some answers: the latter by simulating the emergence and evolution of the first stars in the universe, and the former by gathering telltale glimmers of light from less than half a billion years after the big bang—a time when the first galaxies were in their infancy.

SUPERSTARS

A DECADE OR SO AGO astronomers believed that they had a good handle on how the first generation of stars came to be. Immediately after recombination, the hydrogen atoms that filled the cosmos were spread uniformly through space. In contrast, dark matter, which physicists believe to be made of invisible particles that have not yet been identified, had already begun clumping together in clouds known as halos, averaging somewhere between 100,000 and one million solar masses. Gravity from these halos sucked in the hydrogen. As the gas became increasingly concentrated and heated up, it flared into light, creating the first stars in the universe.

In principle, this first generation of giant stars, known to astronomers as Population III stars, could have broken up the veil of hydrogen gas and reionized the universe. But much

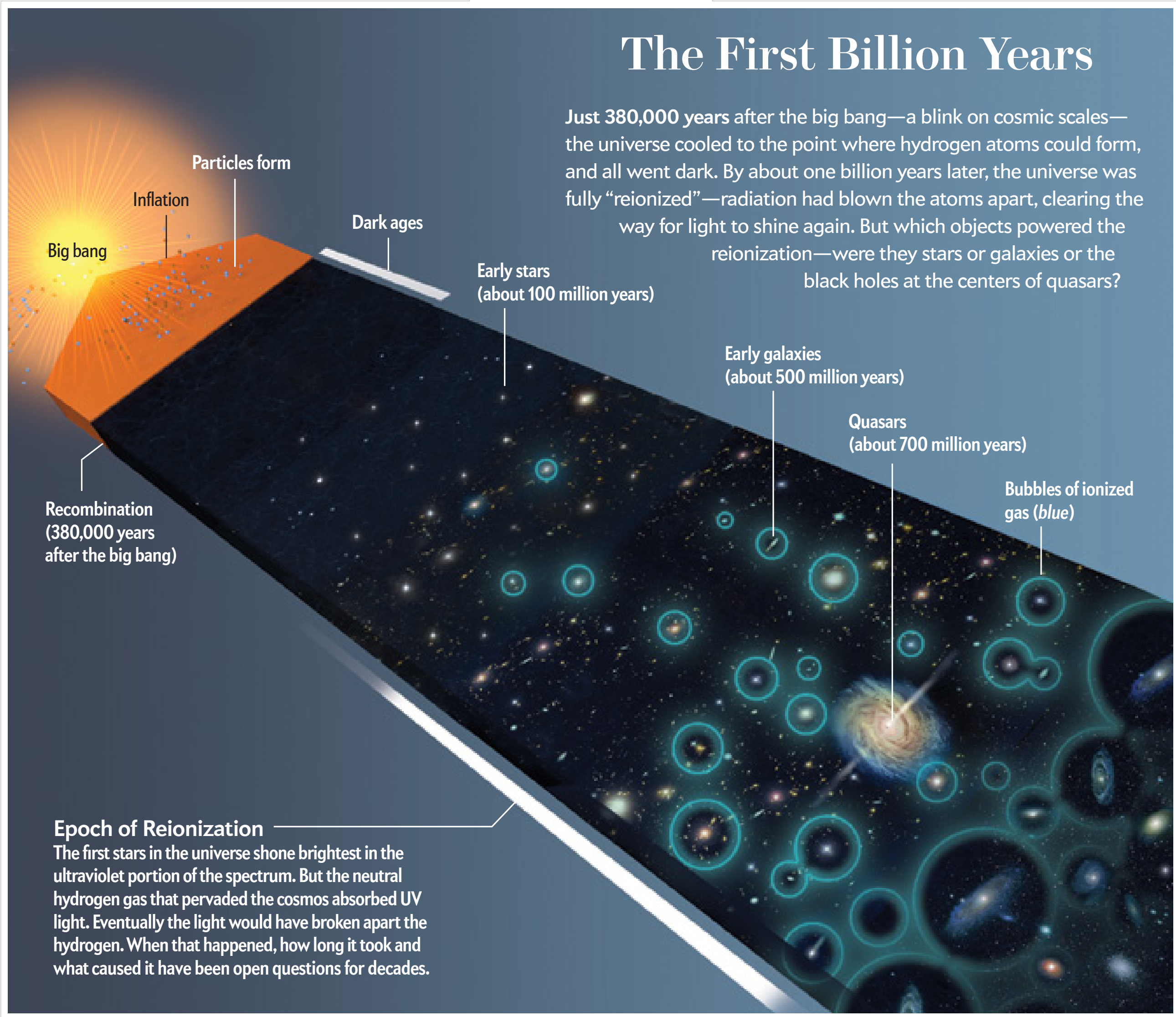
IN BRIEF

The universe's very first stars and galaxies were not like the objects we see today. Astronomers are reaching back in time to probe how the first objects in the universe came to be.

They are particularly interested in what caused the so-called reionization of the universe, when the neutral hydrogen atoms pervading the cosmos were broken up by light.

Observations and computer simulations suggest that the objects driving reionization could be million-solar-mass stars or the gaseous belches of enormous black holes.

PRECEDING PAGES: COURTESY OF ADOLF SCHALLER AND NASA



depends on the exact characteristics of these stars. If they were not bright enough or did not live long enough, they would not be capable of finishing the job.

The characteristics of these stars depend strongly on their size. As of a decade ago, astronomers believed that they would be uniformly gigantic, each with roughly 100 times the mass of the sun [*see box on next page*]. The reason: As a clump of gas tries to collapse under gravity, it heats up. The heat creates so-called radiation pressure that opposes gravity; unless the star can shed some of this heat, the collapse will stall.

The first stars were made mostly of hydrogen, which is relatively terrible at shedding heat. (Stars like our sun also have small but critical traces of elements such as oxygen and carbon, which help them to cool.) As a result, a protostar in the early universe would continue to accumulate hydrogen gas, but the high pressure would prevent it from forming a dense core that would burst into a fusion reaction—one that drives much of the surrounding gas back out into space. The star would just gorge itself on more and more gas until it built a massive, diffuse core.

Now, however, says Thomas Greif, a Harvard University postdoctoral fellow who creates some of the most sophisticated simulations of early star formation, "things look a bit more complicated." These newest simulations include not just gravity but also equations describing the feedbacks generated by increasingly pressurized hydrogen as the gas collapses. It turns out that the collapse of a hydrogen cloud can play out in many different ways. In some cases, the first stars could have been up to a *million* times as massive as the sun. In others, the collapsing cloud would have fragmented, creating several stars of just a few tens of solar masses.

These size differences imply huge variations in the possible lifetimes of the first stars—and therefore in when reionization might have occurred. Giant stars of 100 solar masses or more are the rock 'n' rollers of astronomy: they live fast and die young. Smaller stars would churn through their nuclear fuel more slowly, implying that if stars were responsible for reionization, the process would have been a long-drawn-out one, spanning many hundreds of millions of years.

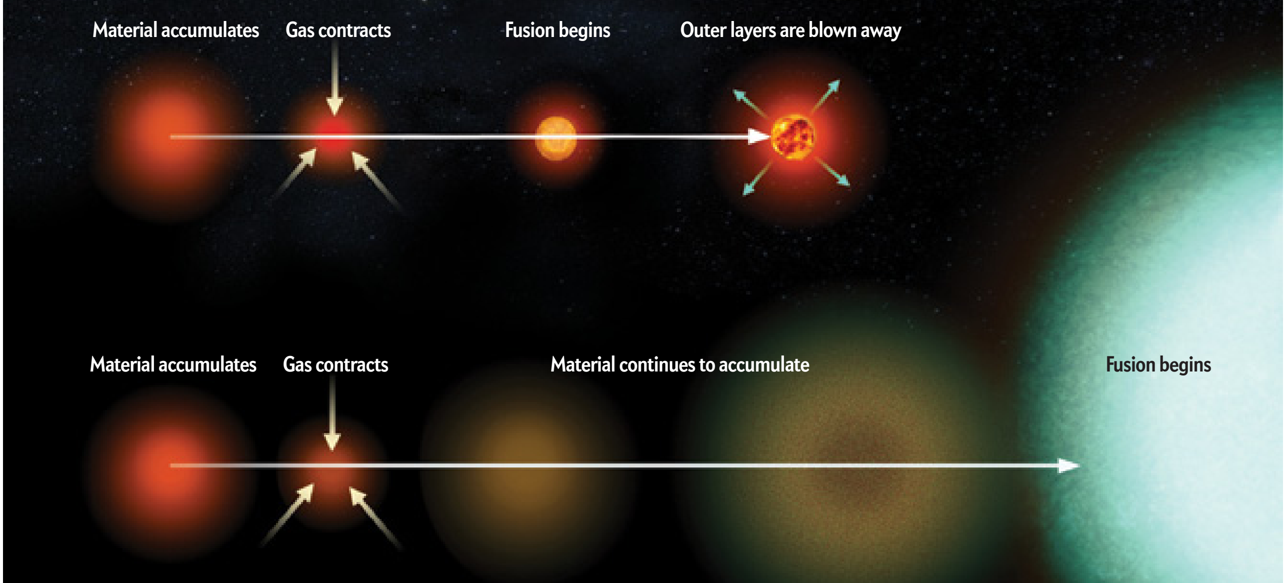
Illustrations by Moonrunner Design

Young Giants of the Universe

Why were the first stars so large? All stars execute a cosmic balancing act—gravity attempts to squeeze them as tight as possible, but the gas pressure inside the star fights against gravity and keeps the star inflated. By comparing star formation in the modern universe with star formation in the early universe, we can begin to understand why the universe's first stars were so massive.

Star Formation Now

Modern galaxies are littered with ingredients such as carbon, oxygen and dust. These materials help gases to cool. Cool clouds have lower pressures. Lower pressure means a collapsing cloud of dust can contract until its core is extremely dense—dense enough to get the hydrogen in its center to undergo thermonuclear fusion. After fusion begins, the sudden burst of energy blows away the outermost layers of the collapsing cloud, leaving a relatively small star behind.



Star Formation Then

The early universe did not have any carbon, oxygen or dust—only hydrogen, with a smattering of helium and lithium. Hydrogen does not cool very efficiently. As gas clouds began to collapse, the hot hydrogen kept the density in early protostars low. Without enough density to initiate fusion, the gas clouds continued to accumulate more and more gas—anywhere from 100 to one million suns' worth. Only then would they get hot and dense enough to initiate fusion.

BLACK LIGHTS

HOWEVER LARGE THEY WERE, all these stars would have ended their existence in fiery supernovae before collapsing into black holes. And these black holes—perhaps more than the stars from which they came—may have fueled the engine of reionization.

Black holes swallow nearby gas voraciously, and as the gas falls in, it is compressed and heated to temperatures of millions of degrees. It is so hot that while most of the gas eventually disappears into the black hole, some spews back out into space in the form of jets, which shine so brightly that the light can be seen halfway across the cosmos. We call these beacons quasars.

From the 1960s through the 1990s, quasars were really the only way to probe the early universe. At first, astronomers had no clue what they were. Quasars looked like nearby stars but had huge redshifts—a reddening of their light caused by the expansion of the universe. The impressive redshifts indicated that quasars were vastly farther away than any stand-alone star could possibly be and were thus vastly brighter as well. The first one ever found, 3C 273, had a redshift of 0.16, indicating that its light had begun traveling about two billion years ago.

"Then, very quickly," says Princeton University astrophysicist Michael A. Strauss, "people found quasars up to redshift 2"—a look-back time of more than 10 billion years. By 1991 Maarten Schmidt, James E. Gunn and Donald P. Schneider, working together at Palomar Observatory in California, had found a quasar with a redshift of 4.9, dating to 12.5 billion years before the present, or just a billion years and change after the big bang.

Yet analyses of the redshift 4.9 quasar found no evidence that its light was being absorbed by neutral hydrogen. Apparently the universe had already been reionized by the time the light from this quasar had begun its journey to Earth.

For most of the 1990s, no one was able to find a quasar any farther away than this one. The failure was not for a lack of powerful instruments—both the Hubble Space Telescope and the Keck telescopes at Mauna Kea in Hawaii came online in the early 1990s, significantly increasing astronomers' ability to see deep into the universe—but because quasars are rare to begin with. They erupt only from the most massive of supermassive black holes. And from our perspective, they do not shine unless their jets of gas happen to be aimed directly at us.

Moreover, those jets blast into existence only when a black hole is actively swallowing gas. For most black holes, that kind of activity peaked between a redshift of 2 and 3, when galaxies were more gas-rich, on average, than they are today. If you look further out than that sweet spot in cosmic time, the number of quasars drops off rapidly.

It was not until 2000, when the Sloan Digital Sky Survey began methodically searching across an enormous swath of sky with the largest digital detectors ever built until that point, that the record was shattered in earnest (the detectors were designed by the same Gunn). "The Sloan was just fabulously successful in finding distant quasars," says California Institute of Technology astronomer Richard Ellis. "They found something like 40 or 50 quasars beyond a redshift of 5.5."

But the survey could not reach back much further than a handful of quasars that it found between redshift 6 and 6.4, and even at that distance there was no sign of neutral hydrogen. It was only with the discovery of a quasar at redshift 7.085, by the UKIRT Infrared Deep Sky Survey at Mauna Kea, that astronomers found small but significant amounts of ultraviolet-absorbing hydrogen obscuring the object's light. This quasar, known as ULAS J1120+0641, shining about 770 million years after the big bang, finally let astrophysicists dip a toe into the era of cosmic reionization—but just a toe because even this close to the big bang, most of the neutral hydrogen had already been destroyed.

Or maybe not. It's possible that this quasar sits in an unusually sparse region of leftover neutral hydrogen and that most other quasars at this distance would have been more completely shrouded. It is equally possible that ULAS J1120+0641 is in an especially dense region; maybe reionization was already complete pretty much everywhere else. Without more examples, astronomers cannot be sure, and the prospects of finding enough quasars at this distance to do a robust statistical study are slim.

ULAS J1120+0641 has plenty to tell astronomers anyway. For one thing, Ellis says, "the number of quasars is falling so steeply with distance that it's inconceivable that massive black holes are a major source of radiation that reionizes the universe." For another, the black hole that powers this particular quasar must have a billion suns' worth of mass in order to generate the amount of energy that makes it visible from so far away. "It's almost impossible to understand how it could have formed in the limited time that the universe had up to that point," Ellis says.

Yet form it did. Abraham Loeb, chair of Harvard's astronomy department, points out that if a first-generation star with 100 solar masses collapsed into a black hole a couple of hundred million years after the big bang, it could conceivably have grown to quasar proportions in the available time if conditions were just right. "But you would need to feed the black hole continuously," he says, and it is hard to imagine how you could do that. "They shine so brightly, they produce so much energy, that they expel the gas out of their vicinity." Without a nearby supply of gas, the quasar goes temporarily dark, allowing gas to accumulate again until it can flare back into life—and blow away its fuel supply once more. "So there is always the notion of a duty cycle," Loeb says. "The black hole is able to grow only for a fraction of the time."

Yet, he says, black holes can also grow by merging with one another, which would accelerate their growth process. In addition, the recent work on star sizes implies that those first black holes may have formed not from stars that were 100 solar masses, but one million solar masses, a suggestion Loeb first put forth in a 2003 paper that he co-authored. "This has become a popular idea," he says, buttressed by simulations such as Greif's. "And because these stars would shine as brightly as the entire Milky Way, you could, in principle, see them with the James Webb Space Telescope," the massive successor to the Hubble telescope that is currently scheduled to launch in 2018.

GALAXY QUEST

EVEN AS THE HUNT for distant quasars has more or less petered out, the search for galaxies closer and closer to the big bang has taken off. Perhaps the most important triggering event was an image called the Hubble Deep Field. It was made in 1995, when Robert Williams, then director of the Space Telescope Science Institute, used a perk of the office known as "director's discretionary time" to aim Hubble at an evidently blank patch of sky and let it stare for a cumulative 30 hours or so to pick up whatever faint objects might be there. "Some very serious astronomers told him it was a waste of time," recalls current director Matt Mountain, "that he wouldn't see anything."

In fact, the telescope picked up several thousand small, faint galaxies, many of which turned out to be among the most distant ever seen. Follow-up Deep Field images—made with Hubble's new, infrared-sensitive Wide Field Camera 3, which was installed during a 2009 servicing mission and is some 35 times more effective than its predecessor—have found even more. "We've gone from four or five galaxies with a redshift of 7 or more," says University of Arizona observer Daniel Stark, Ellis's longtime collaborator, "to more than 100." One of these, described by Ellis, Stark and several co-authors in a 2012 paper, appears to be at a redshift of no less than 11.9, fewer than 400 million years after the big bang.

Like the record-holding quasar, these young galaxies can tell astronomers plenty about the distribution of intergalactic hydrogen at the time. When observers look at their output of ultraviolet light, a significant fraction of what they would expect to see is missing, absorbed by neutral hydrogen that surrounds them. That fraction drops gradually as they look at galaxies that are further from the big bang—until, at about a billion years after the universe was born, the cosmos is fully transparent.

In short, not only did galaxies exist to provide a source for the ionizing radiation, they also reveal how the universe made the transition from neutral to fully ionized. Astronomical detectives have a smoking gun, and they have a victim. There is a catch, however. If you take the 100-odd galaxies found so far above a redshift of 7 and extrapolate across the entire sky, you do not have enough total ultraviolet radiation to ionize all the neutral hydrogen. The gun does not seem to be powerful enough to do the job. The required energy cannot come from black holes, either, given how hard it is to make enough supermassive black holes quickly enough to do so.

Yet the answer may be relatively straightforward. Faint as they seem to us, the galaxies we are able to see at the very edge of Hubble's vision are presumably the brightest of their epoch. There must be many more galaxies at that distance that are simply too dim to see with any existing telescope. If you make that reasonable assumption, Ellis says, "I think most people now believe that galaxies do most of the work in reionizing the universe."

THE EINSTEIN CARD

AS FOR WHAT TRULY NEWBORN GALAXIES look like and when they first turned on, "we're not there yet," Stark admits. "The galaxies we do see are fairly small, and they look much younger than galaxies that have been studied in detail one billion to two billion years later." But they already have as many as 100 million stars, and the mix of their colors (after you correct for the fact that their light is redshifted) suggests their stars are on average redder than you would expect in a very young galaxy. "These objects," Stark says, "look like they've been forming stars for at least 100 million years already. Hubble has taken us close to the precipice, to where we'll see the first generation of stars, but it will take the James Webb Space Telescope to get us there."

Hubble has not exhausted its options, however. The telescope itself can see only to a certain faintness limit without taking absurdly long exposures. Yet the universe has supplied its own natural lenses that can boost Hubble's power. These so-called gravitational lenses take advantage of the fact that massive objects—in this case, clusters of galaxies—warp the space around them, distorting and sometimes magnifying the objects that lie far beyond.

It's almost impossible to understand how the black hole could have grown so large in the limited time that the universe had up to that point. Yet form it did.

In particular, says observer Marc Postman of the Space Telescope Science Institute, "we get a big amplification of any very distant galaxies that lie behind those clusters. They can be 10 or 20 times brighter than comparable unlensed galaxies." Postman is principal investigator for the Cluster Lensing and Supernova Survey with Hubble, a program that has used the technique to identify some 250 additional galaxies between redshift 6 and 8 and a handful more that may go up to redshift 11. From what they have seen so far, the results are consistent with those coming out of the various Deep Field surveys.

Now Hubble is going deeper still: Mountain has devoted some of his own director's discretionary time to a new project called Frontier Fields, in which observers will look for magnified images of faint, distant galaxies that lie behind six especially massive and powerful clusters. Over the next three years, says Jennifer Lotz, the project's lead observer, "we're going to look at each of them for something like 140 orbits of Hubble [each orbit is about 45 minutes' worth of observing time], which will let us probe deeper into the universe than anything we've ever seen."

BURST SEARCH

YET ANOTHER KIND OF COSMIC BEACON, meanwhile, could ultimately prove to be an even better probe of the early universe. When first discovered in the 1960s, gamma-ray bursts—short blasts of high-frequency radiation that pop up in random directions—were an utter mystery. Nowadays astronomers believe that many of them come from the deaths of very massive stars: as the stars collapse to form black holes, they spew jets of gamma rays out into space. When the jets slam into the surrounding clouds of gas, they trigger a secondary, bright afterglow of visible and infrared light that can be seen by conventional telescopes.

Here is how the observations work: When the orbiting Swift Gamma-Ray Burst observatory detects a gamma-ray flash, it swivels to point its onboard telescopes at the spot. At the same time, it beams the location's coordinates to ground-based observers. If their telescopes get there before the flash fades, astronomers can measure the afterglow's redshift and thus the redshift—and age—of the galaxy where the burst went off.

What makes the technique so valuable is that gamma-ray bursts make other cosmic objects look positively feeble. "For the first few hours," says Edo Berger, a Harvard astrophysicist who specializes in the bursts, "they probably outshine galaxies by a factor of a million, and they're 10 to 100 times brighter than quasars." You do not need a long exposure with Hubble to see them. In 2009 a telescope on Mauna Kea reliably measured the redshift of one burst at 8.2, putting it at 600 million years after the big bang.

The flash was so bright, Berger says, that it could have been seen out to a redshift of 15 or even 20, which would be less than 200 million years after the big bang, close to the time the very first stars may have been shining. And it is entirely plausible, he says, that those very massive stars would be exactly the kind to produce gamma-ray bursts as they die. In fact, Berger says, there is reason to think these first-generation stars would create such energetic gamma-ray bursts that they would appear brighter than the ones discovered so far, even though they would be farther away.

Unlike quasars, moreover, which occur only in galaxies with supermassive black holes, and unlike the galaxies Hubble can see, which are the brightest tips of a grand galactic iceberg, gamma-ray bursts are just as powerful in tiny galaxies as they are in big ones. They provide, in other words, a much more representative sample of the universe at any given time.

