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How violent behaviors originate

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Teaching machines creativity and common sense

SCIENTIFIC AMERICAN

INCONCEIVABLE

The science of women's reproductive health has huge gaps.

What we don't know is hurting all of us

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FUTURE OF MEDICINE 2019

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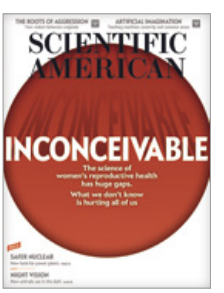
ON THE COVER

Basic facts of human life, such as the purpose of the menstrual cycle, remain surprisingly mysterious. A special report on what we don't know about women's reproductive health, why we don't know it, and where we go from here.



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ON THE WEB

Questions about Male Reproductive Health
A crisis in male fertility has prompted some men to investigate their role in causing—and preventing—pregnancy. *Scientific American*'s Jen Schwartz reports.
Go to www.ScientificAmerican.com/may2019/sperm

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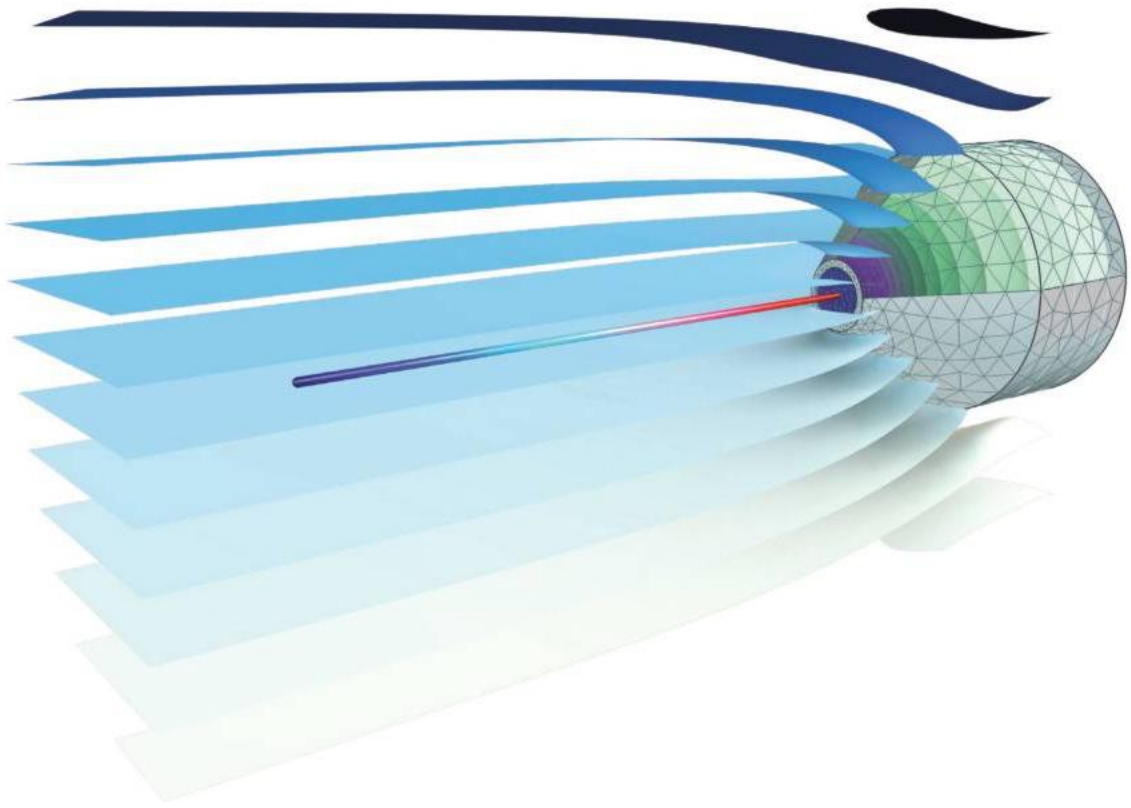
Hearing aids can't solve the cocktail party problem...yet.



Visualization of the total acoustic pressure field around and inside an elastic probe tube extension attached to a microphone case.