The downside, Berger says: 99 percent of gamma-ray bursts are pointed away from Earth, and of the remaining one per day or so that are detected by satellites, only a minuscule fraction are at a high redshift. Gathering a representative sample of extremely high redshift bursts would therefore take a decade or more, and "Swift is probably not going to last" that long, Berger says. Ideally, he notes, someone should launch a successor satellite that could feed burst coordinates to the James Webb telescope or to the three 30-meter-class ground-based instruments

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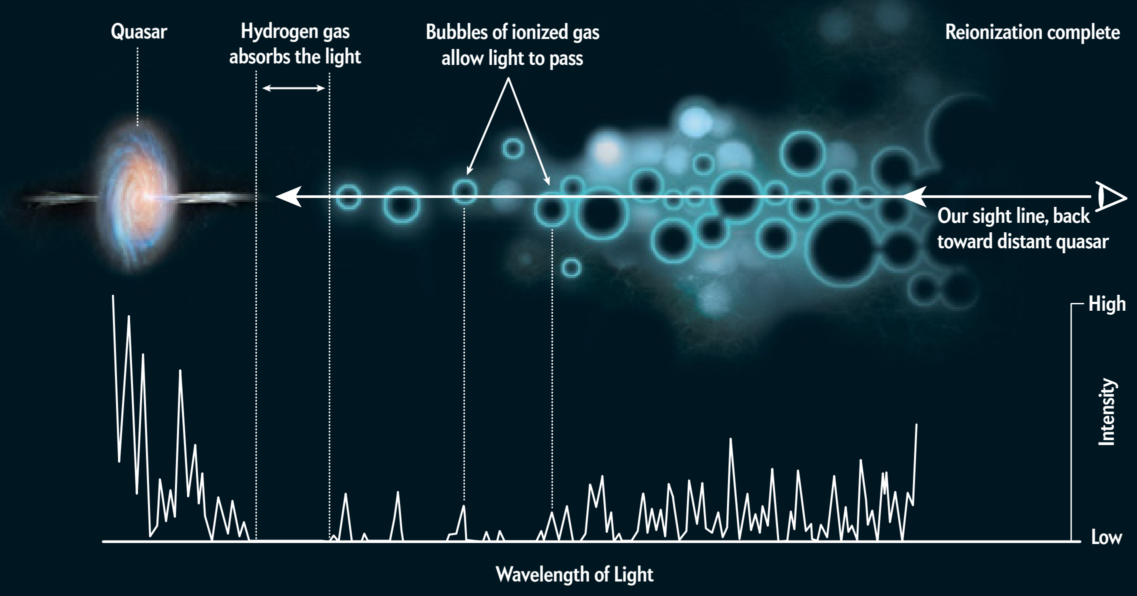
Quasar Quest

Quasars are among the brightest objects in the early universe, beacons that astronomers can spot from more than 10 billion light-years away. As light from the quasar travels through the universe toward our telescopes, two things happen: First, its light gets stretched along the way by the expansion of the universe. In addition, any atomic hydrogen gas will absorb some of the light. Astronomers can therefore plot the absorption of light by wavelength to see how the prevalence of hydrogen gas has changed over time. They have found that isolated bubbles of ionized gas grew larger and more frequent as the universe evolved.



SOURCE: GEORGE DJORGOVSKI *California Institute of Technology* AND ABRAHAM LOEB *Harvard University*

that are expected to be operating within the next decade. Proposals to do so have so far failed to get the go-ahead from either NASA or the European Space Agency.

In any case, once the James Webb telescope and the next generation of gigantic ground-based telescopes begin observations, quasar hunters, galaxy surveyors and those who search for the telltale afterglows of gamma-ray bursts in other electromagnetic wavelengths will be able to catalogue much older and fainter objects than they can today. Their work will help to nail down exactly what was going on in the very early universe.

Radio astronomers, meanwhile, will be looking to instruments such as the Murchison Widefield Array in Australia, the Precision Array for Probing the Epoch of Reionization in South Africa, the Square Kilometer Array, split between those two countries, and the Low Frequency Array (LOFAR), with antennas located in several European countries, to try mapping out slowly disappearing clouds of neutral hydrogen during the first billion years of cosmic history. The hydrogen itself emits radio waves, so in principle, astronomers will be able to look at those emissions at different epochs—each redshifted by a different amount, depending on how far away they are—and take snapshots of the hydrogen as it is gradually eaten away by high-energy radiation as the images come forward in time. And finally, astronomers will be using the Atacama Large Millimeter/submillimeter Array in the high Chilean desert to search for carbon monoxide and other molecules that mark the interstellar clouds where the second generation of stars was born.

When cosmologists first detected the leftover electromagnetic radiation from the big bang in 1965, it galvanized them to try and understand the life history of the universe from its birth right through to the present. They are not quite there yet. But there is every reason to believe that by 2025, the 60th anniversary of that discovery, the last remaining blanks will finally be filled in. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

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For decades anthropologists have debated when and how our ancestors became skilled hunters. Recent discoveries have yielded surprising new insights

By Kate Wong

EVOLUTION

Rise of the Human Predator

HOMO ERGASTER, **as represented here by the 1.6-million-year-old Turkana Boy from Kenya, was probably a capable hunter.**

Some 279,000 years' ago,

on a ridge overlooking a vast lake in central Ethiopia's Rift Valley, hunters painstakingly shaped chunks of greenish black volcanic glass into small, sharp points. After chipping the brittle material to create cutting edges, they attached each point to a shaft of wood, producing a sort of javelin. It might sound like a modest feat of engineering by today's standards. But the technology was nothing less than revolutionary. With it, members of the human lineage had at their disposal a weapon that would allow them to kill much more effectively from afar than a simple wooden spear could. Not only would that development enable our predecessors to hunt a broader range of animals, but it also upped their odds of emerging from the hunt unscathed by putting a safe distance between them and large, dangerous prey, perhaps including the hippos that would have lurked in and around the nearby lake.

As far as technological inventions go, this stone-tipped throwing spear was arguably humanity's crowning achievement at the time. But perhaps more remarkable than the hunting gains it afforded is the fact that the conceptualization, manufacture and use of this seemingly simple device were made possible only through the piecemeal acquisition, over tens of thousands of generations, of traits that helped our forebears acquire meat.

In our era of supermarkets and fast food, it is easy to forget that we humans are natural-born hunters. We certainly don't look the part. We are slow, we are weak, and we lack the killer teeth and claws that other carnivores wield against their quarry. Indeed, compared with other carnivores—from crocodiles to cheetahs—humans appear decidedly ill suited to procuring prey. Yet we are the most lethal predators on earth—a distinction earned long before the advent of vehicles to carry us to our targets and guns to dispatch them.

Over the course of millions of years evolution transformed our mostly vegetarian ancestors (creatures like the famous *Australopithecus afarensis* individual known as Lucy) into a singularly deadly primate. In fact, many of the characteristics that set us apart from our closest living relatives, the great apes—from our ability to run long distances to our oversize brains—may have arisen at least in part as adaptations to hunting. Recent discoveries have illuminated some previously murky phases of this metamorphosis, documenting among other things the debut of our throwing arm and the earliest known evidence of big game hunting. With these new insights, researchers now have the most detailed picture yet of the emergence of the traits that honed our hunting prowess—and in so doing made us human.

BRAVE NEW WORLD

To understand how important a role hunting played in our evolution, we must page back some three million years to a time when early hominins (creatures more closely related to us than to our closest living relatives, the chimpanzees and bonobos) were headed toward a crossroads. The climate was changing, and across Africa the forests and woodlands where our forebears had long foraged for fruit and leaves were giving way to more open grasslands, where such foods were harder to come by. The hominins would have to adapt or die. Some, namely the so-called robust australopithecines, seem to have coped with this environmental change by evolving massive jaws and teeth that could grind up grasses and other tough plant foods. The lineage that includes our genus, *Homo*, took a radically different tack, expanding its diet to include increasing amounts of animal protein and fat. Both approaches stood our predecessors in good stead for a long time. But eventually, around a million years ago, the robust australopithecines went extinct.

PRECEDING PAGE: KENNETH GARRETT *Alamy*

IN BRIEF

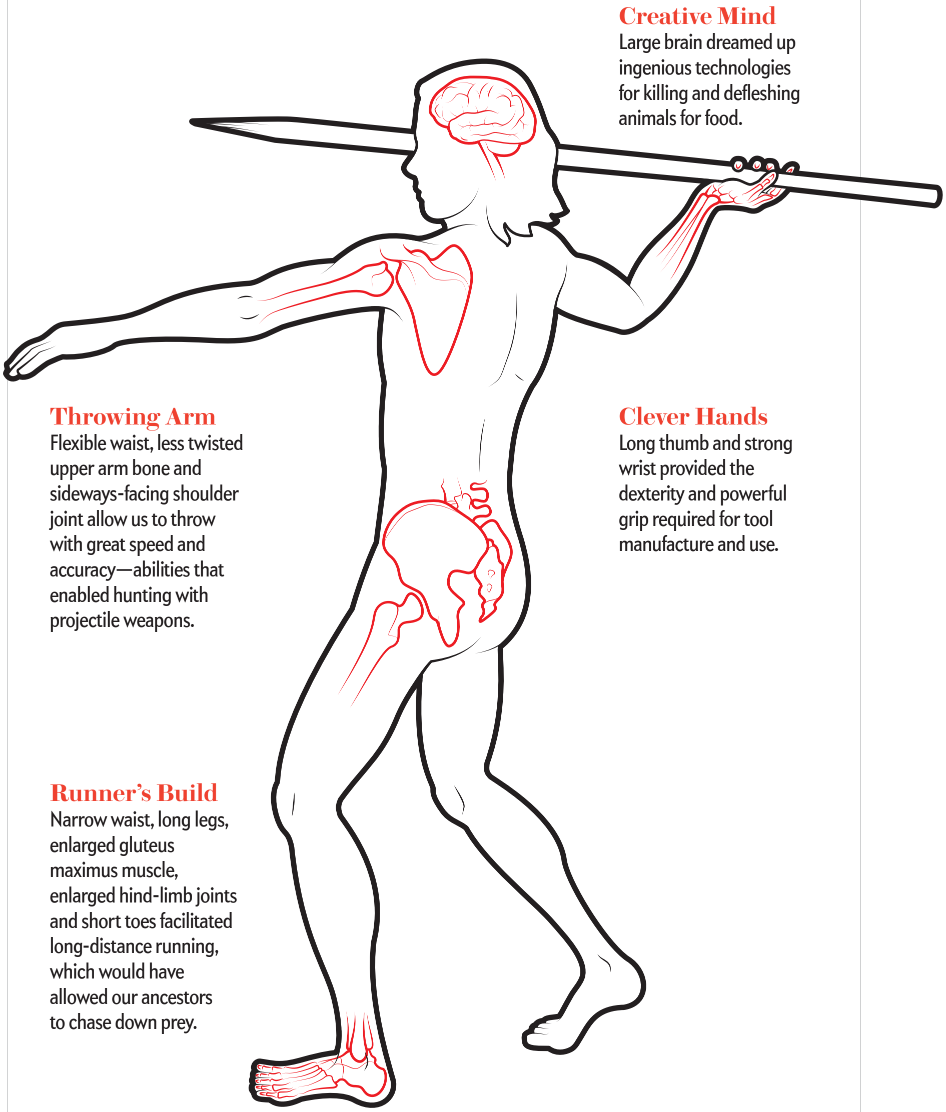
For decades researchers have been locked in debate over how and when human hunting began and how big a role it played in human evolution.

Recent analyses of human anatomy, stone tools and animal bones are helping to fill in the details of this game-changing shift in subsistence strategy.

This evidence indicates that hunting evolved far earlier than some scholars had envisioned—and profoundly impacted subsequent human evolution.

Anatomy of a Hunter

Unlike most predators, we humans are slow, weak and lacking in lethal fangs and claws. But our ancestors evolved a suite of other traits (*representatives of which are shown below*) that more than make up for those shortcomings.



Scientists may never learn exactly why the robusts died out. Perhaps they had become so specialized that when environmental conditions changed again, they could not shift gears and effectively exploit other menu options. Or maybe *Homo* outcompeted them. What is abundantly clear, however, is that in turning to animals for sustenance, the *Homo* lineage hit on a winning strategy, one that would help fuel its rise to world domination.

Numerous changes to the anatomy of our hominin ancestors conspired to make them formidable competitors on the savanna, where sabertooth cats and other large-bodied carnivores had long reigned unchallenged. One important suite of characteristics compensated for our lack of speed. Although, to this day, we humans, with our bipedal form of locomotion, are lousy sprinters compared with quadrupeds, we excel at long-distance running. No other living primate even comes close to this level of running ability. Daniel Lieberman of Harvard University and Dennis Bramble of the University of Utah have proposed that this capability evolved to help hominins hunt, allowing them to pursue their prey until it slowed or collapsed from exhaustion. Judging from the relevant traits that are preserved in the fossil record—such as enlarged hindlimb joints and short toes, among many other characteristics that improved running performance—endurance running originated in *Homo* by around two million years ago.

Physiological changes accompanied these anatomical shifts. With higher activity levels compared with those of their predecessors, hominins needed a way to avoiding overheating. As Nina Jablonski of Pennsylvania State University has theorized, the loss of fur and the gain of special glands in the skin that promote sweating helped our ancestors keep cool while in hot pursuit. With this built-in cooling system, the evolution of which Jablonski estimates was well under way by the time of *Homo ergaster* 1.6 million years ago, humans can outrun a horse in a marathon.

Catching up to fleet-footed prey was only half the battle, however. To close the deal, the hunters needed to be able to deliver the deathblow, preferably with a heavy or sharp object lobbed from a safe distance. Could early *Homo* manage this feat? Modern humans shine at throwing with speed and accuracy. Chimpanzees, in contrast, perform this task dismally. Recently Neil T. Roach of George Washington University and his colleagues set out to determine why we humans are so much better at throwing than chimps are and when this ability evolved. The key to our throwing skills, it turns out, lies in the elastic energy in our shoulder muscles. Studying college baseball players, Roach and his coworkers identified three features present in modern humans but not in chimps that greatly enhance our upper body's range of motion and thus its ability to store and release this energy: a flexible waist, a less twisted upper arm bone and a shoulder socket that faces out to the side rather than upward as it does in apes.

Turning to the fossil record, Roach's team was able to identify when these traits that permitted high-speed throwing evolved. They did not emerge in lockstep but rather in mosaic fashion. The longer waist and straighter upper arm bone appeared early on, in the australopithecines; the shift in shoulder-socket orientation, for its part,debuted some two million years ago in *Homo erectus*.

It is admittedly difficult to establish with certainty that natu-

Illustration by Brownbird Design

ral selection favored any given trait for a particular purpose, such as endurance running or throwing as a means to hunt. In some cases, selection might have initially promoted the trait for a different reason altogether—only to subsequently see it co-opted for another activity. Our tall waist, for example, seems to have originated as part of a package of traits that facilitated upright walking. But later, with the addition of other, complementary features, it took on a new role, helping our ancestors increase their torque production so as to hurl an object at a target with greater force.

EARLIEST SIGNS of hunting are two-million-year-old cutting tools (*1*) and cut-marked animal bones (*2*) from the site of Kanjera South in Kenya. Over time our ancestors invented deadlier hunting weapons, including 500,000-year-old stone-tipped spears from Kathu Pan in South Africa, reconstructed here (*3*), and 71,000-year-old arrowheads or dart points from Pinnacle Point in South Africa (*4*).

Nevertheless, Roach suspects that selection for throwing was driving the shoulder changes that emerged around two million years ago. He thinks so in part because those changes were making our ancestors worse at another important activity: climbing trees, which had long furnished hominins with food and safe haven from ground-dwelling predators. "When you give up going up into trees easily, you need to be getting something else," Roach remarks. A better throwing arm would have afforded *Homo* improved access to animal foods rich in calories while allowing hominins to drive off predators that tried to attack them or steal their kills.

BUTCHERED BONES

ALTHOUGH THE FOSSIL RECORD indicates that hominins had evolved a suite of anatomical features well suited to hunting by two million years ago, it does not establish that they were in fact systematically killing animals for food at that time. To do that, scientists must find telltale traces of hunting in the archaeological record—no easy task. Stone tools and cut-marked bones show that early humans started butchering animals by 2.6 million years ago. But did our ancestors kill the prey themselves, or did they let big cats and other carnivores do the heavy lifting?

For decades experts have debated whether early *Homo* hunted or scavenged. The earliest unequivocal evidence of hunting—wooden spears and animal remains from the German site of Schöningen—was just 400,000 years old. But over the past few years compelling evidence of much earlier hunting has emerged from studies of large assemblages of butchered animal remains from sites in East Africa that date to the time of early *Homo*.

One of these assemblages comes from a site in Tanzania's famed Olduvai Gorge known as FLK Zinj. Some 1.8 million years ago hominins transported carcass after carcass of wildebeest and other large mammals there to carve up and eat. British paleoanthropologist Mary Leakey excavated most of the bones in the 1960s, and scholars have been arguing ever since about whether the animals there were hunted or scavenged. Henry T. Bunn of the University of Wisconsin–Madison was thinking about the problem of distinguishing hunted animals from scavenged ones when it dawned on him that the tactics should leave different signatures in what is called the mortality profile of the bones. For instance, when it comes to hunting large game, such as waterbuck, lions tend to pick off a disproportionately high number of old individuals relative to their frequency in a typical living herd. Thus, if early humans were scavenging kills by lions or other large carnivores at FLK Zinj, the assemblage should show a similar overrepresentation of old individuals. Instead Bunn and his colleagues found, the butchered large mammal remains at the site skew much more heavily to individuals in their prime than to old or juvenile animals, exhibiting the pattern one would expect to see if humans were selecting the animals they wanted and killing them themselves.

In fact, the FLK Zinj pattern closely resembles that of prey hunted nowadays by the Hadza hunter-gatherers in Tanzania and the San in Botswana using bows and arrows. So far as is known, *Homo* had yet to invent long-range projectile weapons such as the bow and arrow at this point. But Bunn thinks that the hominins may have engaged in ambush hunting by parking themselves in trees near water sources and launching sharpened wooden spears at unsuspecting animals at close range as they passed below en route to drink.

Even older traces of hunting have come from western Kenya, at a site called Kanjera South on the shores of Lake Victoria, where Joseph Ferraro of Baylor University, Thomas W. Plummer of Queens College, C.U.N.Y., and their collaborators have unearthed thousands of stone tools and animal bones that were stripped of their flesh and marrow. Most of the bones, which date to about two million years ago, come from small, young antelopes and show little carnivore damage, which supports the idea that hominins hunted the prey rather than acquiring carnivore leavings. Moreover, Plummer says, the antelopes were small enough that if large carnivores had killed them, they would have completely consumed the carcasses rather than leaving any tissue behind.

The Kanjera remains are "the oldest solid evidence for hunting so far," Plummer asserts. Most important, the hominins at this site clearly did not merely prepare an experimental steak dinner only to return to a vegan lifestyle. The bones hail from sediment layers representing hundreds or perhaps thousands of years of

COURTESY OF THOMAS W. PLUMMER (1); COURTESY OF JOSEPH FERRARO (2); COURTESY OF JAYNE WILKINS (3); COURTESY OF TOVE RUTH SMITH AND SIMEN OESTMO (4)

SCIENTIFIC AMERICAN ONLINE Learn more about the evolution of hunting at ScientificAmerican.com/apr2014/hunting

what the team calls "persistent hominin carnivory." These individuals had committed to routine consumption of substantial amounts of animal tissue. It is not the only thing they ate—analyses of the tools from the site show that they were also processing plants, including tubers—but it formed a mainstay of their diet.

DEEP IMPACT

IT IS HARD TO OVERSTATE the impact of *Homo*'s shift to a meaty diet. Trends evident in the fossil and archaeological records indicate that it established a feedback loop in which access to calorie-packed food fueled brain growth, which led to the invention of technologies that permitted our ancestors to obtain even more meat (as well as high-quality plant foods), which in turn powered further expansion of gray matter. As a result, between two million and 200,000 years ago brain size swelled from roughly 600 cubic centimeters on average in the earliest representatives of *Homo* to around 1,300 cubic centimeters in *Homo sapiens.*

Carnivory also would have radically changed the social dynamics among our ancestors, particularly once they began hunting larger prey that could be shared with other members of the group. Travis Pickering of the University of Wisconsin–Madison explains that this development ultimately led to greater social organization in early *Homo,* including a division of labor whereby men hunted large game and women gathered plant foods and both groups returned to a central meeting place at the end of the day to eat. By the time our ancestors were hunting large game such as the wildebeest at FLK Zinj, he thinks, they were organizing themselves in this way. And although today it might sound like an antiquated arrangement, that divvying up of responsibilities between the sexes proved to be a remarkably successful hominin adaptation.

Pickering furthermore suspects that the shift toward meat eating fostered self-control in our forebears. Although conventional wisdom holds that hunting promoted aggression in humans—a view based on observations of chimps hunting aggressively—he believes it cultivated level-headedness. Unlike chimps, which have brute strength and lethal teeth, early humans could not merely overpower their quarry with an aggressive attack. Instead, Pickering argues, "they gained emotional control" and acquired prey using brains not brawn. In his view, the advent of tools that enabled hominins to kill from a distance helped them decouple aggressive emotions from hunting.

Support for this hypothesis comes from Iowa State University primatologist Jill Pruetz's studies of an unusual population of grassland-dwelling chimpanzees in Senegal. Unlike their forest-dwelling counterparts, which hunt large, dangerous monkeys with their bare hands, the Senegalese chimps mostly target tiny nocturnal primates known as bush babies using sharpened sticks that they jab into tree hollows where the tiny primates sleep during the day. Pickering notes that the Senegalese chimps go about their hunting in a far more subdued manner than the forest chimps, which subject their prey to frenzied beatings. Perhaps the "spears" used by these chimps help them keep their cool.

Hunting also made us human in another respect. *H. sapiens* is unique among primates in having colonized every corner of the globe. For the first five million years of hominin evolution, our predecessors remained within the bounds of Africa. But sometime after two million years ago, *Homo* began to expand its reach into other parts of the Old World. Why the sudden wanderlust? Theories abound, but it may well be that hunting led hominins out of the motherland. Back then, much of Eurasia was covered by savanna grasslands similar to those in which *Homo* was accustomed to foraging in Africa. Thus, hominins might have been pursuing game when they took those first fateful steps out of Africa.

Many more hominin migrations ensued in the millennia that followed, each driven by its own unique circumstances. And although our predecessors may not have always been tracking game on these trailblazing journeys, their ability to colonize far-flung places and thrive under wholly new ecological conditions hinged on the physical and behavioral traits that helped *Homo* become the least likely, most successful predator the world has ever known. SA

Kate Wong is a senior editor at Scientific American.

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FUTURE OF MEDICINE 2014

THE RNA REVOLUTION

Long overlooked as a mere cellular housekeeper, RNA has emerged as a path to **a new world of medical treatment**

By Christine Gorman and Dina Fine Maron

Illustrations by Anna Parini

Starting with the double-helical structure of DNA in 1953, the story of molecular biology has featured more characters than a Russian novel. Biologists have identified tens of thousands of molecules that direct and shape the organized chaos within the body's cells, and they have exploited those findings with thousands of drugs and treatments.