Many people are able to naturally solve the cocktail party problem without thinking much about it. Hearing aids are not there yet. Understanding how the human brain processes sound in loud environments can lead to advancements in hearing aid designs.

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comsol.blog/cocktail-party-problem

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

Unhealthful Data Gaps

Have you heard about the "gender data gap"? I recently learned the phrase in an excerpt published in March in the *Guardian* from the book *Invisible Women: Exposing Data Bias in a World Designed for Men,* by Caroline Criado Perez (Abrams, 2019). "The gender data gap," explains Criado Perez, "is both a cause and a consequence of the type of unthinking that conceives of humanity as almost exclusively male."

With the world designed by men and for other men, being a woman actually can be a health hazard. Criado Perez writes about uncomfortable, or even dangerous, mismatches between men's bodies, which are larger and stronger on average, and women's in such areas as seat belts and car seating design, bulletproof vests for law-enforcement officers, mobile phones that can't be cupped with a smaller palm—even the size of cement bags, which are too large and heavy for the average women to heft but don't have to be that way.

You may be, like me, struck by similar—and equally unhealthful—gender data gaps as you read our annual special report on "The Future of Medicine." This year we focus on "Fertile Ground," women's reproductive well-being. Take menstruation. As Virginia Sole-Smith writes in "The Point of a Period," old taboos and squeamishness have resulted in limited research on women's monthly cycles. Little is known about why periods can be painful and what is behind some related disorders. Although women historically had fewer periods over their lifetime because of multiple pregnancies, today they have many more periods on average. Is this harmful? Should women use birth control to skip their periods? We don't know. Says one source in the story: "'What we have now' with women using birth control for long-term [menstrual] suppression 'is the largest uncontrolled medical experiment on women in history.'"

Other stories in the report look at the science of making babies ("Eggs on Ice," by Liza Mundy), birth control ("Set It and Forget It?," by Maya Dusenbery) and the risks of childbirth ("How to Reduce Maternal Mortality," by Monica R. McLemore). More than half the world will benefit from a better understanding of female reproductive health issues: giving women more agency over their reproductive lives is known as one of the most effective solutions to global challenges such as economic inequality. Turn to page 30 for an eye-opening look at what we know, and don't know, about the reproductive lives of half of humanity. A better future for us all may depend on it. SA

Illustration by Nick Higgins


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January 2019

"Reproducing a one-size-fits-all benchmark number for daily steps for all groups in the population could be damaging to public health."
—ARNO MAETENS *VRIJE UNIVERSITY BRUSSELS*

CARBON CALCULATION

In "The Last Resort," Richard Conniff states that "our cars each typically emit 4.6 [metric tons, or about five U.S. short tons] of carbon dioxide a year." I would appreciate an explanation as to how this figure was derived. Assuming an average vehicle is 4,000 pounds, I find it hard to believe that in a given year, an automobile produces more than twice its weight in carbon dioxide.

For example, if a car drives an average of 10,000 miles a year and gets 20 miles per gallon, it will consume 500 gallons of gasoline in a year. Gasoline weighs around six pounds per gallon, so if the assertion from the article is correct, that means burning 3,000 pounds of gasoline would produce more than three times its weight in CO_2.

JOHN CARDWELL
Supply, N.C.

CONNIFF REPLIES: Cardwell's question brings up one of the facts about greenhouse gas emissions that I found hardest to fathom when I first encountered it: although a gallon of gasoline is indeed six pounds, we put more than 19 pounds of CO_2 into the atmosphere for every gallon that our cars burn (not counting additional emissions released by manufacturing and transporting the fuel to market). How could that be?

Gasoline is nearly 90 percent carbon. And through combustion, nearly every carbon atom in the gas combines with two oxygen atoms. Oxygen is 1.33 times heavier than carbon. Thus, for six pounds of gas, more than five pounds of carbon combines with around 14 pounds of oxygen. The Environmental Protection Agency arrived at the figure for a vehicle's annual emissions by assuming the average car has a fuel economy of about 22 miles per gallon and drives about 11,500 miles each year. That adds up to about 523 gallons and produces a dismaying annual total of more than 10,000 pounds, or about 4.6 metric tons, of CO_2.