For decades the stars of the drama came from two camps: DNA, or deoxyribonucleic acid, which acts as a near permanent repository of genetic information, and proteins, which do the genes' handiwork. Protein discoveries have led to such medical advances as synthetic insulin, interferon and next-generation anticancer drugs. And gene therapy, using modified bits of DNA, has made headway against hemophilia, hereditary blindness and other previously intractable diseases.

Overlooked in this march of medical progress was a third type of biomolecule: RNA, or ribonucleic acid. Like its more famous sister, RNA contains genetic information, but it is less chemically stable than DNA and is often degraded by enzymes in the turbulent environment of the cytoplasm.

Although scientists have long known that RNA is intricately involved at some point in almost every cellular process, for most of the biomedical revolution they assigned it a supporting role, in the shadow of DNA and proteins. In the 1950s and 1960s biologists thought of RNA as a kind of Cinderella molecule, ferrying messages, coordinating supplies and generally keeping cells tidy. For decades this view stuck.

But that was before a few fairy godmothers (and godfathers) gave RNA a stunning makeover. A series of discoveries in the late 20th century revealed new forms of RNA that were nothing like humble housekeepers. On the contrary, these RNA molecules exerted an astonishing degree of control over the behavior of DNA and proteins—targeting specific molecules to increase or decrease their activity. By manipulating this RNA, scientists could potentially develop new treatments for cancer, infectious diseases and a wide range of chronic illnesses.

In the past decade or so investigators have raced to exploit this insight. The pace of discovery has accelerated, dozens of start-ups have formed to capitalize on new findings and now some promising treatments are in the offing.

Meanwhile an early trickle of financial interest has grown into a multibillion-dollar torrent. Among recent ventures, Editas Medicine received $43 million in venture capital for its launch at the end of 2013; the company is concentrating its

IN BRIEF

Three of the most important complex molecules in living organisms are DNA, RNA and protein. For decades biologists ascribed the most active roles in the cell to DNA and proteins; RNA was clearly important but rendered more supportive services.

A series of discoveries in the late 20th century revealed several previously unknown forms of RNA that play active, regulatory roles in the cells—determining which proteins are manufactured and in what amounts or even silencing some genes altogether.

These latest insights are allowing scientists to create a new world of experimental medications against bacteria, viruses, cancer and various chronic conditions that should work more effectively and precisely than many currently available drugs.

BREAKOUT PERFORMANCE

RNA Shines in New Roles

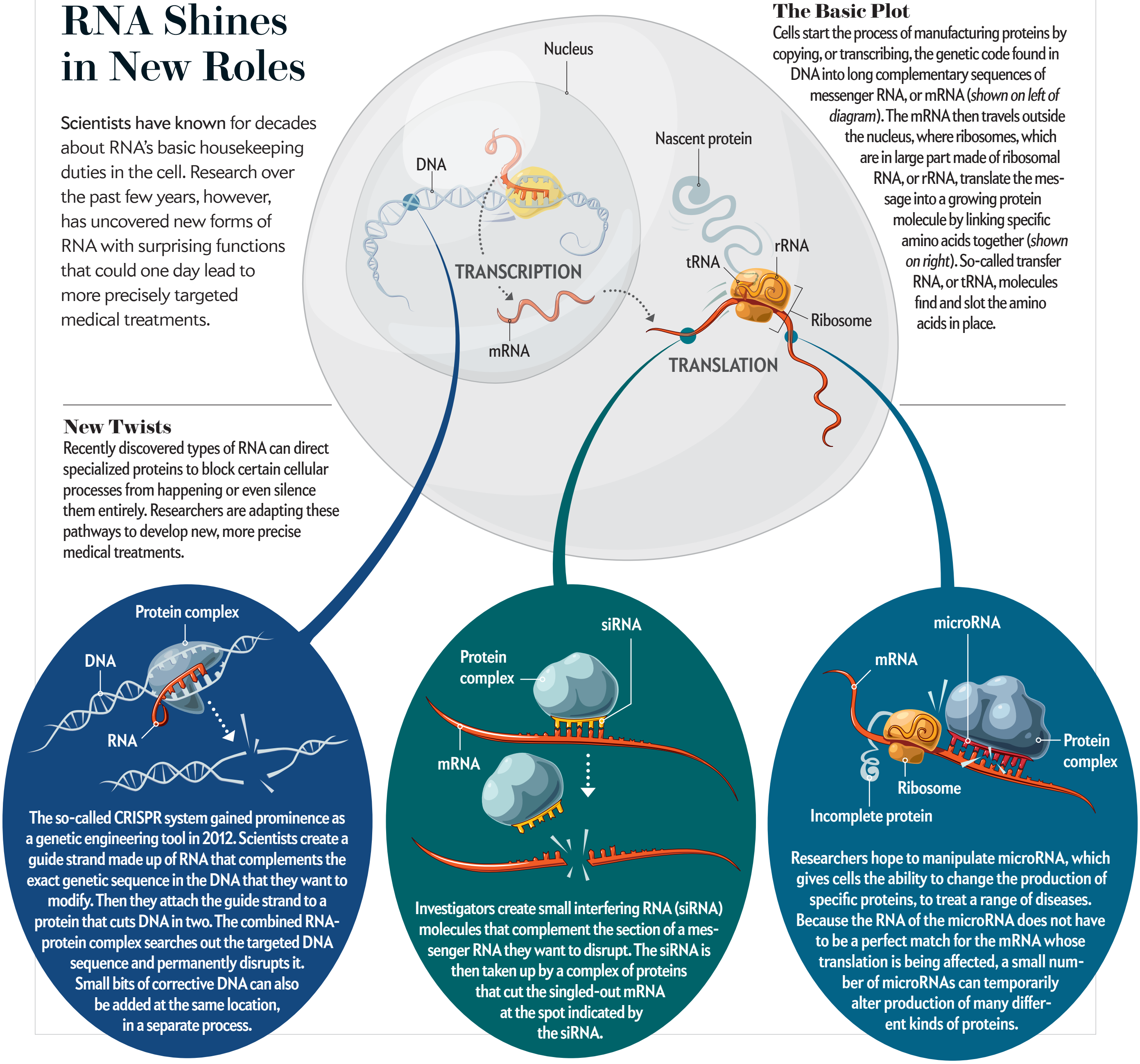
Scientists have known for decades about RNA's basic housekeeping duties in the cell. Research over the past few years, however, has uncovered new forms of RNA with surprising functions that could one day lead to more precisely targeted medical treatments.

The Basic Plot

Cells start the process of manufacturing proteins by copying, or transcribing, the genetic code found in DNA into long complementary sequences of messenger RNA, or mRNA (*shown on left of diagram*). The mRNA then travels outside the nucleus, where ribosomes, which are in large part made of ribosomal RNA, or rRNA, translate the message into a growing protein molecule by linking specific amino acids together (*shown on right*). So-called transfer RNA, or tRNA, molecules find and slot the amino acids in place.

New Twists

Recently discovered types of RNA can direct specialized proteins to block certain cellular processes from happening or even silence them entirely. Researchers are adapting these pathways to develop new, more precise medical treatments.



efforts on the hottest new RNA technology, known as CRISPR. A slightly older company, Alnylam Pharmaceuticals, founded in 2002, received $700 million this past January to develop, among other things, its pipeline of RNA medications for devastating blood conditions, liver diseases and immune disorders.

The funding has come "in waves," says Robert MacLeod, vice president of oncology and exploratory discovery at Isis Pharmaceuticals, which has raised nearly $3.8 billion since it was founded in 1989. Its lead product, Kynamro, received approval from the U.S. Food and Drug Administration in 2013 as an RNA medicine for people with a rare genetic disorder that significantly interferes with their ability to process cholesterol, putting them at an exceptionally high risk of heart attack and stroke.

As with any rapidly expanding field, there have been a few bumps and detours along the way, and not every discovery will likely stand the test of time. Yet medical researchers are practically giddy with excitement—as if they had found a new continent to explore in search of potential breakthroughs.

SUPPORTING ROLE

IT IS EASY TO SEE WHY molecular biologists would assign starring roles to DNA or proteins rather than RNA. DNA's main subunits—adenine, thymine, cytosine and guanine, or A, T, C and G—constitute the basic instruction manual for growing just

Illustration by Josy Conklin

about every living thing on the planet. And one of the most important processes that DNA provides directions (or codes) for is the creation of proteins.

Proteins, for their part, give cells their three-dimensional structure and allow them to perform many jobs; they provide the skin's youthful spring and the heart's lifelong strength. They also turn DNA on and off in response to environmental cues, determine how well cells use sugar and regulate the ability of neurons to relay signals to one another in the brain. The vast majority of today's medicines—from aspirin to Zoloft—work by manipulating proteins, either by blocking their function or by altering the amount that is produced.

Just because most medications affect proteins, however, does not mean that investigators have been able to develop drugs that act on all the proteins they would like to target. The most common pharmaceutical remedies consist of small molecules that can survive being swallowed and passed through the acidic interior of the stomach. Once absorbed from the digestive system, they must fit into the active locations on their target proteins the way a key fits a lock. But there are certain groups of proteins for which this traditional approach will not work. The proteins bury their active sites too far inside narrow channels, or they do not even contain an active site because they make up part of the cell's internal skeleton, which renders them "undruggable," MacLeod says.

This roadblock is what the new RNA medicines are designed to overcome—though how they could do so has not been obvious until recently. As biologists have long known, RNA serves as a talented go-between, copying, or transcribing, DNA's instructions into a complementary sequence (matching a C for every G, for example) and then translating that code into three-dimensional proteins. So-called messenger RNA (mRNA), which is generated in the nucleus, travels to the cytoplasm, where structures called ribosomes and transfer RNA (tRNA) work together to read the message and connect amino acids (nitrogen-containing compounds) into long chains that become proteins. But RNA can do much more.

A STAR IS BORN

The groundwork for RNA's breakout performance was laid in 1993, with the identification of the first microRNAs. These uncharacteristically short stretches of RNA attach themselves to strands of mRNA, preventing ribosomes from making any progress in assembling a protein [*see box on preceding page*]. Cells apparently use microRNAs to coordinate the production schedule of many proteins—particularly early in an organism's development. Five years later researchers made another breakthrough when they demonstrated that different short RNA molecules effectively silenced the translation of a gene into protein by cutting up mRNA. That landmark discovery later netted a Nobel Prize, in 2006.

By this point, everyone—not just RNA specialists—was seemingly interested in using the once overlooked molecule to influ-

A NEW SHOT AGAINST HEPATITIS C

Targeting a microRNA in liver cells could disable a silent killer

By Christine Gorman

Twenty-five years ago no one had even heard of the hepatitis C virus. Today it is a leading cause of liver cancer and a major reason why people get liver transplants. Globally it kills about 350,000 people a year; in the U.S., more people now die of hepatitis C than of AIDS.

ence how proteins were formed. The disruption of mRNA by short RNA molecules was coined RNAi, for RNA interference, and the latter molecules were given such names as siRNA, for small interfering RNA. Meanwhile a wide range of scientists realized that they might be able to deal with undruggable classes of proteins by moving the action further upstream, at the RNA level of the protein-manufacturing process.

To date, more than 200 experimental studies of either microRNAs or siRNAs have been registered through the U.S. government's database of clinical trials for the diagnosis or treatment of everything from autism to skin cancer. Among the most promising are treatments for Ebola virus, an extremely deadly pathogen that terrorism experts fear could be turned into a bioweapon, and hepatitis C, which has triggered long-lasting infections in about 150 million people around the world and is a major cause of liver cancer [*see box at left and box on next page*].

WHAT'S NEXT?

WHEREAS MEDICATIONS containing microRNA or siRNA are furthest along in the race to the clinic, another generation of aspiring starlets is now waiting in the wings. These potential medications would work even further upstream, on the DNA molecule itself. One of the approaches is based on CRISPR sequences found in the DNA of many single-celled organisms and was enthusiastically described in *Science* as the "CRISPR Craze." The other, which depends on the existence of molecules known as long noncoding RNAs, or lncRNAs, still faces some skepticism about its utility.

CRISPR stands for *c*lustered *r*egularly *i*nterspaced *s*hort *p*alindromic *r*epeats, which are oddly repetitive stretches of DNA found in bacteria and archaea (bacterialike organisms). These quirky sequences, in turn, interact with proteins known as CRISPR-associated, or Cas, proteins. Together CRISPR and various Cas proteins form a microbial defense system against viruses.

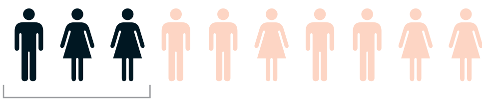
The proteins have one job—to cut DNA in two. They are guided to specific stretches of viral DNA by complementary strands of RNA. Where does the RNA come from? In a microscopic version of jujitsu, cells grab the RNA from the invading virus, turning it into a double agent that guides the Cas proteins to the exact spot where they need to cut.

Although CRISPR elements were first observed in bacteria in 1987, scientists started adapting the system to a wide range of animal, including human, tissue only in 2012. By creating their own guide strands of RNA, investigators could direct the Cas proteins to cut DNA molecules in the nucleus at very precise locations. In essence, they had turned the bacterial defense mechanism into a precision gene-editing tool.

Such exquisitely targeted technology could potentially revolutionize gene therapy—perhaps sooner rather than later.

Currently clinical investigators are only able to inject corrective DNA into patients with defective genes in a scattershot

The infection can be cured—albeit with debilitating side effects. Standard treatment with interferon and ribavirin causes fever, headaches, fatigue, depression and anemia. Such therapy may last as long as 11 months and clears the infection in 50 to 70 percent of cases. The recent addition of protease inhibitors, a class of medications that was first used against HIV, has improved cure rates and lessened treatment time. Unfortunately, the newer drugs work only against the type of hepatitis C most common in North America, Europe and Japan, so they are not equally effective around the world.



At least 30%
of people with hepatitis C are not cured after their first round of standard treatment

RNA medications may better that outlook. In 2013 researchers showed that targeting a particular microRNA in liver cells with an experimental drug called miravirsen dramatically decreased the amount of hepatitis C virus in most patients receiving treatment, in some cases to undetectable levels. The experimental medication consists of a short sequence of DNA whose "letters" are exactly complementary to the RNA letters found on the microRNA, allowing the drug to home in on its objective precisely.

The microRNA in question, known as miR-122, plays a key role in the production of many proteins in the liver. It seems to enhance their manufacture, however, rather than suppressing it as so many microRNAs do. Once the hepatitis C virus gains entry to a cell, it attaches itself to miR-122, ensuring that multiple viral copies are made. Blocking miR-122 ends up blocking virus replication as well.

The main side effect of miravirsen therapy was redness at the injection site, which eventually disappeared. Because the treatment aims at something in the host cells—as opposed to one of the viral proteins (which is how the protease inhibitors work)—it should be effective against all strains of hepatitis C.

Although the intervention was designed to last just four weeks (the infection eventually returned in all the treated patients), there is reason to believe that longer treatment with miravirsen will prove more effective. "The thought is that if you block the viral replication long enough, you can cure the disease," says Harry L. A. Janssen, a senior scientist at the Toronto General Research Institute and a co-author of the miravirsen study, which was published in the *New England Journal of Medicine*. Further tests are ongoing.

***Christine Gorman** writes about health and medicine topics.*

DEFEATING NATURE'S TERRORISTS

An RNA-based treatment may stop the Ebola virus in its tracks

By Ferris Jabr

At first, people infected with the Ebola virus appear to have the flu—fever, chills, muscle aches. Then the bleeding begins. As the virus hijacks cells throughout the body to make copies of itself, it overwhelms and damages the liver, lungs, spleen and blood vessels. Within days organs begin to fail and many patients fall into a coma. Some outbreaks, primarily in Central and West Africa, have killed up to 90 percent of infected individuals.

That terrifying prognosis may be about to change. Using so-called small interfering RNA, or siRNA, Thomas W. Geisbert, now at the University of Texas Medical Branch at Galveston, and his many collaborators have devised a highly promising treatment that has saved the lives of six monkeys infected with the virus. As reported this past January, the treatment has also passed its first safety test in an uninfected human volunteer. One of Geisbert's collaborators, Ian Maclachlan of Burnaby, British Columbia–based Tekmira Pharmaceuticals, and his team have received a $140-million grant from the U.S. Department of Defense to develop the therapy further.

Working together, the scientists engineered an siRNA to prevent the Ebola virus from making a particular protein, without which it cannot replicate itself. "If you knock out that one, in theory you knock out everything," Geisbert says. The researchers also designed another siRNA to thwart manufacture of a second protein that the virus uses to weaken an infected individual's immune system. There is no danger of the siRNAs interfering with typical cellular duties because the targeted viral proteins do not exist in the cells of humans or other mammals.

Maclachlan and his colleagues encapsulated the lab-made siRNAs in little bubbles of fat that cells would readily transport across their membranes. Then they injected the preparation into several rhesus macaques, which had been infected with Ebola virus less than an hour earlier. In one study, two of three monkeys given a total of four doses of the treatment in the first week after exposure survived. In a second study designed to test the effectiveness of a higher dose, all four monkeys that received seven siRNA injections lived. Tests revealed that the treated monkeys had far fewer virus molecules in their blood than is typical for an infected animal. The macaques tolerated the siRNA injections well, and those that survived were still healthy 30 days later.

Outbreaks, primarily in Central and West Africa, have killed **up to 90% of infected individuals**

The study was a "milestone," says Gary Kobinger of the University of Manitoba, who is working on a different Ebola treatment based on antibodies. He believes Geisbert and his team "are leading the effort toward clinical development."

__Ferris Jabr__ is an associate editor at Scientific American.

SCIENTIFIC AMERICAN ONLINE Watch an animation of short RNAs at work in the cell at ScientificAmerican.com/apr2014/rna

manner, hoping that at least some genetic material manages to start working in the right place. Fully developed CRISPR/Cas technology could change that by allowing researchers to choose precisely where a patient's DNA should be modified. "We're going to be seeing quite a few gene therapy trials using CRISPR in the next year," says George M. Church, a professor of genetics at Harvard Medical School, co-founder of Editas and scientific adviser to *Scientific American*. "It basically works right out of the box," he adds. "You can take it out of bacteria with minimal changes. Almost every guide RNA you'd want to make goes to a place that works. It's fast, and it's permanent."

Church expects that Editas will proceed to clinical trials quickly after first completing animal studies. Other recently launched CRISPR-centric companies include Caribou Biosciences and Egenesis.

Finally, the most controversial of the latest RNA discoveries concerns lncRNAs. First described in 2002, these unusually lengthy stretches of RNA originate in the nucleus and look, at first glance, as though they might be mRNAs except that they lack certain sequences of letters required to initiate the translation process.

What could the cell possibly want with all these extra RNA molecules? Some of them undoubtedly result from the transcription of earlier versions of genes that are now broken and no longer functional. (One of the more surprising discoveries of the genetic revolution is that almost all DNA found in the nucleus is transcribed, not just the parts that code for proteins.) Others are probably echoes of long-ago attacks by certain kinds of viruses that can incorporate their genetic material into a cell's DNA, allowing it to be passed on through subsequent generations.

Yet what if some of the lncRNAs represent a previously unsuspected way of regulating the expression of genes—one that does not require potentially dangerous mutations in the DNA or that does not depend on proteins to play the starring role? Think of the DNA as being folded like origami, says RNA researcher John Rinn of Harvard University. With two identical pieces of paper, you could make a plane or a crane, and lncRNA somehow pushes the DNA to make sure the steps occur in the right order. Just as a mistake in origami folding could render the paper crane wingless, too much noncoding RNA, for example, might trigger the growth of a tumor without a single mutation ever having had to occur in the genes of the cell.

Another possibility under investigation is that lncRNA molecules may attach themselves to different parts of a DNA molecule, changing the latter's three-dimensional shape and therefore exposing it to, or hiding it from, further activity.

An entire host of other noncoding RNAs have been proposed and are in various stages of being confirmed as important genetic regulators or dismissed as genetic ghosts. One of the difficulties of studying noncoding RNAs is precisely the fact that they do not give rise to proteins—which makes it harder to prove that they are doing something important. "I think it's just the early days yet," says John Mattick, a leader in research into noncoding RNA and director of the Garvan Institute of Medical Research in Australia. "There's a whole new world emerging here."

Meanwhile considering the broad range of RNA compounds that are being designed and tested brings up what may be the molecule's most appealing feature—its simplicity. Unlike proteins, whose three-dimensional structure must typically be characterized before drug developers can create effective medications, RNA basically consists of a two-dimensional sequence (leaving aside, for the moment, some of the shapes into which RNA molecules can fold). "It's reducing a three-dimensional problem, where the small molecule has to fit perfectly into the protein in a lock-and-key-type fit, to a two-dimensional, linear problem," Isis's MacLeod says. Thanks to the Human Genome Project, researchers already know the most important sequences in the genome. All they need to do is synthesize the complementary RNA strand, and they have created the bull's-eye for their efforts.

Figuring out how to put theory into practice is still a struggle, of course. But for now, at least, the magical glass slipper appears to fit.

> An early trickle of financial interest has turned into a multibillion-dollar torrent. One start-up recently received **$43 million,** and a slightly older company scored **$700 million** to develop its pipeline of RNA medicines.

Christine Gorman *is a senior editor and* ***Dina Fine Maron*** *is an associate editor at* Scientific American.

MORE TO EXPLORE

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FROM OUR ARCHIVES

Journey to the Genetic Interior. Stephen S. Hall; October 2012.

Journey to the Bottom of the Sea

MARINE EXPLORATION

High-tech submersibles are poised to systematically explore the ocean's deepest trenches, answering long-standing questions about exotic creatures, the source of tsunamis and the origin of life on earth

By Mark Schrope

ROBOT DIVER Nereus will usher in an era of advanced deep-sea exploration with a 10,000-meter plunge into the Kermadec Trench.

Mark Schrope is a freelance writer and editor based in Florida who has spent more than seven months at sea on oceanographic expeditions. He also works as a communications consultant for Schmidt Ocean Institute.

On April 10 the U.S. research vessel *Thomas G. Thompson* will steam 900 kilometers northeast from New Zealand and stop in the wide open Pacific Ocean. If all goes according to plan, it will drop Nereus, a robotic vehicle the size of a subcompact car. Nereus will dive, and dive, and dive down to one of the deepest and most hostile places on earth: the Kermadec Trench. It will hit bottom at just beyond 10,000 meters—the extent of Mount Everest, plus a modest Smoky Mountain. There, in frigid, absolute darkness, under water pressure of 15,000 pounds per square inch—the equivalent of three SUVs pushing down on your big toe—Nereus will shine its lights on the unknown. A video camera will stream imagery back up to the *Thompson* along a drifting, fiber-optic filament the width of a human hair, which Nereus will have spooled out as it sank.