FIT INHERITANCE

"Evolved to Exercise," by Herman Pontzer, discusses research showing that over two million years human physiology adapted for a high level of physical activity.

I wondered if there is a relation between our past of body exertion and our hairlessness relative to great apes. Humans can sweat copiously to maintain coolness, which must be done during bouts of prolonged exercise. I would think that sweating would not be nearly as effective soaking through a thick coat of fur. My take is that as we evolved to undergo increasing exertion under a hot sun, we concomitantly lost more and more body hair.

BARRY SILER
Loveland, Colo.

Pontzer states that "our taking fewer than 10,000 daily steps is associated with increased risk of cardiovascular and metabolic disease." That so-called benchmark value of 10,000 steps a day gained popularity in the media mostly because it simplifies matters, and it can be traced back to a marketing slogan for a Japanese pedometer decades ago. Three recent studies, in which I was not involved, reviewed existing evidence for benchmarks in human physical activity, finding large differences between needs for daily activity among children, adolescents, adults and older people, and those with chronic diseases.

I understand the need to be concise in a magazine article. But reproducing a one-size-fits-all benchmark number for all groups in the population, which is not based on scientific research, could possibly be damaging to public health.

ARNO MAETENS
Doctoral researcher in social health sciences, Vrije University Brussels

PONTZER REPLIES: Regarding Siler's suggestion: Skin doesn't fossilize, but most paleontologists would agree that hairlessness and sweating likely evolved along with increased physical activity early in the genus Homo. *Humans are the sweatiest animals on the planet, and our ability to stay cool allows us to keep going in conditions that make other mammals melt.*

The 10,000 steps per day benchmark widely used in public health is a nice, round number that's easily remembered, but Maetens is quite right that it's not necessarily the best fit for all populations. Children should be getting more than that (11,000 to 15,000 is a good goal), while older people and those with limited mobility can aim for less. The good news for anyone anxious about the perfect number of steps for them is that more is almost always better. Barring any health conditions that are aggravated by exercise, there's no evidence that too much walking is ever bad for you, regardless of what my kids say when we're out hiking.

UNOBSTRUCTED PAIN

"What Ails a Woman's Heart," by Claudia Wallis [The Science of Health], discusses research by cardiologist C. Noel Bairey Merz and others on INOCA (ischemia and no obstructive coronary artery disease), a condition in which patients without blocked arteries nonetheless experience poor blood flow through the heart.

If ischemic chest pain can be caused

by peripheral vascular dysfunction, as the article describes, can't that also happen in people in whom testing shows them to have some coronary artery stenosis (blockage or narrowing of the arteries)? In those cases, perhaps the stenosis is a red herring, and coronary artery bypass grafting is the wrong treatment. That could explain some of the patients who don't fare well after bypass surgery.

STEVE WISE
Charlotte, N.C.

BAIREY MERZ REPLIES: Wise makes a good point. Recent evidence from the ORBITA trial demonstrates that angina is not improved by stenting, suggesting that ischemia symptoms may, in fact, more often be caused by coronary microvascular dysfunction.

TRICK OR FEAT

In "The Particle Code," Matthew von Hippel consistently refers to mathematician Alexander B. Goncharov's observation that mathematical period theory can be used to simplify loop computations in particle physics as a "trick." But that observation shows such computations can be decomposed into an alphabet of simpler functions, which can be assembled only according to a simple grammar. That seems quite profound to me. Could the alphabet and the grammar correspond to some underlying structure in particle theory?

DOUG HOOVER
Sunnyvale, Calif.

VON HIPPEL REPLIES: There may well be a deeper meaning to the kinds of "alphabets" that appear in particle physics calculations. Physicists suspect they are related to a result of Nobel laureate Lev Landau, called the Landau equations. But this is still not fully understood.