Scientists onboard the *Thompson* will be glued to their computer screens to see what strange life-forms appear. As they watch, Nereus's robot arm will grab animals and rocks from the trench floor. It will thrust a stiff tube into the seabed and pull up a core sample of the sediment there. And the robot will slurp glassfuls of water in hopes of trapping bacteria and other organisms that manage to survive in the extreme conditions.

Biologists and geologists have every reason to believe Nereus will reveal amazing wonders. But the expedition has a still greater significance. Humans have rarely ventured below 6,000 meters, to the ultradeep trenches worldwide known as the hadal zone. The April expedition, led by the Woods Hole Oceanographic Institution (WHOI), marks the beginning of an era scientists have spent decades fighting and longing for: a systematic exploration of the planet's final frontier. The Nereus mission is "the dawn of hadal science as an enterprise," says Patricia Fryer, a marine geologist at the University of Hawaii at Manoa. "And it's an enterprise that could very well provide us with some incredible discoveries."

Hadal exploration is ready to take off because the stars of funding, technology and publicity have aligned. The public's attention was riveted on the hadal zone in 2012, when movie director and explorer James Cameron piloted a one-man submersible down to the bottom of the deepest place on the planet, in another trench called the Mariana. WHOI has improved the deep-sea technology needed to make Nereus strong yet nimble. Funding is rising. And with other vehicles being built, extended access to the deepest places in the world is becoming realistic.

Money is still tight, of course, and the task is enormous—the trenches of the world's hadal zone occupy an area nearly the size of Australia. Where should deep-sea vehicles go? What should they look for? In interviews with more than a dozen ocean experts, the consensus converges on a small number of top priorities. Among them: Figuring out how creatures survive such crushing pressure. Investigating whether organisms big and small host novel compounds that could lead to new drugs. Determining how tsunami-spawning earthquakes are born. And answering the ultimate question: Could the trenches have spawned the start of life on earth, as some scientists have suspected but have had no way to prove or disprove?

NEW CREATURES GALORE

THE NEREUS MISSION could make strong progress on several priorities in the research agenda—if it survives the water pressure itself and if its robot arm and sensors work. The $8-million robot's greatest strengths are that it can take live video and cover

IN BRIEF

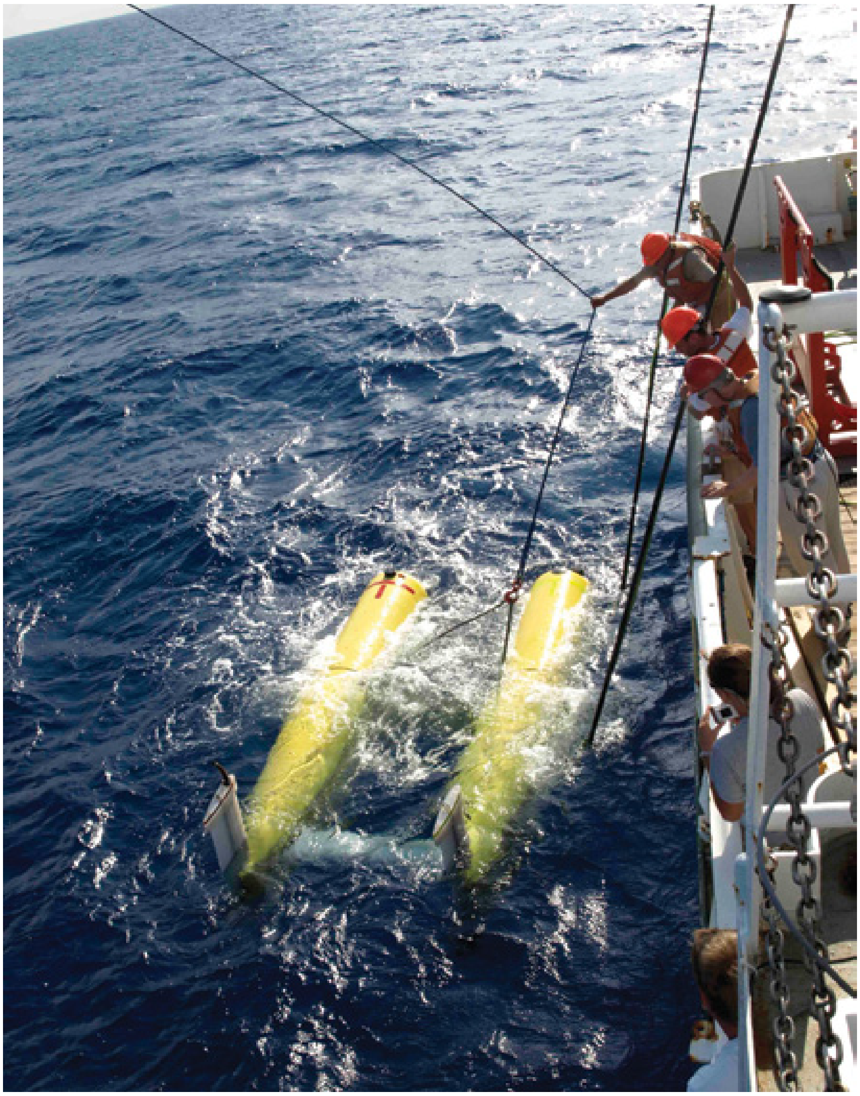
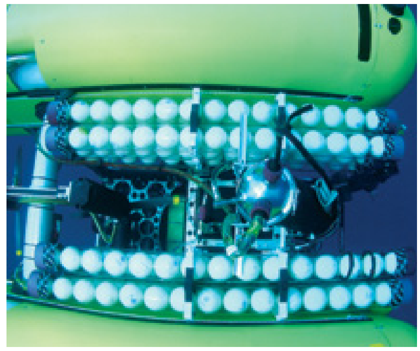
In April the submersible Nereus will dive to the bottom of the Kermadec Trench, at 10,047 meters. It will take live video of strange creatures and collect rock, sediment and water samples.

Technology, money and publicity are finally poised to support the first systematic exploration of the deepest ocean trenches. Research priorities include figuring out how organisms survive the immense water pressure and whether life on earth began there, fueled by chemical energy instead of solar energy.

Unusual compounds found in deep-sea creatures could lead to novel pharmaceuticals, and rocks could reveal why certain tsunamis become so large.

Debate is under way about whether future manned or unmanned missions will provide the best payoff.

PRECEDING PAGES: COURTESY OF ADVANCED IMAGING AND VISUALIZATION LABORATORY, WOODS HOLE OCEANOGRAPHIC INSTITUTION

WORKHORSE: The Nereus robot is a proving ground for technology. The vehicle is lowered from a support ship (*left*). Hollow ceramic flotation spheres (*top*) with walls only 0.127 centimeter thick can withstand 16,500 pounds of pressure per square inch. Underwater video is monitored from the ship (*middle*). On one 10,000-meter dive, Nereus nabbed a leathery sea cucumber (*bottom*).

COURTESY OF CHRIS R. GERMAN *WHOI* (*Nereus*); COURTESY OF ADVANCED IMAGING AND VISUALIZATION LABORATORY, WHOI (*flotation packages*); COURTESY OF WHOI (*observation room*); COURTESY OF TIMOTHY SHANK *WHOI* AND NATIONAL SCIENCE FOUNDATION (*animal specimen*)

far more ground and collect more rock, sediment and water samples than the many "landers" that researchers have dropped off ships in the past—the small pods that sink to one spot on the bottom, providing useful but limited information. Nereus can also stay submerged for up to 12 hours, and even if the tether breaks it can return to the ship on its own.

Those capabilities mean Nereus may be well suited for surveying bizarre life-forms—the first order of business on the agenda. Until now, scientists have been searching in isolated places. Nereus will take them on an extended virtual trip through the Kermadec Trench, collecting all kinds of biological samples as it goes. "I think we'll be surprised," says Timothy Shank, a WHOI deep-sea biologist and chief scientist for the April mission. "It'll be things we haven't thought about, even though we think we've thought about everything. That's what's driving me."

A visitor to the laboratory where Shank stores preserved samples of brittle stars, shrimp, tube worms and other deep-ocean dwellers, will see shelves marked with names of intriguing locations around the globe, such as the Galápagos Rift or the Mid-Atlantic Ridge. But not a single shelf sports the name of a hadal trench because so few samples have been collected.

With rare exceptions, manned and unmanned vehicles have been designed to plunge only a little past the top of the hadal zone, the 6,000-meter level. Intense pressure and other factors make operating deeper much more complicated and expensive. The full hadal depths remain virtually unexplored.

Only four vehicles have made it to the deepest spot on the planet—the 10,989-meter depression called Challenger Deep in the Mariana Trench, near Guam. Don Walsh, a U.S. Navy officer, and Swiss ocean engineer Jacques Piccard made the first trip in 1960 in *Trieste,* a massively fortified, blimp-shaped bathyscaphe. Nobody saw the spot again until 1995, when the Japan

SOURCES: WHOI AND "HADAL TRENCHES: THE ECOLOGY OF THE DEEPEST PLACES ON EARTH," BY ALAN J. JAMIESON ET AL., IN *TRENDS IN ECOLOGY & EVOLUTION*, VOL. 25, NO. 3; MARCH 2010

Exploring the World's Deepest Ocean Trenches

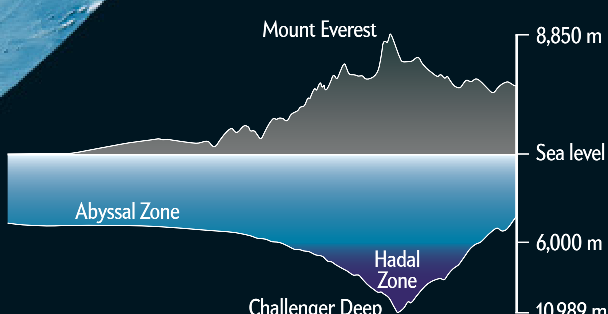
The most remote, mysterious places on the planet are the incredibly deep and long ocean trenches. Most of the 14 major trenches are in the Pacific Ocean (*list at far left*). They are generally only a few kilometers across at the bottom, but they can be up to 2,000 kilometers long and together make up the hadal zone (*below*), which is nearly the size of Australia. They are almost entirely unexplored, however. Scientists on ships have dropped dozens of small "lander" pods that hit bottom and take video or collect limited samples, but only a few robotic vehicles (*triangles*) and manned submersibles (*squares*) have made the trip. Researchers are angling for more of these missions, in hopes of finding the world's most bizarre creatures as well as the true origin of life on earth.

Oceans Apart

Three quarters of the deep ocean trenches are in the Pacific because tectonic plates there often converge, one diving down underneath the other. Fewer plates lie below the Atlantic, and many of them diverge—they spread apart from one another, forming new seafloor. The deepest trenches are depicted here; another 20 or so shallower ones are not shown.

Hadal Zone

Line up dozens of Mount Everests, turn them upside down, jam them all the way into the seafloor, then pull them back out. The phenomenal gash that would remain approximates an ocean trench (*below*), which forms when two massive tectonic plates butt together and one slides down under the other into oblivion. Exploration of these hadal zones (deeper than 6,000 meters) has been limited but could pick up (*map above left*).



Map by XNR Productions

Agency for Marine-Earth Science and Technology (JAMSTEC) sent down a remotely operated vehicle named Kaiko. The Nereus came next, reaching Challenger Deep in 2009. Three years later Cameron did it in person in his private *DEEPSEA CHALLENGER* submersible.

Most of the dives collected scientific samples, but the trips were primarily engineering tests—prove you can make it there, and you can make it anywhere. Kaiko offered great promise for long-term science, but after limited work in hadal regions it was lost at sea during a massive storm in 2003. Its main replacement can dive to only 7,000 meters. Another vehicle, Abismo, can go to 10,000 meters but has dramatically reduced capabilities and has seen little action.

Shank is hoping Nereus will soon fill a shelf marked Kermadec. The expedition is part of the Hadal Ecosystems Studies program, or HADES, funded by the National Science Foundation—the umbrella under which scientists from the U.S., U.K., New Zealand and Japan will begin tackling the hadal agenda.

Earlier expeditions focused on the flat center of the Challenger Deep, a sediment plain, because of its superlative depth, but that is not the most interesting spot scientifically. The most intriguing parts of trenches are the rocky outcrops and slopes along the sidewalls.

Researchers chose the walls of Kermadec as their first target because the waters above harbor lots of life, which in turn can mean more food drifting down toward life at the bottom. (In contrast, the Mariana Trench lies underneath a relatively unproductive sea.) Because Nereus can run for hours, investigators hope it will not only see but snare creatures for genetic analyses—as long as the animal is not too large or too quick a swimmer.

Kermadec "is meant to be a landmark for the first systematic exploration and a benchmark for future studies," Shank says. "Then we'll go into other trenches for comparison." And he is confident they will get that chance: "Momentum is so strong."

Each trench could have its own unique set of life-forms, but HADES leaders are cautious about this proposition. Researchers once thought seamounts (underwater mountains) each harbored unique species, but further work revealed that that assumption was wrong, mostly because exploration had been too limited.

THRIVING UNDER PRESSURE

THE SECOND BIOLOGICAL PRIORITY is almost as basic as the first: figuring out how cells in critters big and small can function under such immense pressure. Understanding the mechanisms could lead to new kinds of medical compounds for people.

The mystery goes back to Walsh and Piccard's 1960 dive. They spent 20 minutes on the bottom and reported seeing a flatfish, but they had no cameras. Biologists now question that observation.

"There's no way they saw a flatfish, absolutely no way," says Jeffrey C. Drazen, a deep-sea fish specialist and a HADES leader. Work suggests fish simply cannot withstand such pressure. The deepest fish ever definitively observed were seen on video at about 7,700 meters. Walsh acknowledges he is not an ichthyologist but defends his sighting. "All I can say is I think I've seen a few fish. But they keep telling me I didn't see one."

In the 1990s Paul Yancey, a biologist at Whitman College, discovered that as depth increases, fish cells have increasingly higher concentrations of trimethylamine *N*-oxide (TMAO)—the same chemical that makes fish stink. That pattern has held down to about 7,000 meters—the deepest Yancey and Drazen, now a collaborator, have samples for.

Exactly how TMAO might stabilize proteins against pressure is not clear, and its effectiveness may have limits. In the fish bloodstream, TMAO functions something like salt, helping to maintain the osmotic pressure that determines whether water will diffuse in or out. At about 8,000 meters, a fish's saltiness should roughly match seawater. According to the hypothesis, if a fish went much deeper, so much water would diffuse into its cells that it would not survive. Scientists cannot prove a negative outcome, but if they do not find fish at deeper hadal depths they would have a pretty strong case against fish in those regions.

That said, Yancey says he would be happy if Nereus proves him wrong. "I'd love to have that fish, to figure out what's going on."

Based on the little information available, other creatures such as crabs and shrimp also seem limited to about 8,000 meters. But on the few past missions researchers have seen organisms such as sea cucumbers as well as crustaceans called amphipods. Microbes have been ubiquitous. Yancey thinks these life-forms could have additional protein-stabilizing chemicals, or piezolytes, which he found in amphipods that Cameron's team collected.

Biomedical researchers were already studying another compound that Yancey turned up, scyllo-inositol, as a potential treatment for Alzheimer's disease, which is one of several that involve protein-folding problems. That relevance has biologists excited about discovering potentially useful protein stabilizers in organisms that survive in the trenches.

Doug Bartlett, a microbiologist at the Scripps Institution of Oceanography, has also done initial work with hadal bacteria collected by landers and with sediment Cameron was able to grab. Bartlett will be studying bacteria in water, sediment and animal samples Nereus collects, and he hopes to eventually get samples in containers that maintain hadal pressures, so he can observe how cells survive in real time.

CARBON AND TSUNAMIS

BECAUSE SO LITTLE HADAL WORK has been done, a single data set from Nereus or another mission could help address top priorities in multiple disciplines. That is the case with the critical question of how much carbon is raining down or sliding down into the trenches.

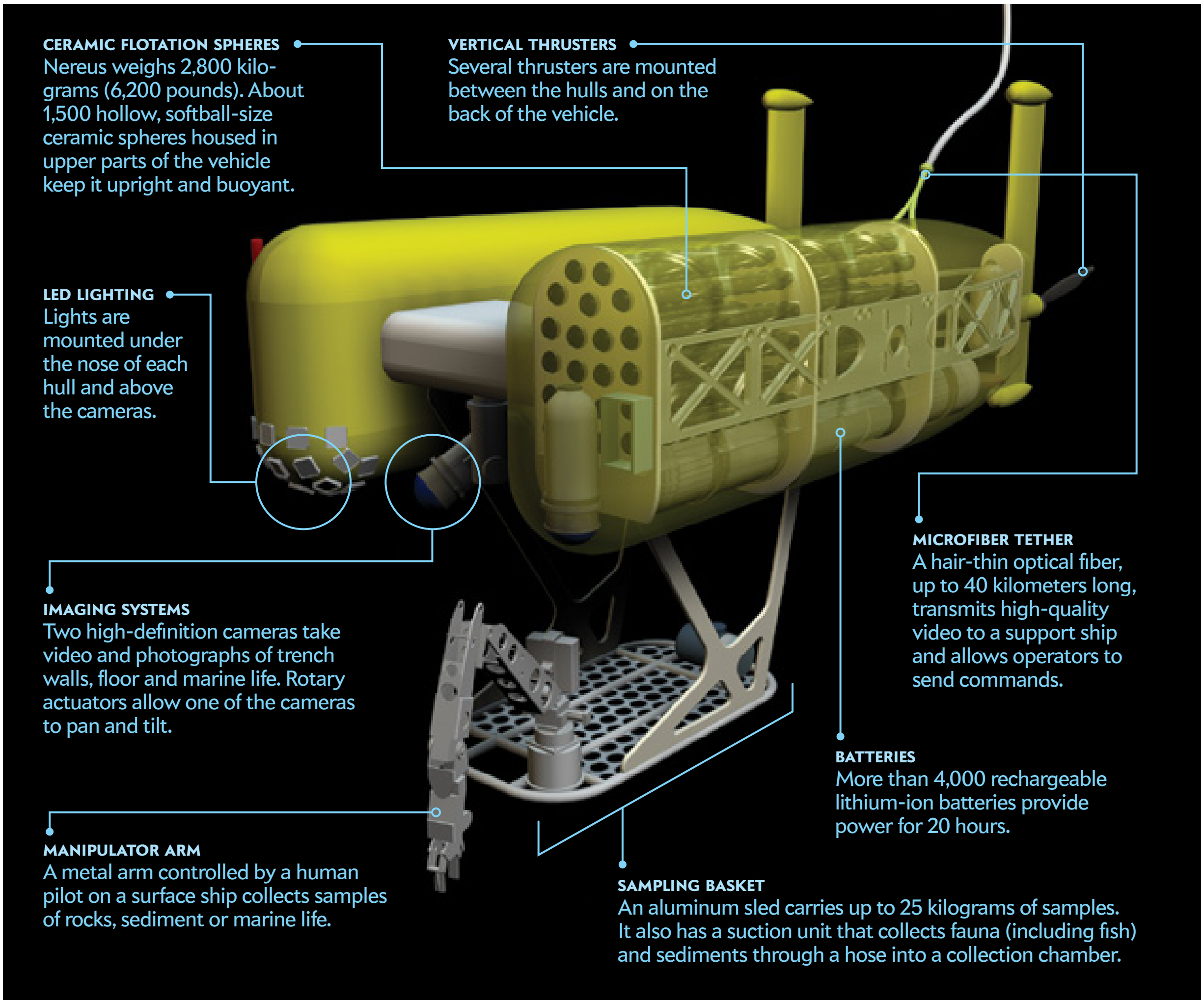
For ocean organisms, carbon-based molecules are food. The cascade includes all kinds of pleasantries, such as dead algae and fish as well as poop from shallower residents. Levels can decrease with depth because much of what sinks gets consumed on its way to the bottom. But trenches could also be acting like funnels that concentrate organic matter from above and from sediment that slumps down the walls. Knowing where carbon concentrates might tell biologists where to find the greatest diversity of animals, and ample food could mean more and larger animals than expected.

Geochemists are fixated on that same carbon because the oceans absorb roughly 40 to 50 percent of the carbon dioxide that humans and nature emit into the atmosphere, slowing the greenhouse effect. Researchers think a lot of the carbon may get buried on the seafloor, but they cannot say even within a factor of 10 how much carbon is in the trenches.

Nereus will collect sediment that the HADES team will analyze for carbon. They will also measure oxygen to assess biolog-

Anatomy of Nereus

Nereus is the world's most capable unmanned deep-sea diver. This month the remotely operated vehicle will descend 10,000 meters to the bottom of the Kermadec Trench, tethered to a ship at the surface. Since Nereus's last deep dive, to the Mariana Trench in 2009, the Woods Hole Oceanographic Institution has upgraded its flotation, cameras and lighting (*details below*). If the craft's basket and robot arm are removed, it can also operate as a free-swimming autonomous underwater vehicle, giving researchers a tour of the seafloor.



COURTESY OF WHOI

ical activity there. "I've got the world's deepest oxygen sensors that I'm dying to actually get into the trench," Drazen says.

Geologists are interested in another aspect of the trench floor that could hit the public much closer to home, literally.

The magnitude 9 Tohoku earthquake that caused the devastating 2011 tsunami and Fukushima nuclear reactor meltdown in Japan occurred in the Japan Trench. Many scientists were shocked that a quake so large was possible there, says Hiroshi Kitazato of JAMSTEC. Researchers have drilled sediment cores there from surface ships and have a few rock samples from a robot that can go to 7,000 meters.

But the trench is 1,500 meters deeper, and the epicenter was well below the seafloor. Experts are not even sure how to survey such areas appropriately, says Gerard Fryer, a geophysicist at the Pacific Tsunami Warning Center in Honolulu. "A huge amount will be learned if we can get some eyes down there." Deeper rock samples could improve understanding of how stress progresses in fault zones, and more sediment samples could help researchers assess evidence that the types of sediment in trenches could affect the magnitude of quakes.

The other process that comes up when geologists make their hadal wish list is serpentinization. It is key to understanding the long-term balance between how tectonic plates are built and destroyed. The destruction occurs where trenches form, when two plates butt up against each other and one slides down underneath. Much of the material melts, and serpentinization, which involves water reacting with certain rocks, is key to maintaining this part of the balance.

Deep Thoughts, from James Cameron

The filmmaker discusses the need for more aquatic exploration and why, when it comes to the ocean's deepest abysses, there's nothing like being there in person

James Cameron is the only solo diver to ever reach the deepest spot on the planet—the Challenger Deep, nearly 11,000 meters down in the Mariana Trench, southwest of Guam. An upcoming documentary film will commemorate his feat, which the movie director (Avatar, Titanic) *and explorer achieved on March 26, 2012. Cameron gained respect among scientists by going to great lengths to ensure the dive included significant research goals. He has since donated his* DEEPSEA CHALLENGER *submersible to the Woods Hole Oceanographic Institution, which was scheduled to hold a major robotic expedition this April* [see accompanying article].

Scientific American *sat down with Cameron during a trip to Woods Hole, where his own team was working with the organization's engineers. Edited excerpts follow.*

INTO THE ABYSS: James Cameron hopes his solo journey to the bottom of the world's greatest ocean trench will inspire additional exploration and discovery.

What was it like to finally sit on the bottom of the Challenger Deep?
There was a tremendous sense of accomplishment and pride in the team, knowing the obstacles everybody had to overcome. Certainly there was no sense of jeopardy. That wasn't in my mind at all. I trusted the engineering. There was a sense of privilege getting to look at something no human eyes had seen before. But at the same time I was wondering if that was a xenophyophore [large single-celled organism] outside my window. My initial impression was that it was very lunar and desolate. It turned out that was deceptive. There were all sorts of little critters, but I could see only a few. Others we saw on the high-definition video when researchers went through it. There's only so much you can learn on a given dive. Thirty feet to the left or right of me could be the discovery of the century. It whets the appetite and makes you want to do more.

Why hasn't there been more focus in recent years on human-occupied vehicles for deep-sea research?
Human-occupied vehicles still have a critically important role to play, but they are inherently larger than ROVs [remotely operated vehicles] and AUVs [autonomous underwater vehicles], and operations are more expensive. Given the current climate for deep-ocean science funding, which is, well, abysmal, many researchers' only chance for access to extreme depths is with simple robotic landers, AUVs or ROVs. But it's a self-fulfilling prophecy to say that human-occupied vehicles won't yield the science return if all you ever build are unmanned vehicles. This is why disruptive projects like *DEEPSEA CHALLENGER* are important—they shake up ossified belief systems.

> "If the government doesn't support exploration, it's going to have to be done using private sources or commercial sources, and that's where we are right now."

What's your take on the state of government-funded ocean exploration?
It's a failed paradigm at this point. If the government doesn't support exploration, it's going to have to be done using private sources or commercial sources, and that's where we are right now.

What aspects of deep-trench research do you find most intriguing?
Finding evidence to support the hypothesis that the emergence of life might have been powered by chemical reactions driven by subduction [the tectonic process that forms trenches] could be a really fruitful area. We know tectonics has been going on pretty much since the earth's formation, and here we've got a nice, constant, long-duration energy source. With that hypothesis in mind, when I was on the bottom I felt like I was looking at the cradle of life itself.

What do you want to do next?
We haven't made a decision. I'd like to see hybrid AUV/ROV systems built to explore the hadal depths [below 6,000 meters] and would support such a project if someone else were driving it. But I can't run such a project myself for a few years—my day job will be the *Avatar* sequels. I will come back to it. We've barely scratched the bottom. We've thrown just a handful of darts at the board. *—Mark Schrope*

COURTESY OF MARK THIESSEN *National Geographic*

SCIENTIFIC AMERICAN ONLINE For a first-person account of Don Walsh's historic 1960 dive, see ScientificAmerican.com/apr2014/schrope

Or so scientists think. Rock and sediment samples from trenches, along with detailed views of surrounding areas, could go a long way to proving or disproving theories, says Daniel Lizarralde, a geologist at WHOI. Nereus could bring that information from Kermadec or its mission to Mariana later this year. "This would be the first confirmation that processes that seem logical actually take place in reality," Patricia Fryer says.

CRADLE OF LIFE

SERPENTINIZATION MAY ALSO HOLD part of the answer to the ultimate question of whether life on earth emerged from the deepest sea. The process releases heat, hydrogen, methane and minerals—a recipe for chemical-based, or chemosynthetic, life. In some deep-sea locations, chemical reactions supply the energy that living organisms run on, not photosynthetic energy from the sun. Some scientists reason that life might have begun at hydrothermal vents—holes in the seafloor where seawater that has cycled into the rock below reemerges, heated and loaded with chemicals and minerals. Most of us have seen the images of huge tube worms that have been found at these places.

Vents tend to be ephemeral, however, so some scientists now question whether they could have really spawned life. A newer hypothesis proposes that serpentinization in trenches could have more readily fueled the first life because it occurs across much larger areas and is sustained for much longer in geologic time. Cameron says this idea is what most compelled him during his visit to the Challenger Deep: "I felt like I was looking at the cradle of life itself."

In fact, during Cameron's test dives before the full descent, his team dropped an instrumented lander into the Sirena Deep, a location close to Challenger Deep and only slightly shallower. The fiberglass box, about the size of a refrigerator, had water samplers, a baited trap, a video camera and other devices. On one deployment it happened to land in front of what appeared to be a stringy, white microbial mat. "It was like playing darts blindfolded and throwing a bull's-eye," Cameron says.

Kevin Hand, a planetary scientist and astrobiologist at the NASA Jet Propulsion Laboratory who worked on the expedition, made the discovery while reviewing video footage. When the lander hit bottom, it must have kicked up some microbes, which were captured by a sampler. Early results suggest that the bacteria have genes that would enable them to use compounds released by serpentinization to create energy.

Of course, there is no reason hydrothermal vents could not also exist in the deepest trenches. The species seen at shallow vents are odd enough; add the daunting pressure of a trench, and there is no telling what kind of strange life might be found.

UNDERWATER SPACE RACE

THE AGENDA FOR HADAL SCIENTISTS is exciting but for now will be difficult to accomplish, with only one primary vehicle, Nereus, at their disposal. Cameron has given WHOI rights to the technologies developed for his sub, as well as the sub itself, but the institute has no plans yet to dive with it, in part because of insurance issues.

The options could increase by the end of 2015. The Schmidt Ocean Institute, founded by Google executive chairman Eric Schmidt and his wife, Wendy Schmidt, is working with WHOI to build a Nereus successor called N11K. It will have a greater payload for samples and two robot arms instead of one so it can grab hold of the seafloor with one arm and really dig into it with the other. [Disclosure: I am a consultant for Schmidt on media communications.]

Manned vehicles are not likely to play a major role, at least for the next few years. As in the U.S. space program, debate is under way over the relative merits of human-occupied vehicles. Shank and Patricia Fryer say video cannot replace a person's 3-D visual ability to make sense of what is seen at deep, dark depths.

Cameron adds that manned missions provide inspiration [*see box on opposite page*]. Indeed, Virgin Group founder Richard Branson and partner Chris Welsh, an entrepreneur, intend to pilot a one-person submersible to the deepest spot in each of the planet's five loosely defined oceans. Problems with their prototype vehicle's clear dome have slowed the project.

Triton Submarines in Vero Beach, Fla., has designed a three-person sub that would reach the deepest trenches but has not acquired the funding needed to build it. China, which recently christened a 7,000-meter manned vehicle, is designing one to reach full hadal depth, as is Japan, but both projects are years from completion.

At JPL, Hand is designing a small autonomous vehicle that could be launched in groups over the side of a small vessel. He says the cost target is about $10,000 a pod, so fleets would be possible and losing one would not be catastrophic. He, along with engineers from JPL and from Cameron's group, is seeking NASA funding. "We want to take some capabilities and lessons learned from robotic exploration of worlds like Mars and beyond and bring that capability and the talent to bear on the exploration of our ocean," Hand says.

As exploration technology and money expand, researchers will face the welcome challenge of deciding which trenches and troughs to plumb next. Very different creatures might live in the remote conditions of the 8,428-meter-deep South Sandwich Trench just above Antarctica. The Puerto Rico Trench could offer valuable information about connections between trenches. And there are a few open seafloor plains in the hadal zone that researchers would love to compare against trenches.

Patricia Fryer is trying to secure funding for a workshop that would bring together deep-sea scientists from around the world to discuss priorities and the best ways to move forward. Prior research was piecemeal, and as in outer space, coordinated international work could most efficiently exploit funding and expertise, rather than a competitive race to the bottom among nations. "I think the community of marine scientists is ready" to complete a systematic hadal agenda, Fryer says. Drazen agrees: "We have the technology now to explore these places. And people are champing at the bit, ready to go." SA

MORE TO EXPLORE

Hadal Trenches: The Ecology of the Deepest Places on Earth. Alan J. Jamieson et al. in *Trends in Ecology & Evolution,* Vol. 25, No. 3, pages 190–197; March 2010.

Nereus mission site: www.whoi.edu/main/nereus

FROM OUR ARCHIVES

Threatening Ocean Life from the Inside Out. Marah J. Hardt and Carl Safina; August 2010.

The Blue Food Revolution. Sarah Simpson; February 2011.

NEUROSCIENCE

THE GENETIC GEOGRAPHY OF THE BRAIN

The first detailed maps of what our genes are doing inside our brains show how very different we are from mice and challenge a long-held theory of how our gray matter works

By Ed Lein and Mike Hawrylycz

Illustration by Scotty Reifsnyder

Ed Lein is a neurobiologist and **Mike Hawrylycz** is an applied mathematician at the Allen Institute for Brain Science in Seattle. Together they have played leading roles in the design and analysis of the brain atlas projects for the mouse, rhesus macaque and human brains.

As you read these words, your eyes scan the page, picking up patterns to which your mind assigns meaning. Meanwhile your heart contracts and relaxes, your diaphragm rises and drops to control your breathing, your back muscles tense to maintain your posture, and a thousand other basic tasks of conscious and subconscious life proceed, all under the coordinated control of roughly 86 billion neurons and an equal number of supporting cells inside your skull. To neuroscientists like us, even the simple act of reading a magazine is a wondrous feat—as well as an example of perhaps the hardest problem in science today: in truth, we cannot yet fully explain how the human brain thinks and why the brain of a monkey cannot reason as we do.

Neuroscientists have intensely studied the human brain for more than a century, yet we sometimes still feel like explorers who have landed on the shores of a newly discovered continent. The first to arrive plotted the overall boundaries and contours. In the early 1900s German scientist Korbinian Brodmann sliced up human brains and placed them under his microscope to examine the cerebral cortex—the exterior layers of gray matter that handle most perception, thought and memory. He parceled this cortex into several dozen regions based on the topology of the organ and how the cells in each area appear when labeled with various stains.

A view gradually took hold that each region, each cluster of cells of a particular kind, handles a specific set of functions. Some neuroscientists challenged this theory that function is parceled by location. But the parcellation model has returned to vogue with the emergence of new tools, most prominently functional magnetic resonance imaging (MRI), which records what parts of the brain "light up" (consume oxygen) as people read, dream or even tell lies. Researchers have been exploiting this technology to construct "maps" that relate what they see using these tools to real-world human behavior.

A newer school of thought, however, postulates that the brain is more like an informal social network than one having a rigid division of labor. In this view, the connections that a neuron has made with other brain cells determine its behavior more than its position does, and the behavior of any given region is influenced strongly by its past experience and current situation. If this idea is correct, we can expect to see overlapping activity among the particular locations that handle the brain's responsibilities. Testing this hypothesis will be tricky; brain circuits are hard to trace, and the billions of neurons in a human brain connect at perhaps 100 trillion links, or synapses. But projects are under way to develop the new tools needed for the job [*see box on opposite page*].

In 2003, as the Human Genome Project published the sequence of code letters in human DNA, we and our colleagues

IN BRIEF

A mammoth effort to create a genetic "atlas" of the human brain has succeeded in mapping the activity of all genes throughout the entirety of six typical adult brains.

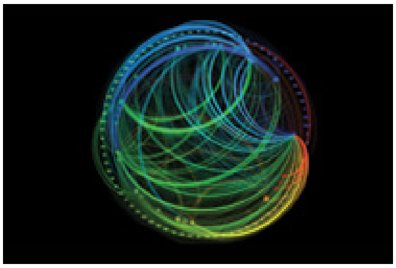
The new atlas reveals profound differences between mice and human brains that raise questions about the widespread use of mice as experimental proxies for people.

The atlas, along with other projects under way to map the detailed structure of the brain, will serve as landmark references in the search for the causes and cures of neurological disease.

OTHER BRAIN PROJECTS

Big Science at Work

Several well-funded, multiyear projects are under way in the U.S. and Europe to disentangle the daunting complexity of the brain. Some are tracing neural connections within brains. Others are making ultrahigh-resolution three-dimensional models of the human brain or mapping gene "expression," or activity, in the brains of other animals.

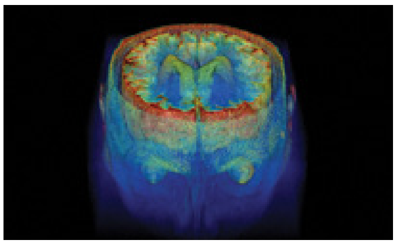


↑ **SyNAPSE** is a DARPA program that aims to create digital analogues of the brain from neurosynaptic chips that include 10 billion electronic neurons joined by 100 trillion synapses. In 2012 a group at IBM reported that a proof-of-concept supercomputer simulation at Lawrence Livermore National Laboratory had simulated half a second of activity among 530 billion highly simplified neurons connected at almost 137 trillion synapses. **http://research.ibm.com/cognitive-computing/neurosynaptic-chips.shtml**

Mouse Brain Connectivity Atlas project at the Allen Institute for Brain Science in Seattle infects neurons with viruses that make fluorescent proteins as they work their way down the cells. The glowing viruses trace the extended, branching arms of the nerve cells, which link up in complex, extended circuits. **http://connectivity.brain-map.org**

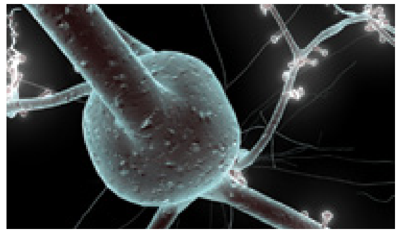
Non-Human Primate Brain Atlas project is mapping gene expression in the brains of rhesus macaque monkeys as they develop from an early prenatal stage to four years old. The NIH-funded project is now under way at the Allen Institute. **http://blueprintnhpatlas.org**

BigBrain project, a collaboration of scientists in Germany and Canada, has produced a 3-D model of a human brain from a 65-year-old woman at a resolution of 20 microns, which is nearly sharp enough to make out single cells. **https://bigbrain.loris.ca**

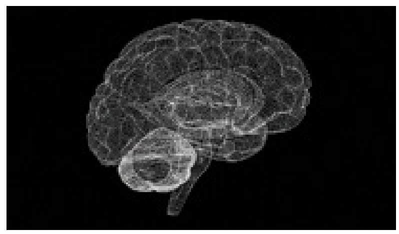


↑ **Human Connectome Project,** which was launched in 2010 by the NIH and a consortium of universities, is recruiting 1,200 healthy adults—including hundreds of pairs of twins and their nontwin siblings—to gather detailed brain images, genetic sequences and behavioral profiles for a reference database. **http://humanconnectome.org**

EyeWire, developed at the Massachusetts Institute of Technology, lets members of the public do some of the work involved in mapping the paths of brain neurons. **http://eyewire.org**



↑ **Blue Brain Project,** a joint effort started in 2005 by IBM Research and the Swiss Federal Institute of Technology in Lausanne, has been using a supercomputer to build a virtual brain in software. The project has simulated a pinhead-size column of about 10,000 layered neurons from a rat's cortex. **http://bluebrain.epfl.ch**



↑ **Human Brain Project,** a successor to the Blue Brain Project, was launched in October 2013 by the European Union. The 10-year project has a budget of $1.6 billion and aims to create a "CERN for brain research," with high-powered computing capabilities comparable to those used by the particle physics center outside Geneva that runs the Large Hadron Collider. **http://humanbrainproject.eu**

COURTESY OF IBM RESEARCH (SyNAPSE); COURTESY OF ZACH WISE AND NEW YORK TIMES (*Human Connectome Project*); COURTESY OF EPFL AND BLUE BRAIN PROJECT (*Blue Brain Project and Human Brain Project*)

at the Allen Institute for Brain Science in Seattle saw an opportunity to use the new catalogue of 20,000 or so human genes and rapidly improving gene-scanning systems to look at the human brain from a new perspective—one that might inform this debate. We realized that by combining the tools of genetics with those of classic neuroscience, we could plunge deep into the jungle of the uncharted continent: we could actually map which parts of the genome are active, and which are dormant, throughout the entire volume of the brain. We expected that this map would show a very different set of genes turned on in, say, the part of the brain that handles hearing from those parts that control touch, movement or reasoning.

Our goal, which ultimately took nearly a decade to achieve, was to produce three-dimensional atlases plotting where individual genes operate in the brains of healthy humans and, for comparison, mice. (We are now working to add monkeys as well.) Such molecular maps provide invaluable benchmarks for what is "normal"—or at least typical—in much the same way that the reference DNA sequence produced by the Human Genome Project does. We expect these atlases to accelerate progress in neuroscience and drug discovery while allowing investigators to explore their fundamental curiosity about the structure of the human mind.

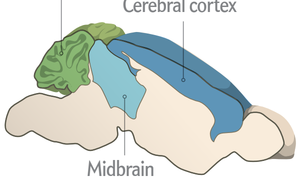
Already these new views of the inner working of human and rodent brains have produced some surprises. One big one: although every person is unique, the patterns of gene activity

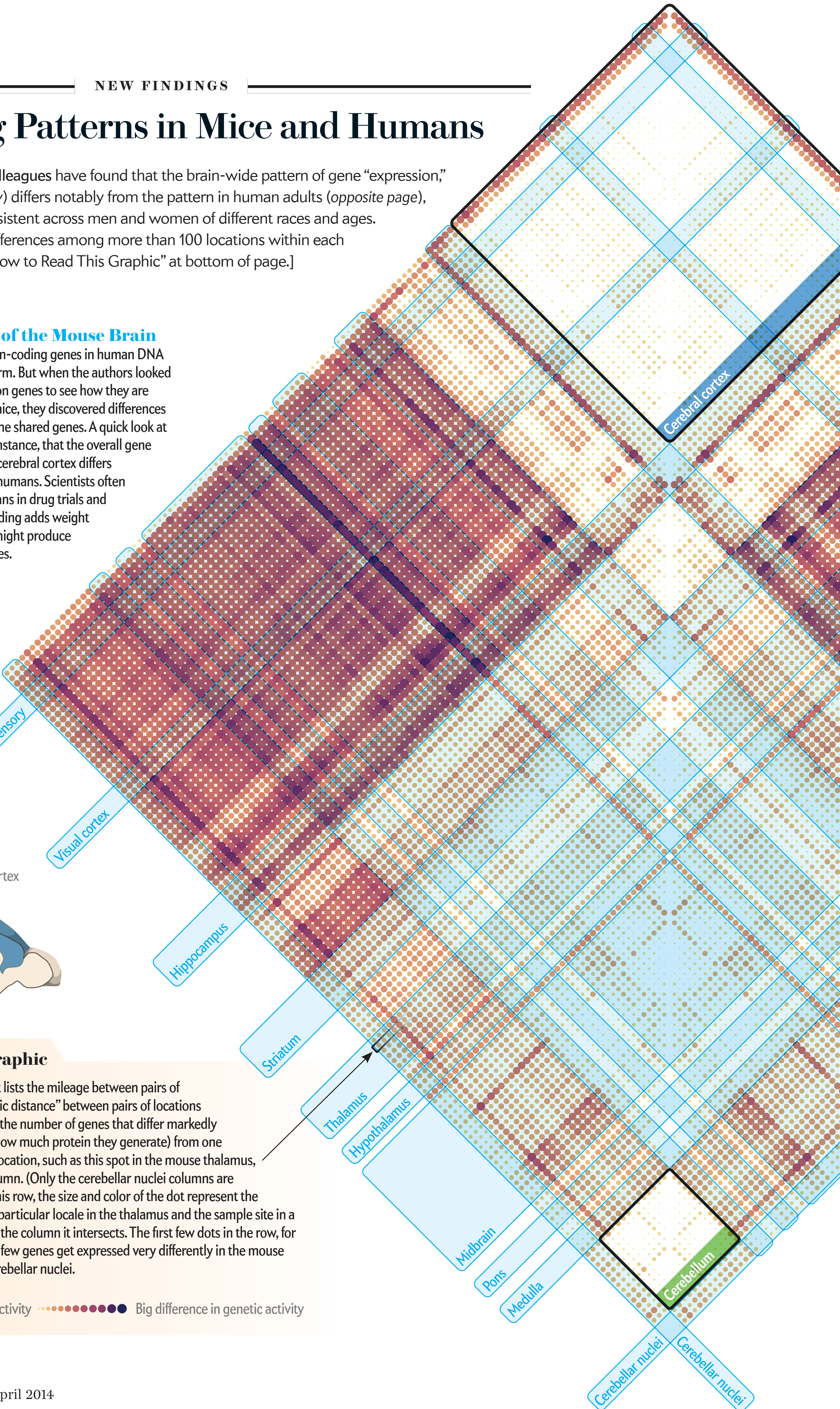
Surprising Patterns in Mice and Humans

The authors and their colleagues have found that the brain-wide pattern of gene "expression," or activity, in mice (*below*) differs notably from the pattern in human adults (*opposite page*), which is remarkably consistent across men and women of different races and ages. The grids plot activity differences among more than 100 locations within each brain. [For details, see "How to Read This Graphic" at bottom of page.]

Genetic Geography of the Mouse Brain

About 90 percent of the protein-coding genes in human DNA also appear in mice in some form. But when the authors looked at about 1,000 of these common genes to see how they are actually used in the brains of mice, they discovered differences in activity for about a third of the shared genes. A quick look at the graphics here reveals, for instance, that the overall gene activity pattern outside of the cerebral cortex differs noticeably between mice and humans. Scientists often study mice as proxies for humans in drug trials and neuroscience research; this finding adds weight to concerns that the practice might produce misleading results in some cases.