ERRATUM

In "The Particle Code," by Matthew von Hippel, the lower graph in the box showing "Euler's formula visualized as a circle, then projected through time" inaccurately represented the curve for cosine (x). The corrected illustration can be seen at www.scientificamerican.com/eulers-formula-projected

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— Dr. Lynette Sholl

"It's an emerging area of science that's becoming increasingly important to our understanding of disease and understanding of treatment for patients"
— Dr. Andrew Beck

Hot Topics in Science: Biomarkers Beyond the News

New York, NY | January 16, 2019

SCIENTIFIC AMERICAN'S Custom Media Group, in partnership with Bristol-Myers Squibb, hosted an event at the Springer Nature Campus to explore one of the hottest topics in medicine: using biomarkers and cutting edge technology, like digital pathology and artificial intelligence, to help detect disease. It's having a fundamental impact on how drugs are developed, how diseases are diagnosed and how doctors work together. Scientists, media outlets and industry leaders in biotechnology and drug discovery joined in timely discussions and a networking reception.

Key speakers included **Dr. Saurabh Saha**, SVP & Global Head of Translational Medicine, Bristol-Myers Squibb, **Dr. Lynette Sholl** of Harvard Medical School, **Dr. Suzanne Topalian** of Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy, and **Dr. Andrew Beck**, CEO of PathAI.

Climate-Friendly Capitalism

Investors are making companies act on global warming—and they can do even more

By the Editors

It's May, which means "proxy season" in the corporate world. This is the time of year when publicly traded companies hold their shareholder meetings, and investors can vote on resolutions to change corporate policies. The votes can have plenty of clout because huge private investment firms such as BlackRock and Vanguard weigh in, as do major public shareholders such as California's and New York's employee retirement funds with billions of dollars in stock under their control. When they want something, CEOs listen.

Recently more and more of these resolutions have pushed companies to act on climate change and reduce greenhouse gas emissions. Two years ago, for instance, investor proposals forced Shell to sell off carbon-rich oil sands assets. Investors also made the company tie 10 percent of executive bonus pay to success in cutting emissions. And earlier this year BP, bowing to investor pressure, agreed to align future capital spending with the targets of the 2015 Paris climate accord, reducing emissions enough to keep global temperature rise below two degrees Celsius. That could mean cuts as high as 50 percent, depending on the country.

This year and going forward, investors should exert more of this leverage on these and other companies. That is because politicians, especially in the U.S., have abjectly failed to address the threats that climate change poses to health, national security and the environment. President Donald Trump has repeatedly said he does not see climate change as a problem, despite strong and steadily growing scientific evidence from the world's researchers—and his own government agencies. This year the White House took steps to create a panel, chaired by someone who believes mounting carbon dioxide is *good* for the planet, to attack this overwhelming scientific consensus. On a local level, the state of Washington recently voted down a tax on carbon emissions.

The businesses that generate large amounts of greenhouse gases, in contrast, have proved willing to change their ways when investors insist on it. Of the more than 600 largest publicly traded companies in the U.S., 64 percent have now made commitments to reduce emissions, according to Ceres, a nonprofit group that tracks corporate sustainability. Many of those moves have come in response to proposals made at these annual shareholder gatherings. In addition to the actions taken by BP and Shell, Chevron has agreed to set an emissions-reduction target for methane, another powerful heat-trapping gas.

Companies' desire to avoid embarrassing proxy-season showdowns has given rise to another investor force—a shareholder network called Climate Action 100+, whose members have $32 billion in assets under management and try to push corporate changes outside of these yearly meetings. One success earlier this year: international mining giant Glencore said it will not grow its coal-mining business any larger and will develop targets for emissions reductions. Climate Action 100+ is also pressing nonenergy businesses that generate a lot of emissions, such as steel manufacturers, to line up behind science-based reduction goals.

The motive of these investment funds is not unfettered altruism. While they hold oil company stock, they also invest in real estate along coastlines threatened by rising seas, in health care firms whose costs will increase, and in dozens of other sectors that stand to take a substantial hit if climate change is not brought under control. So they have to take a long-term and global view.

It's time to push this wave of capital pressure even further. The Ceres report notes that most of the climate commitments it tracks are vaguely worded: only 36 percent of the agreements specify deadline-driven, quantitative targets for reduction. Companies also need to adopt sustainability targets for things like water use. More shareholders need to push for more of these specific goals and tie them to executive pay to ensure accountability.

Such demands can be tricky. The U.S. Securities and Exchange Commission has rules that prevent investors from micromanaging businesses. Exxon, in fact, has asked the SEC for permission to block a proposal calling for it to align emissions with the Paris accord. But the commission needs to give shareholders the right to protect their investments. And investor activists need to keep working to bring science and business together. Because money talks—or it walks—it can accomplish things that politicians won't. SA

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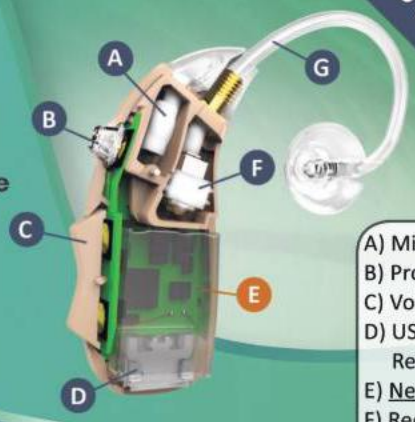

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Janice Phillips is an associate professor at Rush University College of Nursing, director of nursing research and health equity at Rush University Medical Center, and a Public Voices Fellow with The OpEd Project.

If You're Poor, Don't Get Cancer

People without resources have higher death rates

By Janice Phillips

Although the U.S. has experienced a 27 percent decline in cancer death rates during the past 25 years, the drop has not benefited everyone equally: poor individuals and people of color have significantly higher mortality than this average.

One reason for the disparity is that people living in poverty have lower rates of routine screening, as well as a lower likelihood of getting the best possible treatment, and African-American, Native American and Hispanic people are more likely to be living in poverty than are whites and Asians. A recent study in the journal *Cancer Epidemiology, Biomarkers & Prevention,* for example, shows that black and Hispanic women in Chicago were less likely to be diagnosed at top-tier centers as compared with their white counterparts.

When I worked as a nurse clinician in an underserved community on Chicago's South Side, an area known for high breast cancer mortality rates, I saw how hard it was to refer women with symptoms of breast problems to our leading academic medical centers for care. Uninsured women, in particular, were more often than not referred to our county hospital, which had fewer resources and reduced state-of-the-art diagnostic capability. Even today zip code and insurance status can influence whether or not women receive breast cancer care at centers of excellence.

And although breast cancer survival overall has improved over time, the American Cancer Society affirms that disparities remain: the five-year survival rate is 92 percent for white women but 83 percent for black women; the latter group is more likely to have more aggressive tumor types and to be diagnosed at a later stage of the illness, both of which are contributing factors to cancer outcomes. In 2015 black women were 39 percent more likely to die from breast cancer as compared with white women.

I have identified additional treatment barriers affecting women as young as 20 in my own studies with African-Americans. African-American women younger than 40 have shared with me that providers do not take them seriously when they present with breast concerns, claiming that they are too young to have breast cancer. I know from firsthand experience that young African-American women and their families are frustrated with the health care delivery system, especially if they are uninsured or underinsured.

Cancer advocates have sounded the alarm about these disparities for years. In 2007, for example, the Metropolitan Chicago Breast Cancer Task Force found a 68 percent higher death rate for black women as compared with white women. These findings helped to shape public policy and inform citywide and statewide initiatives aimed at addressing system issues such as access to high-quality mammography screening. I was thrilled to see these attempts to lower barriers in the health care system itself, rather than the traditional focus on changing behavior in patients, who should not be blamed when hospitals, doctors and insurance companies fail to provide them with good care. Because of the tremendous efforts of the task force and other partners, Chicago is leading the nation in reducing the racial gap in breast cancer mortality when compared with the other nine U.S. cities with the largest African-American population in a 2017 study. (The reduction in breast cancer mortality in the city may be attributed, in part, to the task force's comprehensive work.)