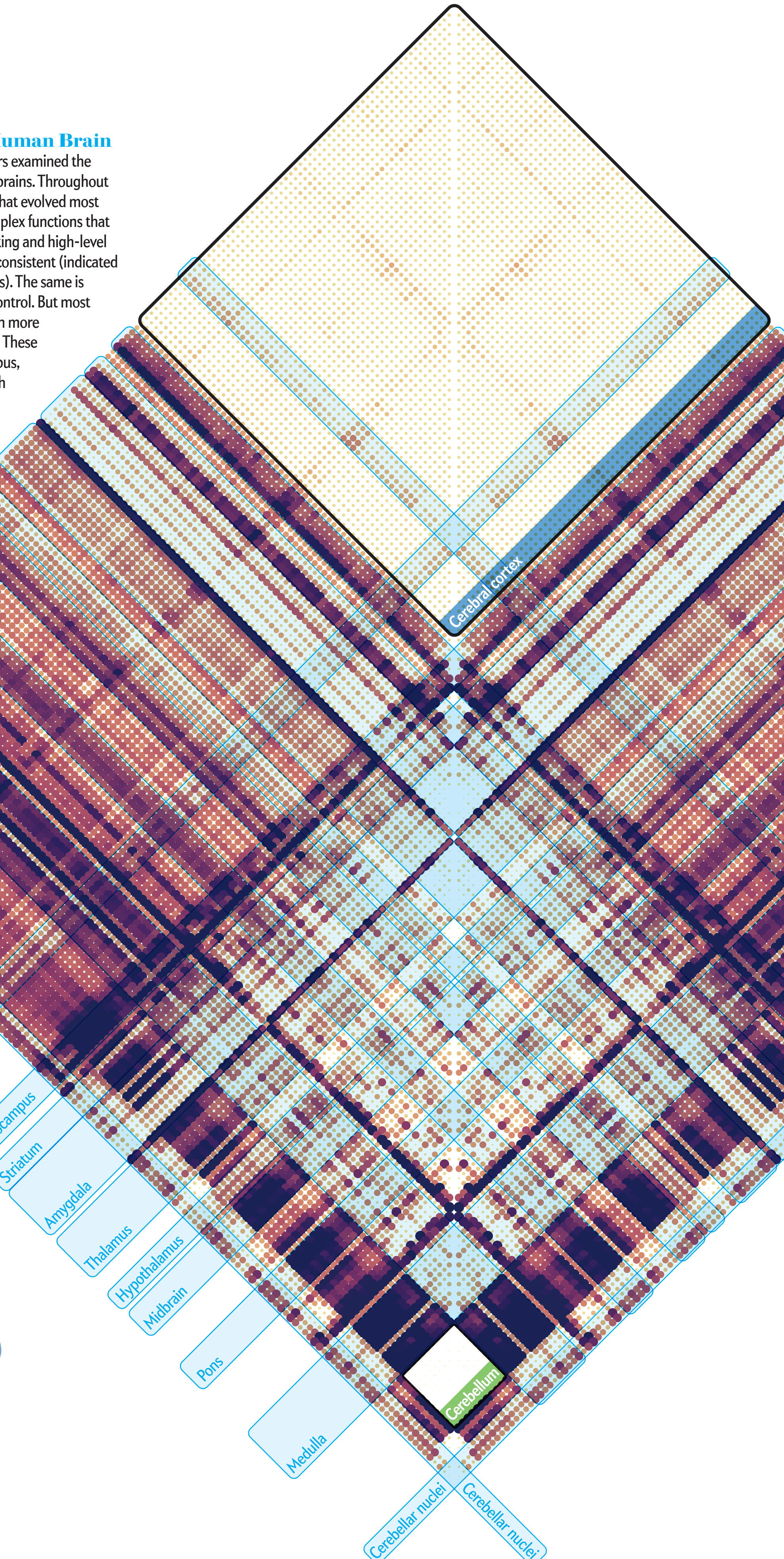
How to Read This Graphic

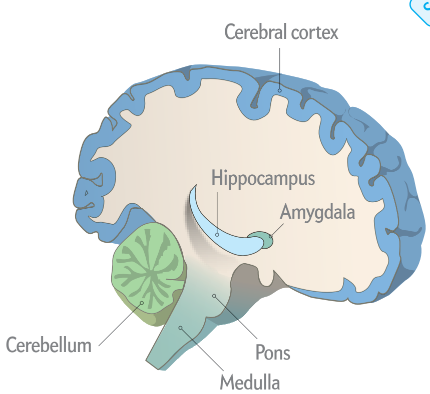
Like the table in a road atlas that lists the mileage between pairs of cities, this chart plots the "genetic distance" between pairs of locations in the brain—or more precisely, the number of genes that differ markedly in their activity level (that is, in how much protein they generate) from one place to another. Each physical location, such as this spot in the mouse thalamus, appears as both a row and a column. (Only the cerebellar nuclei columns are labeled here.) At each point in this row, the size and color of the dot represent the activity difference between this particular locale in the thalamus and the sample site in a part of the brain represented by the column it intersects. The first few dots in the row, for example, indicate that relatively few genes get expressed very differently in the mouse thalamus than they do in the cerebellar nuclei.

Very little difference in genetic activity ●●●●●●● Big difference in genetic activity

Genetic Geography of the Human Brain

Another surprise surfaced when researchers examined the detailed pattern of gene activity in human brains. Throughout the cerebral cortex—the part of our brain that evolved most recently and is most involved in highly complex functions that are unique to humans, such as reading, talking and high-level reasoning—genetic activity is remarkably consistent (indicated by the relatively plain, light-colored patches). The same is true of the cerebellum, a center of motor control. But most of the other regions of the brain show much more internal variation in gene expression levels. These include structures—such as the hippocampus, pons and medulla—that humans share with birds and other very distantly related vertebrates and that handle simpler functions such as breathing, hunger and sleep.





SOURCE: MIKE HAWRYLYCZ

Graphic by Jan Willem Tulp, Illustration by Jen Christiansen (brains) are remarkably similar from one human brain to the next. Despite our differences, people share a common genetic geography in their brains. Moreover, within each individual, we unexpectedly found no major differences in gene actions between the left brain and right brain. And although mice are used as proxies for humans in most neuroscience research and early drug trials, it is clear from these new results that, at a genetic level, humans are not simply large mice. This discovery calls into question the use of mice as models for understanding the neurobiology of our own species.

FROM MOUSE TO HUMAN

NO ONE HAD EVER MADE a complete genetic map of a mammal's brain before. To work out the many details, we started small, with a mouse brain. Mice have about as many genes as humans do, but their brains are a mere 3,000th the mass of ours.

Within three years we had processed more than a million slices of mouse brain, dousing each one with visible markers that stick wherever a particular gene is expressed—meaning that the gene is used; it is copied from the DNA into a short piece of RNA called a transcript. RNA transcripts are intermediate steps en route to the final product encoded by a gene, which is usually a protein that does work in the cell, such as carrying out an enzymatic reaction or serving as some piece of cellular machinery. Some RNA transcripts do useful work directly without ever being translated into protein form, and we were able to look for about a thousand kinds of such noncoding RNAs in addition to all the protein-coding genes.

> **The fundamental similarity of genetic activity in human and monkey brains points to the wiring among the neurons, rather than the genetic activity within the cells, as the likely source of our distinctiveness.**

Beyond honing our techniques, the mouse project handed us one of our first surprises. Of course, as in a human, almost every cell in a mouse contains a complete set of chromosomes and thus at least one copy of every gene in the animal's genome. In mature cells, a sizable fraction of these genes are silent at any given moment—no RNA is being made from them. Yet when we completed the mouse atlas in 2006, we saw that many genes—more than four out of every five—possessed by mice were functioning somewhere in the animals' brains at the time they died. (Neurobiologists know that, for the most part, patterns of genetic activity shift during life on a timescale of hours and persist for many hours after death.) As we began to make plans to create a human brain atlas, we wondered whether human brains would show a similarly high level of genetic activity—and more important, whether the specific patterns of activity would closely resemble those that we observed in mice.

We received our first human brain in the summer of 2009, from a 24-year-old African-American man whose brain had been donated by his family, scanned by MRI to make a virtual 3-D model of the intact organ, and then frozen solid, all within 23 hours of his accidental death—fast enough to lock in the normal RNA patterns. Aside from asthma, he had been healthy.

To deal with the 3,000-fold increase in size from the mouse brain project, we switched to a different method to measure gene expression. The frozen brain was cut into thin slices, which were stained and photographed in high detail. Anatomists then used lasers to snip microscopic samples from about 900 structures that we had preselected at positions throughout the brain. Molecular biologists tested each sample using a DNA microarray, a mass-produced gadget that simultaneously measures the amount of RNA present from every individual protein-coding gene in the human genome.

After we had collected data in this way from the first brain, we put all the results together into a computer database. We could select any gene and see how much of its corresponding RNA was present in each of the 900 sampled structures and thus how actively that gene was being expressed in the hours before the donor died. As we chose one gene after another, it was a thrill to see very different patterns emerge. Now the real exploration could begin.

SHADES OF GRAY MATTER

EARLY ON, AS WE ANALYZED THE DATA on the first brain thoroughly, we saw unexpectedly that gene expression patterns in the left hemisphere were mirrored, almost exactly, in the right hemisphere. The idea that the left side of the brain is specialized for certain functions, such as math and language, and that the right side contributes more to artistic and creative thought may be well established in popular culture, but we saw no evidence of such differences in the genetic patterns within this brain. We confirmed that finding with the second brain we examined. The results were so conclusive that we have studied just one hemisphere on each of the four brains we have processed since; this discovery accelerated the construction of the atlas by a year or more.

As we had seen in mice, the great majority of genes—84 percent of the different kinds of RNA transcripts we looked for—were active somewhere within the six human brains. The organ performs an uncommonly wide span of jobs, and the atlas revealed that distinct collections of genes are at work in each major region, contributing to its particular functions.

The donors of the brains we studied included both men and women, young and old, black, white and Hispanic. Some of them had big brains; others were smaller. Despite these differences,

SCIENTIFIC AMERICAN ONLINE See a slide show of brain images at ScientificAmerican.com/apr2014/allen

all six brains had highly consistent patterns of gene activity. More than 97 percent of the time, when we saw lots of RNA being made from a gene in a section of one brain, the same was happening in a majority of the others.

We began examining the sets of genes active in various parts of the brain. For example, we compared the genes being used most heavily in the ancient midbrain, which humans share with reptiles, against those highly active in the cerebral cortex. Neurologists have long known that cells in the more primitive parts of the brain—structures such as the hypothalamus, the hippocampus and the pons (responsible for managing body temperature, hunger, spatial memory and sleep)—cluster into distinct nuclei that behave rather differently from one another. We found that many of these nuclei express distinct sets of genes. Within these primal structures is a cacophony of genetic voices clamoring at once.

The cortex, on the other hand, is different in both its cellular structure and its genetic activity. The cortex consists of a wide variety of cell types arranged into a sheet with six layers of gray matter. It evolved relatively recently and expanded to become proportionally much more prominent in humans than in other animals; the gray matter is what gives rise to the unique complexity of human behavior and individual personality. We naturally wondered: In this most human part of the brain, does the complexity of function arise from huge differences among the genes being expressed in one part of the cortex versus another? Brodmann divided the cortex into dozens of well-defined parcels, after all, and we expected that the different roles each parcel plays in human behavior arise from correspondingly different suites of genes being put to use.

But the atlas suggests that the answer is no: gene activity in the cortex for any given cell type is remarkably homogeneous within the gray matter, all the way from the forehead to the back of the skull.

We did find that each cortical cell type has a distinct genetic signature. But remarkably few sharp boundaries show up in the genetic geography—with the notable exception of the visual cortex at the back of the brain, which processes input from the eyes. The cerebellum, which sits at the base of the brain and is another structure that expanded in humans recently, is similarly a sea of homogeneity.

These results are hard to reconcile with the Brodmann-inspired idea that the cortex divides neatly into parcels devoted to particular functions whose behavior is governed by the genes at work inside them. The atlas instead supports an alternative theory: genes define each of the various cell types, as well as the basic blueprint for a small column of cortex that arranges cells of those different kinds in a predefined way from the surface of the brain to the bottom of the cortex. But the cortex as a whole consists of many copies of that canonical column. How the cortex behaves overall appears to depend much more on the specific ways that neurons are wired into circuits—and the history of stimuli hitting those circuits—than it does on shifts in genetic activity from one Brodmann region to another.

MORE LIKE MONKEYS

When we compared roughly 1,000 genes active in the cortex of both mouse and human, we were amazed to find that nearly a third of them are being expressed quite differently. Some genes are silent in one species but not the other, for instance, whereas many others are used at much different rates.

The degree of similarity between mouse and human matters because almost all neurological experiments and drug trials are performed first on mice. Rodents are cheap, grow quickly, and are easy to control and examine. Yet therapies that succeed in mice rarely translate directly to effective treatments in people. The variance in gene expression between the two species could help explain why that is.

In striking contrast, the data we have analyzed so far on rhesus macaque monkeys suggests that fewer than 5 percent of genes are expressed in their brains in a significantly different way than in ours. Our consortium's work on a brain atlas for monkeys is still under way, so that number may change as we gather more data. Nevertheless, the observation that genetic activity in human and monkey brains is so fundamentally similar again points to the wiring among the neurons of our brains, rather than the genetic activity within the cells, as the likely source of our distinctiveness as a species. Moreover, it is clear that we need to put more detailed information about the human brain in the hands of researchers and pharmaceutical companies to help them distinguish those drug targets that can be modeled in mice from those that should be studied in animals more closely related to humans.

Since we released the brain atlas for the mouse in 2007, it has been used in more than 1,000 scientific studies. For the human brain atlas, which was opened to public view with the first two brains in 2010, the next logical steps are to improve the resolution and scope of the map. We have learned that we will not ultimately understand the role that gene activity plays in brain function until we measure gene expression patterns in individual brain cells. Doing that is truly a grand challenge for an organ as large and complex as the human brain. But new technologies are emerging that allow neurogeneticists to measure protein-coding RNA from single cells. These tools also enable detection of all transcribed pieces of RNA, which could clarify whether RNAs that do not give rise to proteins—the so-called dark matter of the genome—play important roles in the brain.

To make it easy for scientists who are researching disorders of the brain, such as autism, Alzheimer's disease and Parkinson's disease, to use the atlas, the Allen Institute has made all our data—as well as a point-and-click viewer called Brain Explorer—freely available online. We hope these early attempts to understand human brain function through its genetic map will pave the way for others to build on it in unforeseen ways. SA

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CLIMATE CHANGE

False Hope

The rate of global temperature rise may have hit a plateau, but a climate crisis still looms in the near future

By Michael E. Mann

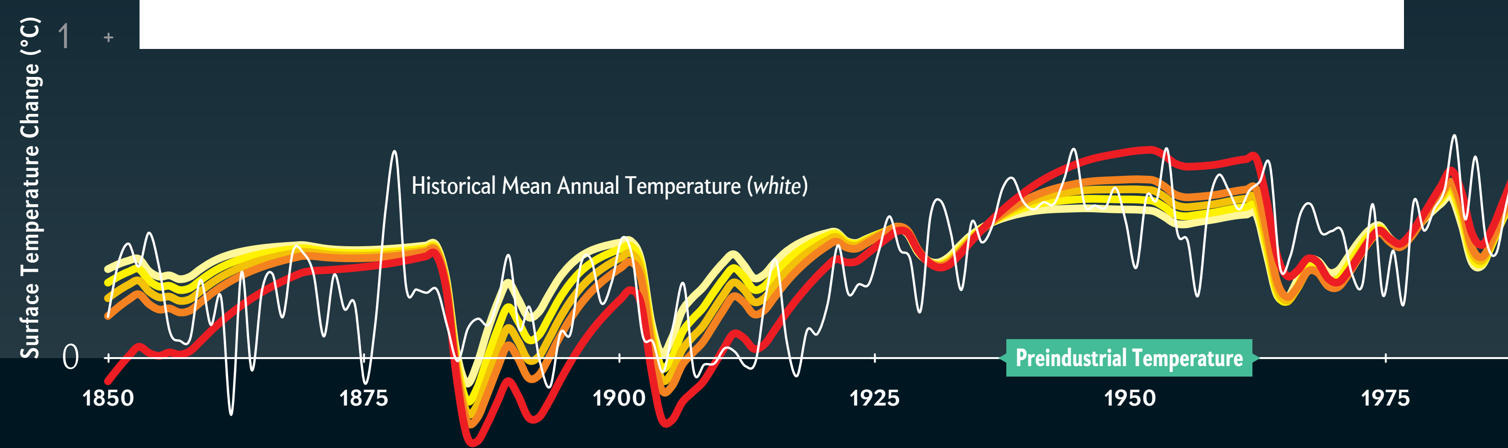
"Temperatures have been flat for 15 years—nobody can properly explain it," the *Wall Street Journal* says. "Global warming 'pause' may last for 20 more years, and Arctic sea ice has already started to recover," the *Daily Mail* says. Such reassuring claims about climate abound in the popular media, but they are misleading at best. Global warming continues unabated, and it remains an urgent problem.

The misunderstanding stems from data showing that during the past decade there was a slowing in the rate at which the earth's average surface temperature had been increasing. The event is commonly referred to as "the pause," but that is a misnomer: temperatures still rose, just not as fast as during the prior decade. The important question is, What does the short-term slowdown portend for how the world may warm in the future?

The Intergovernmental Panel on Climate Change (IPCC) is charged with answering such questions. In response to the data, the IPCC in its September 2013 report lowered one aspect of its prediction for future warming. Its forecasts, released every five to seven years, drive climate policy worldwide, so even the small change raised debate over how fast the planet is warming and how much time we have to stop it. The IPCC has not yet weighed in on the impacts of the warming or how to mitigate it, which it will do in reports that were due this March and April. Yet I have done some calculations that I think can answer those questions now: If the world keeps burning fossil fuels at the current rate, it will cross a threshold into environmental ruin by 2036. The "faux pause" could buy the planet a few extra years beyond that date to reduce greenhouse gas emissions and avoid the crossover—but only a few.

A SENSITIVE DEBATE

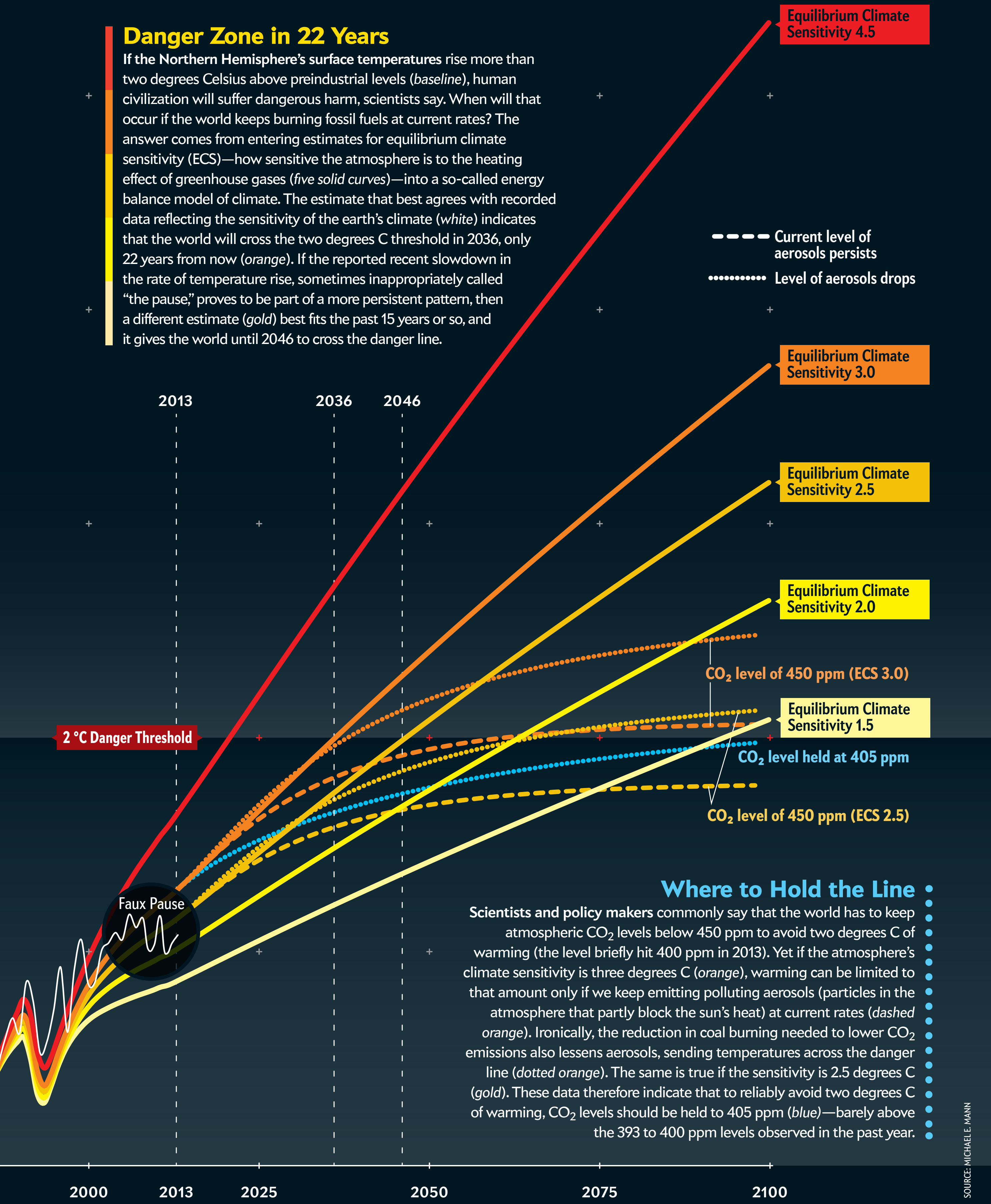
THE DRAMATIC NATURE of global warming captured world attention in 2001, when the IPCC published a graph that my co-authors and I devised, which became known as the "hockey stick." The shaft of the stick, horizontal and sloping gently downward from left to right, indicated only modest changes in Northern Hemisphere temperature for almost 1,000 years—as far back as our data went.



SCIENTIFIC AMERICAN ONLINE Detailed information on the energy balance model simulation is available at ScientificAmerican.com/apr2014/mann

Danger Zone in 22 Years

If the Northern Hemisphere's surface temperatures rise more than two degrees Celsius above preindustrial levels (*baseline*), human civilization will suffer dangerous harm, scientists say. When will that occur if the world keeps burning fossil fuels at current rates? The answer comes from entering estimates for equilibrium climate sensitivity (ECS)—how sensitive the atmosphere is to the heating effect of greenhouse gases (*five solid curves*)—into a so-called energy balance model of climate. The estimate that best agrees with recorded data reflecting the sensitivity of the earth's climate (*white*) indicates that the world will cross the two degrees C threshold in 2036, only 22 years from now (*orange*). If the reported recent slowdown in the rate of temperature rise, sometimes inappropriately called "the pause," proves to be part of a more persistent pattern, then a different estimate (*gold*) best fits the past 15 years or so, and it gives the world until 2046 to cross the danger line.