Even though the impact is greatest for women of color, it extends to uninsured adults of every ethnic background. For example, people without insurance are more likely to postpone or forgo health care altogether—and a recent Gallup poll noted that three in 10 Americans do not seek medical care or defer treatment because of cost. And this problem is getting worse: a study by the Kaiser Family Foundation showed an increase in the number of uninsured from 2016 to 2017 of nearly 700,000—primarily in states without Medicaid expansion. Eleven percent of blacks and 19 percent of Hispanics are uninsured as compared with 7 percent of whites.

Surviving cancer should not be determined by your ethnicity or your income level. But until the gap in access to affordable good care is eliminated, that will be the prognosis. SA

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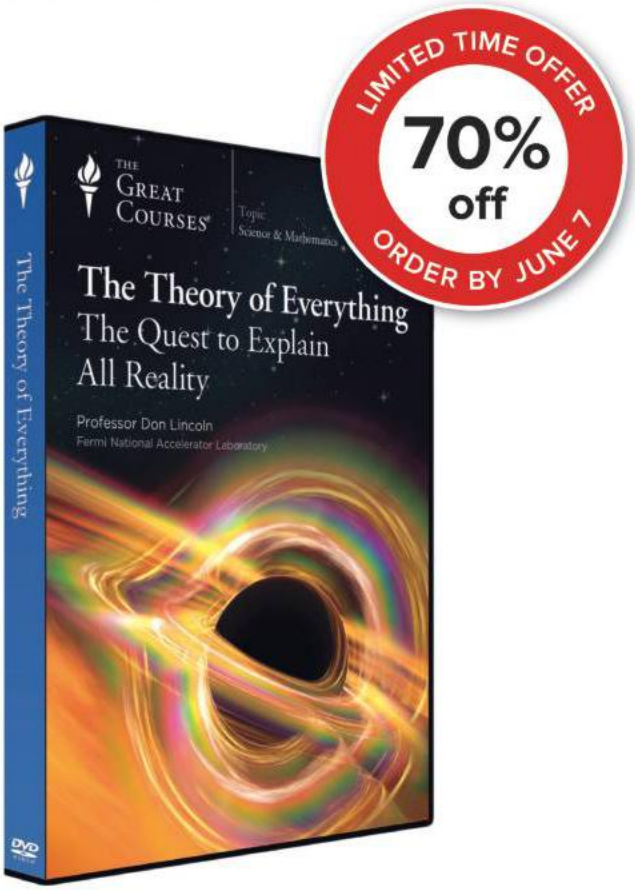

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ADVANCES

Devastation caused by Hurricane Sandy in New Dorp Beach on Staten Island in 2012.

ROBERT NICKELSBERG *Getty Images*

INSIDE

ADAPTATION

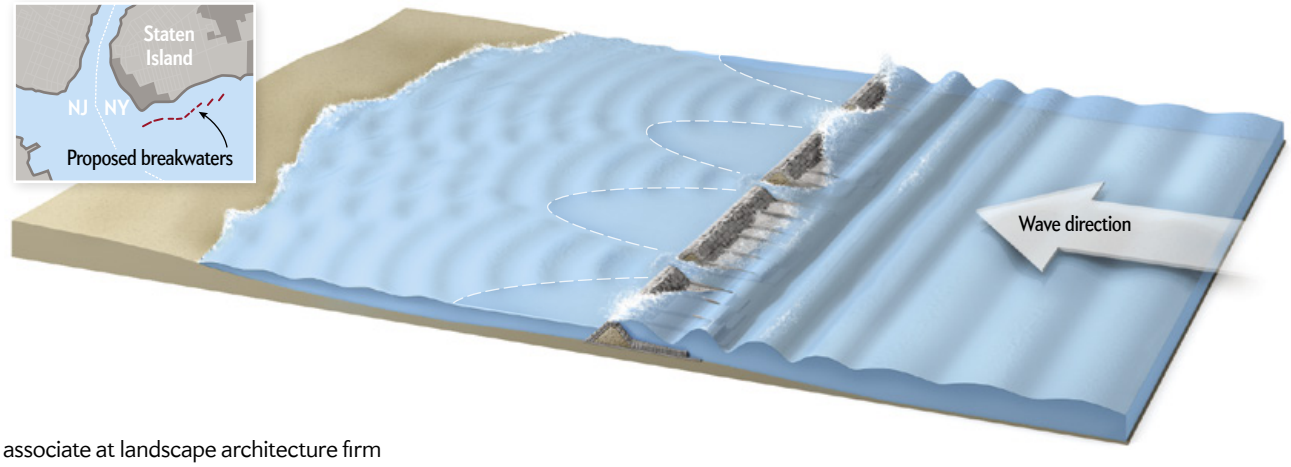
Breaking Waves

New York State aims to build "living" barriers off Staten Island for storm defense and ecological restoration

Hurricane Sandy caused widespread havoc when it made landfall in the Caribbean and on North America's East Coast (as a post-tropical cyclone) in 2012. The storm killed more than 40 people in New York City alone. "Never in its recorded history had the city experienced a storm of this size," local officials wrote in a report. "Never had a storm caused so much damage. Never had a storm affected so many lives."

As climate change and rising seas promise even more destructive storms, New York and other coastal communities are thinking about how to better protect themselves. Part of New York's plan is to create "living," oyster-encrusted barriers off southern Staten Island, to shield the highly vulnerable neighborhood of Tottenville from storm waves. The project—called Living Breakwaters—involves building structures to weaken storm waves, reduce coastal erosion and revitalize the local ecosystem, as well as educating the community.

Large, dense clusters of oysters once helped to protect Tottenville from storm waves and filter surrounding waters. But a combination of dredging, overharvesting and pollution virtually destroyed them. "It used to be that oyster reefs would provide a lot of structural habitat, but now there's just a sandy bottom," explains Brad Howe,



The Living Breakwaters will consist of an array of nine barriers off the coast of Staten Island. During a storm, the breakwaters will dissipate wave energy directly (during impact) and indirectly (as waves pass through the gaps and spread out), resulting in smaller waves at the shore.

an associate at landscape architecture firm SCAPE, which designed Living Breakwaters along with a team of engineers and ecologists. Sandy underscored why this kind of ecological degradation is so problematic—the storm hit Tottenville with some of the most powerful waves in the region, causing fatalities and knocking houses off their foundations.

The New York Governor's Office of Storm Recovery plans to begin building a 3,200-foot array of nine separate barriers, or "breakwaters," as early as this summer. Each has a stone trunk that sits partly underwater, between 730 to 1,200 feet offshore. The barriers are designed to dissipate wave energy (*graphic*). Five of them are meant to keep waves under three feet high during a "100-year storm"—an event that has a 1 percent chance of occurring in a given year—in a scenario with 30 inches of sea-level rise. The other four breakwaters will protect against erosion and attenuate waves during smaller storms.

"You'll still see wave action at the shoreline, but there will be significantly smaller waves."
—*Joe Marrone*, Arcadis engineer

During a storm, "you'll see waves breaking onto the breakwaters themselves, but you'll also see waves come through the gaps [between the barriers]," explains Joe Marrone, an engineer at design and consultancy firm Arcadis, who is working with SCAPE on the project. "As they come through the gaps, they spread out, and the height of the waves is reduced," he says. "So you'll still see wave action at the shoreline, but there will be significantly smaller waves."

By reducing the amount of wave energy pounding the shore, the breakwaters should slow erosion and leave more sediment to help build the beach. The gaps between the barriers are meant to allow some natural sediment to migrate and to let the system flush itself out.

Most of the structures will feature fingerlike ridges jutting into the ocean to provide habitat for fish and other aquatic animals. "The idea is to try to structurally mimic naturally occurring reef formations," Howe says. The breakwaters will incorporate materials that will help support marine life, and a group called the Billion Oyster Project plans to install the bivalves on and around the barriers.

The Living Breakwaters will also include a "floating water hub"—a boat that will serve as an educational space, giving community members and students access to the breakwaters. "It's about fostering this idea of social resilience, connecting people who live in the community back to the shoreline," Howe says.