Where to Hold the Line

Scientists and policy makers commonly say that the world has to keep atmospheric CO_2 levels below 450 ppm to avoid two degrees C of warming (the level briefly hit 400 ppm in 2013). Yet if the atmosphere's climate sensitivity is three degrees C (*orange*), warming can be limited to that amount only if we keep emitting polluting aerosols (particles in the atmosphere that partly block the sun's heat) at current rates (*dashed orange*). Ironically, the reduction in coal burning needed to lower CO_2 emissions also lessens aerosols, sending temperatures across the danger line (*dotted orange*). The same is true if the sensitivity is 2.5 degrees C (*gold*). These data therefore indicate that to reliably avoid two degrees C of warming, CO_2 levels should be held to 405 ppm (*blue*)—barely above the 393 to 400 ppm levels observed in the past year.

Graphic by Pitch Interactive

The upturned blade of the stick, at the right, indicated an abrupt and unprecedented rise since the mid-1800s. The graph became a lightning rod in the climate change debate, and I, as a result, reluctantly became a public figure. In its September 2013 report, the IPCC extended the stick back in time, concluding that the recent warming was likely unprecedented for at least 1,400 years.

Although the earth has experienced exceptional warming over the past century, to estimate how much more will occur we need to know how temperature will respond to the ongoing human-caused rise in atmospheric greenhouse gases, primarily carbon dioxide. Scientists call this responsiveness "equilibrium climate sensitivity" (ECS). ECS is a common measure of the heating effect of greenhouse gases. It represents the warming at the earth's surface that is expected after the concentration of CO_2 in the atmosphere doubles and the climate subsequently stabilizes (reaches equilibrium).

The preindustrial level of CO_2 was about 280 parts per million (ppm), so double is roughly 560 ppm. Scientists expect this doubling to occur later this century if nations continue to burn fossil fuels as they do now—the "business as usual" scenario—instead of curtailing fossil-fuel use. The more sensitive the atmosphere is to a rise in CO_2, the higher the ECS, and the faster the temperature will rise. ECS is shorthand for the amount of warming expected, given a particular fossil-fuel emissions scenario.

It is difficult to determine an exact value of ECS because warming is affected by feedback mechanisms, including clouds, ice and other factors. Different modeling groups come to different conclusions on what the precise effects of these feedbacks may be. Clouds could be the most significant. They can have both a cooling effect, by blocking out incoming sunlight, and a warming effect, by absorbing some of the heat energy that the earth sends out toward space. Which of these effects dominates depends on the type, distribution and altitude of the clouds—difficult for climate models to predict. Other feedback factors relate to how much water vapor there will be in a warmer atmosphere and how fast sea ice and continental ice sheets will melt.

Because the nature of these feedback factors is uncertain, the IPCC provides a range for ECS, rather than a single number. In the September report—the IPCC's fifth major assessment—the panel settled on a range of 1.5 to 4.5 degrees Celsius (roughly three to eight degrees Fahrenheit). The IPCC had lowered the bottom end of the range, down from the two degrees C it had set in its Fourth Assessment Report, issued in 2007. The IPCC based the lowered bound on one narrow line of evidence: the slowing of surface warming during the past decade—yes, the faux pause.

Many climate scientists—myself included—think that a single decade is too brief to accurately measure global warming and that the IPCC was unduly influenced by this one, short-term number. Furthermore, other explanations for the speed bump do not contradict the preponderance of evidence that suggests that temperatures will continue to rise. For example, the accumulated effect of volcanic eruptions during the past decade, including the Icelandic volcano with the impossible name, Eyjafjallajökull, may have had a greater cooling effect on the earth's surface than has been accounted for in most climate model simulations. There was also a slight but measurable decrease in the sun's output that was not taken into account in the IPCC's simulations.

Michael E. Mann is Distinguished Professor of Meteorology at Pennsylvania State University and contributed to the International Panel on Climate Change work that received the 2007 Nobel Peace Prize. His book *The Hockey Stick and the Climate Wars: Dispatches from the Front Lines* (Columbia University Press, 2012) is in paperback, with a foreword by Bill Nye the Science Guy.

Natural variability in the amount of heat the oceans absorb may have played a role. In the latter half of the decade, La Niña conditions persisted in the eastern and central tropical Pacific, keeping global surface temperatures about 0.1 degree C colder than average—a small effect compared with long-term global warming but a substantial one over a decade. Finally, one recent study suggests that incomplete sampling of Arctic temperatures led to underestimation of how much the globe actually warmed.

None of these plausible explanations would imply that climate is less sensitive to greenhouse gases. Other measurements also do not support the IPCC's revised lower bound of 1.5 degrees C. When all the forms of evidence are combined, they point to a most likely value for ECS that is close to three degrees C. And as it turns out, the climate models the IPCC actually used in its Fifth Assessment Report imply an even higher value of 3.2 degrees C. The IPCC's lower bound for ECS, in other words, probably does not have much significance for future world climate—and neither does the faux pause.

For argument's sake, however, let us take the pause at face value. What would it mean if the actual ECS were half a degree lower than previously thought? Would it change the risks presented by business-as-usual fossil-fuel burning? How quickly would the earth cross the critical threshold?

A DATE WITH DESTINY: 2036

MOST SCIENTISTS CONCUR that two degrees C of warming above the temperature during preindustrial time would harm all sectors of civilization—food, water, health, land, national security, energy and economic prosperity. ECS is a guide to when that will happen if we continue emitting CO_2 at our business-as-usual pace.

I recently calculated hypothetical future temperatures by plugging different ECS values into a so-called energy balance model, which scientists use to investigate possible climate scenarios. The computer model determines how the average surface temperature responds to changing natural factors, such as volcanoes and the sun, and human factors—greenhouse gases, aerosol pollutants, and so on. (Although climate models have critics, they reflect our best ability to describe how the climate system works, based on physics, chemistry and biology. And they have a proved track

IN BRIEF

The rate at which the earth's temperature has been rising eased slightly in the past decade, but temperature is still increasing; calling the slowdown a "pause" is false.

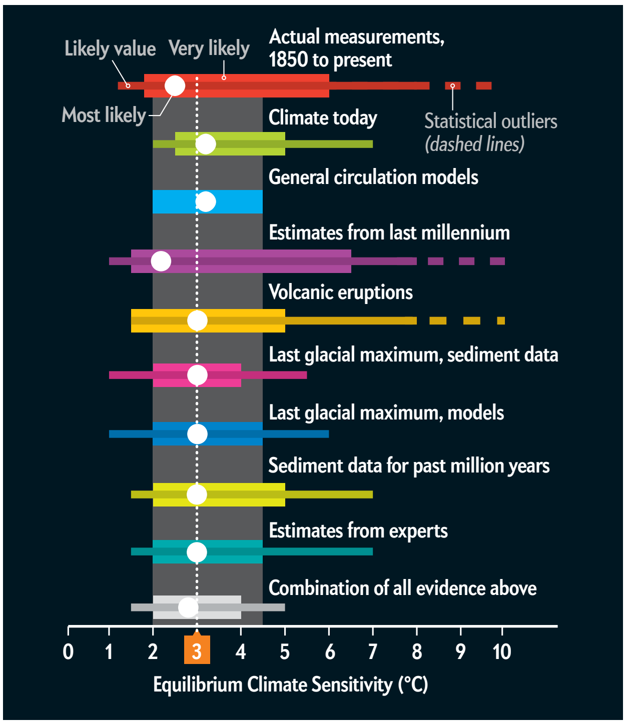
New calculations by the author indicate that if the world continues to burn fossil fuels at the current rate, global warming will rise to two degrees Celsius by 2036, crossing a threshold that will harm human civilization.

To avoid the threshold, nations will have to keep carbon dioxide levels below 405 parts per million.

PREDICTING THE FUTURE

A Solid Line of Evidence

Determining when the planet's atmosphere will cross the dangerous warming threshold of two degrees C [*see graph on pages 78 and 79*] depends on how sensitive the atmosphere is to rising CO_2 levels. The most likely value for this equilibrium climate sensitivity (*horizontal axis*) is just below three degrees C. Why? Because many independent calculations of temperature in the distant past, as well as many climate models, place the number very close to this value (*various color bars*). The product of all the lines of evidence appears at the bottom (*gray bar*).



SOURCE: "THE EQUILIBRIUM SENSITIVITY OF THE EARTH'S TEMPERATURE TO RADIATION CHANGES," BY RETO KNUTTI AND GABRIELE C. HEGERL, IN *NATURE GEOSCIENCE,* VOL. 1; NOVEMBER 2008

record: for example, the actual warming in recent years was accurately predicted by the models decades ago.)

I then instructed the model to project forward under the assumption of business-as-usual greenhouse gas emissions. I ran the model again and again, for ECS values ranging from the IPCC's lower bound (1.5 degrees C) to its upper bound (4.5 degrees C). The curves for an ECS of 2.5 degrees and three degrees C fit the instrument readings most closely. The curves for a substantially lower (1.5 degrees C) and higher (4.5 degrees C) ECS did not fit the recent instrumental record at all, reinforcing the notion that they are not realistic.

To my wonder, I found that for an ECS of three degrees C, our planet would cross the dangerous warming threshold of two degrees C in 2036, only 22 years from now. When I considered the lower ECS value of 2.5 degrees C, the world would cross the threshold in 2046, just 10 years later [*see graph on pages 78 and 79*].

So even if we accept a lower ECS value, it hardly signals the end of global warming or even a pause. Instead it simply buys us a little bit of time—potentially valuable time—to prevent our planet from crossing the threshold.

CAUTIOUS OPTIMISM

THESE FINDINGS HAVE IMPLICATIONS for what we all must do to prevent disaster. An ECS of three degrees C means that if we are to limit global warming to below two degrees C forever, we need to keep CO_2 concentrations far below twice preindustrial levels, closer to 450 ppm. Ironically, if the world burns significantly less coal, that would lessen CO_2 emissions but also reduce aerosols in the atmosphere that block the sun (such as sulfate particulates), so we would have to limit CO_2 to below roughly 405 ppm.

We are well on our way to surpassing these limits. In 2013 atmospheric CO_2 briefly reached 400 ppm for the first time in recorded history—and perhaps for the first time in millions of years, according to geologic evidence. To avoid breaching the 405-ppm threshold, fossil-fuel burning would essentially have to cease immediately. To avoid the 450-ppm threshold, global carbon emissions could rise only for a few more years and then would have to ramp down by several percent a year. That is a tall task. If the ECS is indeed 2.5 degrees C, it will make that goal a bit easier.

Even so, there is considerable reason for concern. The conclusion that limiting CO_2 below 450 ppm will prevent warming beyond two degrees C is based on a conservative definition of climate sensitivity that considers only the so-called fast feedbacks in the climate system, such as changes in clouds, water vapor and melting sea ice. Some climate scientists, including James E. Hansen, former head of the NASA Goddard Institute for Space Studies, say we must also consider slower feedbacks such as changes in the continental ice sheets. When these are taken into account, Hansen and others maintain, we need to get back down to the lower level of CO_2 that existed during the mid-20th century—about 350 ppm. That would require widespread deployment of expensive "air capture" technology that actively removes CO_2 from the atmosphere.

Furthermore, the notion that two degrees C of warming is a "safe" limit is subjective. It is based on when *most* of the globe will be exposed to potentially irreversible climate changes. Yet destructive change has already arrived in some regions. In the Arctic, loss of sea ice and thawing permafrost are wreaking havoc on indigenous peoples and ecosystems. In low-lying island nations, land and freshwater are disappearing because of rising sea levels and erosion. For these regions, current warming, and the further warming (at least 0.5 degree C) guaranteed by CO_2 already emitted, constitutes damaging climate change today.

Let us hope that a lower climate sensitivity of 2.5 degrees C turns out to be correct. If so, it offers cautious optimism. It provides encouragement that we can avert irreparable harm to our planet. That is, if—and only if—we accept the urgency of making a transition away from our reliance on fossil fuels for energy. SA

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Integral calculus originated in a 17th-century debate that was as religious as it was scientific

By Amir Alexander

MATHEMATICS

THE SECRET SPIRITUAL HISTORY OF CALCULUS

EDITORS' NOTE: Countless students learn integral calculus—the branch of mathematics concerned with finding the length, area or volume of an object by slicing it into small pieces and adding them up. What few realize is that their calculus homework originated, in part, in a debate between two 17th-century scholars. In 1635 Italian mathematician Bonaventura Cavalieri declared that any plane is composed of an infinite number of parallel lines and that any solid is made of an infinite number of planes. His "method of indivisibles" became a forerunner of integral calculus—but not before surviving attacks from Swiss mathematician Paul Guldin, ostensibly for empirical reasons. Amir Alexander of the University of California, Los Angeles, has found far more personal motives for the dispute. In this adaptation of a chapter from his forthcoming book, he explains that Guldin and Cavalieri belonged to different Catholic orders and, consequently, disagreed about how to use mathematics to understand the nature of reality.

Paul Guldin's critique of Bonaventura Cavalieri's indivisibles is contained in the fourth book of his *De Centro Gravitatis* (also called *Centrobaryca*), published in 1641. Cavalieri's proofs, Guldin argued, were not constructive proofs, of the kind that classical mathematicians would approve of. This was undoubtedly true: in the conventional Euclidean approach, geometric figures are constructed step-by-step, from the simple to the complex, with the aid of only a straight edge and a compass, for the construction of lines and circles, respectively. Every step in a proof must involve such a construction, followed by a deduction of the logical implications for the resulting figure.

Cavalieri, however, proceeded the other way around: he began with ready-made geometric figures such as parabolas, spirals, and so on, and then divided them up into an infinite number of parts. Such a procedure might be called "deconstruction" rather than "construction," and its purpose was not to erect a coherent geometric figure but to decipher the inner structure of an existing one.

Adapted from Infinitesimal: How a Dangerous Mathematical Theory Shaped the Modern World, *by Amir Alexander, by arrangement with Scientific American/Farrar, Straus and Giroux, LLC, and Zahar (Brazil).*

Photograph by Plamen Petkov

Guldin next went after the foundation of Cavalieri's method: the notion that a plane is composed of an infinitude of lines or a solid of an infinitude of planes. The entire idea, Guldin insisted, was nonsense: "No geometer will grant him that the surface is, and could in geometrical language be called, 'all the lines of such a figure.'"

In other words, because lines have no width, no number of them placed side by side would cover even the smallest plane. Cavalieri's attempt to calculate the area of a plane from the dimensions of "all its lines" was therefore absurd. This then led Guldin to his final point: Cavalieri's method was based on establishing a ratio between all the lines of one figure and all the lines of another. But, Guldin maintained, both sets of lines are infinite, and the ratio of one infinity to another is meaningless. No matter how many times one might multiply an infinite number of indivisibles, they would never exceed a different infinite set of indivisibles.

When taken as a whole, Guldin's critique of Cavalieri's method embodied the core principles of Jesuit mathematics. Christopher Clavius, the founder of the Jesuit mathematical tradition, and his descendants in the order believed that mathematics must proceed systematically and deductively, from simple postulates to ever more complex theorems, describing universal relations between figures. Constructive proofs were the embodiment of precisely this ideal. The approach produced a rigorous and hierarchical mathematical logic, which, for the Jesuits, was the main reason why the field should be studied at all: it demonstrated how abstract principles, through systematic deduction, constructed a fixed and rational world whose truths were universal and unchallengeable. In this, Clavius pointed out, Euclidean geometry came closer to the Jesuit ideal of certainty, hierarchy and order than any other science. It follows that Guldin's insistence on constructive proofs was not a matter of pedantry or narrow-mindedness, as Cavalieri and his friends thought, but an expression of the deeply held convictions of his order.

The same was true of Guldin's criticism of the division of planes and solids into "all the lines" and "all the planes." Not only must mathematics be hierarchical and constructive, but it must also be perfectly rational and free of contradiction. Yet Cavalieri's indivisibles, as Guldin pointed out, were incoherent at their very core because the notion that the continuum was composed of indivisibles simply did not stand the test of reason. "Things that do not exist, nor could they exist, cannot be compared," he thundered, and it is therefore no wonder that they lead to paradoxes and contradiction and, ultimately, to error."

To the Jesuits, such mathematics was far worse than no mathematics at all. The purpose of mathematics, after all, was to bring proper order and stability to the world, whereas the method of indivisibles brought only confusion and chaos. If this flawed system was accepted, then mathematics could no longer be the basis of an eternal rational order. The Jesuit dream, of a strict universal hierarchy as unchallengeable as the truths of geometry, would be doomed.

In his writings, Guldin did not explain the deeper philosophical reasons for his rejection of indivisibles, nor did Jesuit mathematicians Mario Bettini and Andrea Tacquet, who also attacked Cavalieri's method. At one point, Guldin came close to admitting that there were greater issues at stake than the strictly mathematical ones, writing cryptically, "I do not think that the method [of indivisibles] should be rejected for reasons that must be suppressed by never inopportune silence." But he gave no explanation of what those "reasons that must be suppressed" could be. As mathematicians, the three had the job of attacking the indivisibles on mathematical, not philosophical or religious, grounds. Their mathematical credibility would only suffer if they announced that they were motivated by theological or philosophical considerations.

Those involved in the fight over indivisibles knew, of course, what was truly at stake, as Stefano degli Angeli, a Jesuat mathematician hinted when he wrote facetiously that he did not know "what spirit" moved the Jesuit mathematicians. With very few exceptions, the debate remained mathematical, a controversy between highly trained professionals over which procedures could be accepted in mathematics.

When Cavalieri first encountered Guldin's criticism in 1642, he immediately began work on a detailed refutation. Initially he intended to respond in the form of a dialogue between friends, of the type favored by his mentor, Galileo Galilei. But when he showed a short draft to Giannantonio Rocca, a friend and fellow mathematician, Rocca counseled against it. It was safer, Rocca

Amir Alexander is a historian of mathematics at the University of California, Los Angeles, and author of *Geometrical Landscapes: The Voyages of Discovery and the Transformation of Mathematical Practice* (Stanford University Press, 2002) and *Duel at Dawn: Heroes, Martyrs, and the Rise of Modern Mathematics* (Harvard University Press, 2010).

IN BRIEF

In the 17th century Italian mathematician Bonaventura Cavalieri proposed that every plane is composed of an infinite number of lines and every solid of an infinite number of planes. One could use these "indivisibles," he said, to calculate length, area and volume—an important step on the way to modern integral calculus.

Swiss mathematician Paul Guldin, Cavalieri's contemporary, vehemently disagreed, criticizing indivisibles as illogical. But the men argued for more than purely mathematical reasons.

They were members of two religious orders with similar spellings but very different philosophies: Guldin was a Jesuit and Cavalieri a Jesuat. The former believed in using mathematics to impose a rigid logical structure on a chaotic universe, whereas the latter was more interested in following his intuitions to understand the world in all its complexity.

PRECEDING PAGE: FOOD STYLING BY KAREN EVANS warned, to stay away from the inflammatory dialogue format, with its witticisms and one-upmanship, which were likely to enrage powerful opponents. Much better, Rocca advised, to write a straightforward response to Guldin's charges, focusing on strictly mathematical issues and refraining from Galilean provocations. What Rocca left unsaid was that Cavalieri, in all his writings, showed not a trace of Galileo's genius as a writer, nor of his ability to present complex issues in a witty and entertaining manner. It is probably for the best that Cavalieri took his friend's advice, sparing us a "dialogue" in his signature ponderous and near indecipherable prose. Instead Cavalieri's response to Guldin was included as the third "Exercise" of his last book on indivisibles, *Exercitationes Geometricae Sex,* published in 1647, and was entitled, plainly enough, "In Guldinum" ("On Guldin").

For the Jesuits, the purpose of mathematics was to construct the world as eternally unchanging. For Cavalieri, it was the reverse.

Cavalieri did not appear overly troubled by Guldin's critique. He denies that he posited that the continuum is composed of an infinite number of indivisible parts, arguing that his method did not depend on this assumption. If one believed that the continuum is composed of indivisibles, then, yes, "all the lines" together do indeed add up to a surface and "all the planes" to a volume, but if one did not accept that the lines compose a surface, then there is undoubtedly something there—in addition to the lines—that makes up the surface and something in addition to the planes that makes up the volume. None of this, he contended, had any bearing on the method of indivisibles, which compares all the lines or all the planes of one figure with those of another, regardless of whether they actually compose the figure.

Cavalieri's argument here may have been technically acceptable, but it was also disingenuous. Anyone reading his 1635 book *Geometria Indivisibilibus* or *Exercitationes* could have no doubt that they were based on the fundamental intuition that the continuum is composed of indivisibles. Guldin was perfectly correct to hold Cavalieri to account for his views on the continuum, and the Jesuat's defense seems like a rather thin excuse.

Cavalieri's response to Guldin's insistence that "an infinite has no proportion or ratio to another infinite" was hardly more persuasive. He distinguished between two types of infinity, claiming that "absolute infinity" indeed has no ratio to another "absolute infinity," but all the lines and all the planes have not an absolute but a "relative infinity." This type of infinity, he then argued, can and does have a ratio to another relative infinity. As before, Cavalieri seemed to be defending his method on abstruse technical grounds, which may or may not have been acceptable to fellow mathematicians. Either way, his argument bore no relation to the true motivation behind the method of indivisibles.

That motivation came to light in Cavalieri's response to Guldin's charge that he did not properly "construct" his figures. Here Cavalieri's patience was at an end, and he let his true colors show. Guldin had claimed that every figure, angle and line in a geometric proof must be carefully constructed from first principles; Cavalieri flatly denied this. "For a proof to be true," he wrote, "it is not necessary to describe actually these analogous figures, but it is sufficient to assume that they have been described mentally."

And here is the true difference between Guldin and Cavalieri, between the Jesuits and the indivisiblists. For the Jesuits, the purpose of mathematics was to construct the world as a fixed and eternally unchanging place, in which order and hierarchy could never be challenged. That is why each item in the world had to be carefully and rationally constructed and why any hint of contradictions and paradoxes could never be allowed to stand. It was a "top-down" mathematics, whose purpose was to bring rationality and order to an otherwise chaotic world.

For Cavalieri and his fellow indivisiblists, it was the exact reverse: mathematics begins with a material intuition of the world—that plane figures are made up of lines and volumes of planes, just as a cloth is woven of thread and a book compiled of pages. One did not need to rationally construct such figures, because we all know that they already exist in the world. All that was needed was to assume them and then to investigate their inner structure. If we encounter seeming paradoxes and contradictions, they are bound to be superficial, resulting from our limited understanding, and can either be explained away or used as a tool of investigation. But they should never stop us from investigating the inner structure of geometric figures and the hidden relations between them.

For classical mathematicians such as Guldin, the notion that you could base mathematics on a vague and paradoxical intuition was absurd. "Who will be the judge" of the truth of a geometric construction, Guldin mockingly asked Cavalieri, "the hand, the eye or the intellect?" Cavalieri thought Guldin's insistence on avoiding paradoxes was pointless pedantry: everyone knew that the figures did exist and it made no sense to argue that they should not. Such nitpicking, it seemed to Cavalieri, could have grave consequences. If Guldin prevailed, a powerful method would be lost, and mathematics itself would be betrayed. SA

MORE TO EXPLORE

The Discovery of Infinitesimal Calculus. H. W. Turnbull in *Nature,* Vol. 167, pages 1048–1050; June 30, 1951.

Exploration Mathematics: The Rhetoric of Discovery and the Rise of Infinitesimal Methods. Amir R. Alexander in *Configurations,* Vol. 9, No. 1, pages 1–36; Winter 2001.

The Skeleton in the Closet: Should Historians of Science Care about the History of Mathematics? Amir Alexander in *Isis,* Vol. 102, No. 3, pages 475–480; September 2011.

FROM OUR ARCHIVES

Leibniz. Frederick C. Kreiling; May 1968.

New Models of the Real-Number Line. Lynn Arthur Steen; August 1971.

Resolving Zeno's Paradoxes. William I. McLaughlin; November 1994.

YARETA, a flowering shrub, 2,000-plus years old, in Chile

The Oldest Living Things in the World

by Rachel Sussman. University of Chicago Press, 2014 ($45)

A colony of 80,000-year-old aspen trees in Utah, 400,000-year-old bacteria living in the Siberian permafrost and a shrub that has been self-propagating in Tasmania for 43,000 years are among the millennia-old organisms that photographer and writer Sussman traveled to seven continents to see. Her oversize book includes photographs, travel stories and interviews with scientists who study these impressive organisms.

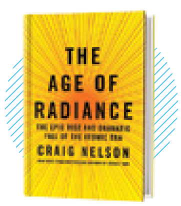
You Are Here: From the Compass to GPS, the History and Future of How We Find Ourselves

by Hiawatha Bray.
Basic Books, 2014 ($27.99)

Around 300 years ago ship captains had no way of knowing their precise longitude at sea. Now many people carry in their pockets the technology to pinpoint their exact geographic coordinates from nearly anywhere on the earth. "Few technological marvels have been as marvelous as humanity's victory over the mysteries of location," writes journalist Bray. In this history of navigation, he tells the story of how we learned to find our way around the planet ever more accurately and explores the implications of our "locational transparency." After all, Bray says, "we can find anyplace with ease, but others can also find us."

The Age of Radiance: The Epic Rise and Dramatic Fall of the Atomic Era

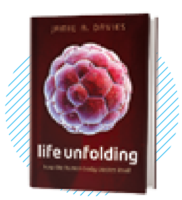
by Craig Nelson.
Scribner, 2014 ($29.99)



"Your family is radioactive; your friends are radioactive; your pets are radioactive; and the earth itself throws off a gaseous froth of radon," writes journalist Nelson in this history of the atomic age. The book begins with the 1890s discovery of the first known radioactive elements and traces humankind's manipulation of radiation through to the 2011 nuclear disaster in Fukushima, Japan. Along the way, Nelson explains the science behind nuclear power, radiotherapy and the atomic bomb and brings to life the historical figures, such as Marie and Pierre Curie, Albert Einstein and J. Robert Oppenheimer, who defined the era. Ultimately Nelson argues that the atomic age is in its twilight and that eventually both nuclear power and nuclear weapons will be nearly eradicated.

Life Unfolding: How the Human Body Creates Itself

by Jamie A. Davies. Oxford University Press, 2014 ($29.95)



Children are not the only ones who wonder where babies come from. Scientists, too, are still trying to answer this question on its most basic levels. Human bodies, after all, are not built like bridges by external engineers—they build themselves. University of Edinburgh biologist Davies describes what we know and what we do not know about how tiny individual components come together to create the complexity of life, laying out the major insights that have been gleaned over the past decade. "The story that is being unearthed … is an astonishing one," Davies writes. "It is the story of something every one of us has done, and it is therefore a story that belongs to us all."

SCIENTIFIC AMERICAN ONLINE
For more recommendations, go to
ScientificAmerican.com/apr2014/recommended

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

The Science of Lying

When are we most (and least) likely to lie?

"Could switching to Geico really save you 15 percent or more on car insurance? Was Abe Lincoln honest?" So intones the Geico commercial spokesperson, followed by faux vintage film footage of Mary Lincoln asking her husband, "Does this dress make my backside look big?" Honest Abe squirms and shifts, then hesitates and, while holding his thumb and forefinger an inch apart, finally mutters, "Perhaps a bit," causing his wife to spin on her heels and exit in a huff.

The humor works because we recognize the question as a disguised request for a compliment or as a test of our love and loyalty. According to neuroscientist Sam Harris in his 2013 book *Lying* (Four Elephants Press), however, even in such a scenario we should always tell the truth: "By lying, we deny our friends access to reality—and their resulting ignorance often harms them in ways we did not anticipate. Our friends may act on our falsehoods, or fail to solve problems that could have been solved only on the basis of good information." Maybe Mary's dressmaker is incompetent, or maybe Mary actually could stand to lose some weight, which would make her healthier and happier. Moreover, Harris says, little white lies often lead to big black lies: "Very soon, you may find yourself behaving as most people do quite effortlessly: shading the truth, or even lying outright, without thinking about it. The price is too high." A practical solution is to think of a way to tell the truth with tact. As Harris notes, research shows that "all forms of lying—including white lies meant to spare the feelings of others—are associated with poorer-quality relationships."

Most of us are not Hitlerian in our lies, but nearly all of us shade the truth just enough to make ourselves or others feel better. By how much do we lie? About 10 percent, says behavioral economist Dan Ariely in his 2012 book *The Honest Truth about Dishonesty* (Harper). In an experiment in which subjects solve as many number matrices as possible in a limited time and get paid for each correct answer, those who turned in their results to the experimenter in the room averaged four out of 20. In a second condition in which subjects count up their correct answers, shred their answer sheet and tell the experimenter in another room how many they got right, they averaged six out of 20—a 10 percent increase. And the effect held even when the amount paid per correct answer was increased from 25 to 50 cents to $1, $2 and even $5. Tellingly, at $10 per correct answer the amount of lying went slightly *down*. Lying, Ariely says, is not the result of a cost-benefit analysis. Instead it is a form of self-deception in which small lies allow us to dial up our self-image and still retain the perception of being an honest person. Big lies do not.

Psychologists Shaul Shalvi, Ori Eldar and Yoella Bereby-Meyer tested the hypothesis that people are more likely to lie when they can justify the deception to themselves in a 2013 paper entitled "Honesty Requires Time (and Lack of Justifications)," published in *Psychological Science.* Subjects rolled a die three times in a setup that blocked the experimenter's view of the outcome and were instructed to report the number that came up in the first roll. (The higher the number, the more money they were paid.) Seeing the outcomes of the second and third rolls gave the participants an opportunity to justify reporting the highest number of the three; because that number had actually come up, it was a justified lie.

Some subjects had to report their answer within 20 seconds, whereas others had an unlimited amount of time. Although both groups lied, those who were given less time were more likely to do so. In a second experiment subjects rolled the die once and reported the outcome. Those who were pressed for time lied; those who had time to think told the truth. The two experiments suggest that people are more likely to lie when time is short, but when time is not a factor they lie only when they have justification to do so.

Perhaps Mary should not have given Abe so much time to ponder his response. SA

SCIENTIFIC AMERICAN ONLINE
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Illustration by Izhar Cohen

The ongoing search for fundamental farces

Steve Mirsky has been writing the Anti Gravity column since Derek Jeter had a total of 12 base hits in the major leagues. He also hosts the *Scientific American* podcast Science Talk.

Numbers Game

To paraphrase Inigo Montoya, this baseball stat—"I do not think it means what you think it means"

The lush green expanse of the outfield. The pop of horsehide ball hitting cowhide mitt. The search for hastily discarded syringes. Yes, baseball is back.

On the sacred day when I first discovered the game, the holy trinity of stats was AVG (batting average), HR (home runs) and RBI (runs batted in). Today we have OBP, OPS, UZR and WAR—and plenty more alphabet soup.

To become more nimble with these numbers, back in January I headed to a little collectible store on East 11th Street in Manhattan called Bergino Baseball Clubhouse to hear a talk by Smith College economics professor Andrew Zimbalist, co-author with former New York Mets number cruncher and current Smith visiting math prof Benjamin Baumer of *The Sabermetric Revolution: Assessing the Growth of Analytics in Baseball*. (That's right—they analyze the analyses. Who watches the watchmen? These guys.)

First, what on turf is sabermetrics? Legendary stat man Bill James coined the term, adding "metrics" to a slightly revised acronym for the Society for American Baseball Research, "SABR." "Sabermetrics," Zimbalist explained, "refers to the use of statistical analysis to understand and evaluate player performance, team strategy and front-office strategy." Sadly, it does not refer to exactly how far down onto his sword a general manager has to fall if his team underperforms.

Sabermetrics got a big boost among the general public from the 2003 book, and later 2011 movie, *Moneyball,* a story of the surprisingly good 2002 Oakland Athletics. The team's key was deep stats that found low-priced and underappreciated players. And its big stat was OBP, "on-base percentage" (more or less hits plus walks divided by plate appearances), because, as the old baseball adage goes, "A walk is as good as a hit."

In reality, a walk is clearly not as good as a hit when the hit is a home run, even though the homer counts the same as a hit in calculating batting average. Which is why one of the most popular ways to measure hitting now is OPS, "on-base plus slugging percentage," which weights for power. Hence, Lou Gehrig's insane 1928 World Series OPS of 2.433 against the St. Louis Cardinals, off a paltry .545 batting average.

Zimbalist took issue with some of *Moneyball*'s claims. For example, the focus on on-base percentage doesn't explain how the A's team OBP dropped from .360 in 2000, to .345 in 2001, to .339 in its annus mirabilis. But his most salient comments were for those of us who cite Albert Einstein at least as often as Theo Epstein.

Zimbalist and Baumer write in *The Sabermetric Revolution* that "beyond the rags-to-riches theme, [the book *Moneyball*] echoes another well-worn refrain in modern culture—the perception that quantification is scientific." If all you do is count, you could tally up a million apples falling off apple trees without coming up with a theory of gravity.

At his talk, Zimbalist also criticized two of the newer stats. UZR, for "ultimate zone rating," alleges to measure notoriously difficult-to-quantify defense. "When Derek Jeter is in the bottom 10 percent of UZR one year and the next year he's in the top 10 percent, you have to question, What is UZR measuring?" A stat that rated the degree of facial symmetry of the models Jeter dates would undoubtedly have a higher correlation from one year to the next.

Finally, there's "wins above replacement," or WAR, which purports to figure the number of wins a player adds to his team total over a standard-issue substitute. The obvious and necessary follow-up question becomes, WAR: What is it good for? Perhaps not absolutely nothing but less than it may appear.

"These are now proprietary metrics," Zimbalist said. "The people who generate these are selling their metrics to teams.... The numbers they're using to feed into their algorithms ... and how they weight all these different numbers—they don't tell us.... And as long as it's a black box, it doesn't make a heck of a lot of sense."

Zimbalist pointed to David Wright, third baseman for the Mets, who received virtually identical WAR values from three different organizations. But the internal aspects of the total stat we do know about were all over the place. So the convergence on a similar value is reminiscent of the four statisticians who went duck hunting. All four missed the duck, but because the average of their shots was where the duck was, they announced, "We got him!" Yeah, about as much as the Cards' pitching staff got out Lou Gehrig. SA

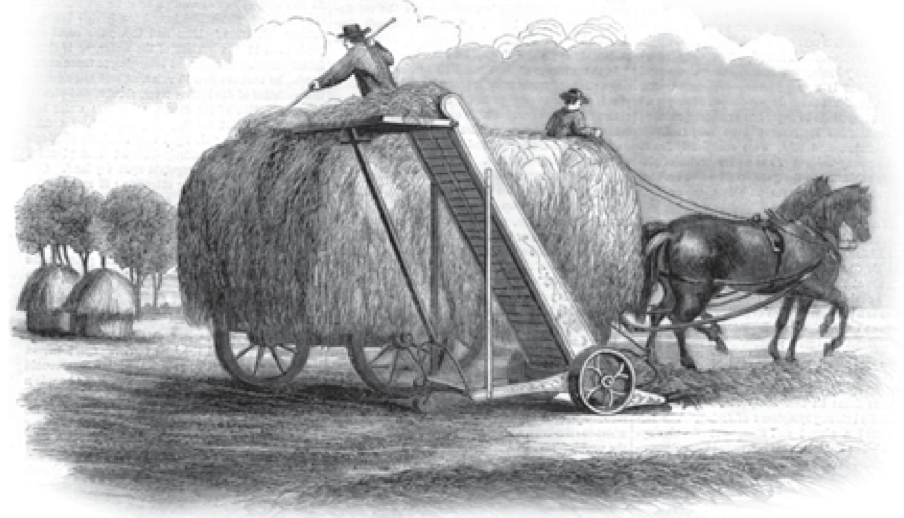
SCIENTIFIC AMERICAN ONLINE Hear Andrew Zimbalist's conversation on the Science Talk podcast at ScientificAmerican.com/apr2014/sabermetrics

Illustration by Matt Collins

50, 100 & 150 Years Ago

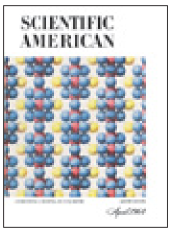
compiled by Daniel C. Schlenoff

Innovation and discovery as chronicled in *Scientific American*



MECHANICAL HELP: Horse-powered harvesting machine, 1864

SCIENTIFIC AMERICAN, VOL. X, NO. 14; APRIL 2, 1864



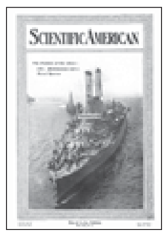
April 1964

LSD and Psilocybin

"The hallucinogens are currently a subject of intense debate and concern in medical and psychological circles. At issue is the degree of danger they present to the psychological health of the person who uses them. This has become an important question because of a rapidly increasing interest in the drugs among laymen. The recent controversy at Harvard University, stemming at first from methodological disagreements among investigators but subsequently involving the issue of protection of the mental health of the student body, indicated the scope of popular interest in taking the drugs and the consequent public concern over their possible misuse."

Dyson Review

"James R. Newman's review of *Interstellar Communication* in your February issue is written with his usual mixture of wit and wisdom. All of us who think seriously about the detection of extraterrestrial intelligence know that we suffer from one basic limitation. Our imagined detectors detect technology rather than intelligence. And we have no idea whether or not a truly intelligent society would retain over millions of years an interest in or a need for advanced technology. Under these circumstances it is best to admit frankly that we are searching for evidence of technology rather than of intelligence. —Freeman J. Dyson"



April 1914

Age of the Sun, Revisited

"Adopting the well-known hypothesis of [Hermann von] Helmholtz, which attributes the production of the heat emitted by the sun to its contraction, an idea can be formed of the sun's duration. If one gives to the sun a coefficient of expansion intermediate between that of mercury and that of gas, one arrives at the conclusion that it has taken one to three millions of years for the sun to contract to its present radius. Finally, the sun will take 200 millions of years to contract from its present radius to half that radius, and even then its temperature at the surface will be 3,000 degrees."

Reading Is Obsolete

"The schools have been remiss in that they have not with sufficient alacrity adapted themselves to the changing conditions of social and economic life. Nearly three fourths of the children who leave

SCIENTIFIC AMERICAN ONLINE See more ingenious devices from 1864 at ScientificAmerican.com/apr2014/great-gizmos-1864

school when the law allows, do so not because of direct economic pressure in the home, but because the school has lost its grip upon the children. This is to be explained by the fact that the schools continue to give to all the children just that particular pabulum which was satisfactory a generation or two ago to a small fraction—a selected fraction—of the children. But the mass of the children are different from that selected fraction in just this, that they are thing-minded, motor-minded, not word- or symbol-minded, like their teachers."

April 1864

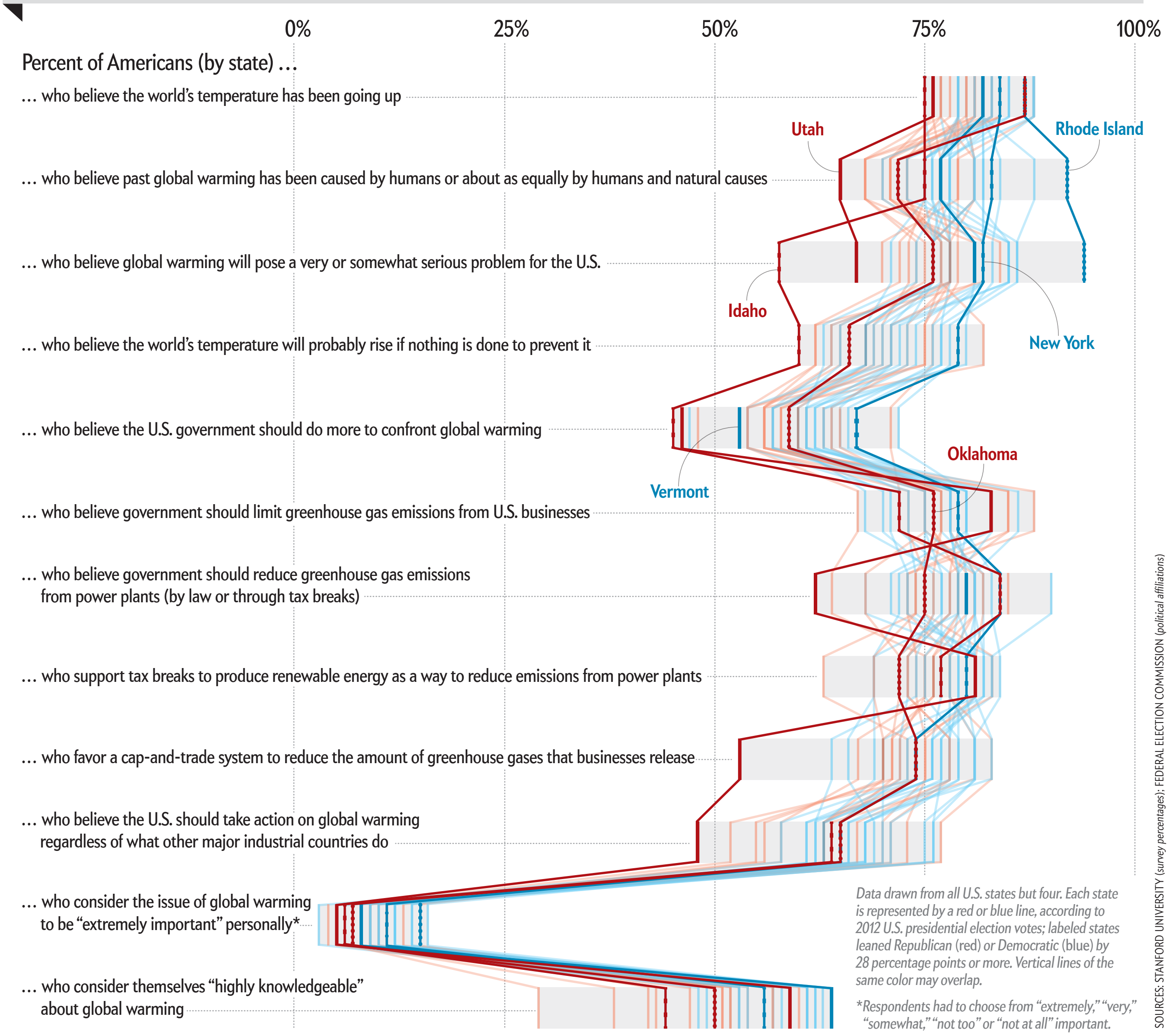
Mechanical Muscle

"The labor of loading hay in the field is very fatiguing on a hot summer's day, and on large farms, where heavy crops are grown, the labor is very severe. It is desirable that this work should be done by machinery, not only to exempt the farmer from hard work, but to facilitate the operation, and thus greatly lessen the cost of production. By the use of the self-loading arrangement, herewith illustrated (*opposite page*), the farmer or his assistants can ride from one end of the field to the other, as the machine is operated by the progress of the team."

Vultures Everywhere

"One of the most alarming signs of the times in which we live is the extraordinary and villainous speculations now rife in Wall street, in the shape of gold and other mining operations. Bogus companies are forming every day, whose foundations are as the 'baseless fabric of a vision.' We warn the people to beware of these swindlers—they should shun them as they would the gambling-hells of the city. These vile schemes are incubated and hatched in the region of the Stock Exchange, and are designed to entrap the innocent and unwary. Every one of them ought to be indicted by the Grand Jury, and the guilty swindlers sent to Sing Sing."

Rising Temperatures and What to Do about Them



On Climate, the People Agree

U.S. public opinion varies over a surprisingly narrow range

From what politicians and commentators say in the media, the U.S. would seem torn asunder over the matter of climate change. Not so, according to an assessment of 21 surveys encompassing almost 20,000 people in 46 states, which found ample agreement about global warming and what to do about it. In each state, a majority of those polled believe that temperatures are rising and that human actions are part of the cause (*first two questions above*)—and this consensus holds for residents of states that voted strongly Republican in the 2012 presidential election (*red*). More than 60 percent of Americans in every state favor government-imposed limits on greenhouse gas emissions from businesses and power plants. "A huge percentage of the public supports legislation that politicians have yet to pass," says Jon Krosnick, a senior fellow at Stanford University who led the analysis.

People also agree on another point: fewer than half the residents in states nationwide indicate that global warming is "extremely important" to them personally. —*Mark Fischetti*

SCIENTIFIC AMERICAN ONLINE
For more on how concerned Americans are about climate change, see ScientificAmerican.com/apr2014/graphic-science

Graphic by Jen Christiansen


ONE DAY HE MAY LOOK BACK AND SAY THAT
THE FUTURE STARTED HERE
At Lockheed Martin, when we envision the future, we see a world of never-ending possibility. But that future will never be realized unless we prepare today's students for tomorrow's challenges. That's why it is vitally important for young people to study science, technology, engineering, and math. And it's also why Lockheed Martin is proud to be the founding and presenting sponsor of the USA Science & Engineering Festival.
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