Other places are also trying to build in cooperation with nature—rather than simply trying to hold it back—as they adapt to climate change. The Dutch city of Rotterdam has built "green," vegetation-covered roofs to absorb rainfall and a public plaza that also serves as a stormwater basin. Norfolk, Va., has developed a strategy to protect some areas from sea-level rise and coastal storms and to withdraw from others. "Even under the current U.S. national [political] climate, there are things happening," says Phil Berke, a professor of land use and environmental planning at Texas A&M University. "Cities like New York City, Miami, Norfolk and others are doing this on their own."

Some experts have concerns, however. "Certainly incorporating green aspects makes [projects such as Living Breakwaters] more resilient," says Katherine Greig, senior fellow at the University of Pennsylvania's Wharton Risk Management and Decision Processes Center. "But the notion that that's going to be the answer is troubling to me. Does it give people in those neighborhoods a false sense of security about what their risk is? Are the most vulnerable people going to be protected behind these infrastructure investments?"

SCAPE, however, says it has worked to address such concerns: "Our design team, along with the Governor's Office of Storm Recovery, has made a continued effort to engage and educate the community of Tottenville about the risks they face now and in the future and about how the Living Breakwaters reduce some of that risk but do not eliminate all risk." —*Annie Sneed*

Illustration by Emily Cooper

CHEMISTRY

Metal with Your Beer?

Filtration method may introduce a small amount of heavy metals

GETTY IMAGES

When you sip a beer or sample wine, you could get more than a pleasant buzz—the drinks may contain low levels of heavy metals. These elements accumulate in the body and can cause medical problems, so health organizations worldwide have set or proposed standards for acceptable levels in some food and beverages. Researchers have now pinpointed a silty filtration material as the culprit behind traces of inorganic arsenic, cadmium and lead in beer and wine.

Brewers and vintners sometimes use a substance called diatomaceous earth (DE) in the final stages of filtration to produce a clear, shelf-stable product. Consisting of the fossilized remains of tiny aquatic organisms, the substance removes unwanted particles without affecting flavor. Previous experiments suggested that DE filtration leaches arsenic into fruit juice, but it was not known if the same held for alcoholic drinks.

Benjamin Redan, Lauren Jackson and their colleagues at the U.S. Food and Drug Administration tested the arsenic content of small batches of lab-made alcoholic beverages—including lager, ale, red wine and white wine—before and after they were filtered with three types of food-grade DE. The researchers found arsenic levels increased up to eightfold—in some cases, above the FDA's proposed limit of 10 parts per billion for apple juice (the closest beverage for which the agency has issued standards). Noticeable levels of arsenic and other contaminants were also found in some commercially available wines. The findings were published in March in the *Journal of Agricultural and Food Chemistry.*

"The levels of heavy metals detected are not a risk for human health, except in the case of massive daily beer consumption, but the issue of heavy metal content in foodstuffs is fundamental," says Stefano Buiatti of the University of Udine in Italy, who was not involved in the study.

The researchers found they could reduce arsenic in filtered products by adjusting the quantity of DE used or changing the filtration time, for example. The food industry already employs alternative purification methods. "Membrane-filtration technology for beer filtration is of great interest in the brewing community," says Joseph Palausky, technical committee chair of the American Society of Brewing Chemists. "But there are other more traditional and established techniques—such as cold stabilization or maturation and centrifugation—that are in use in the industry." —*Rachel Berkowitz*

NEURAL ENGINEERING

Decoding Speech

New approach is a step toward translating thoughts into machine-spoken words

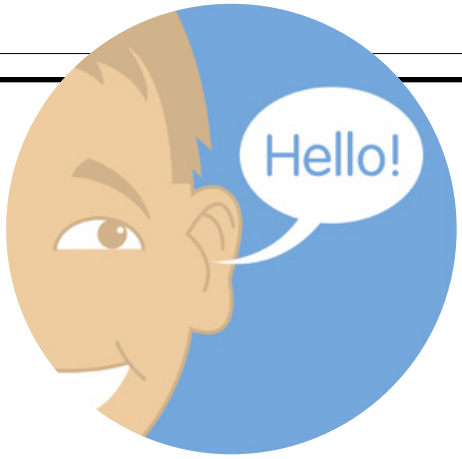


Illustration by Thomas Fuchs

Neurological conditions that can cause paralysis, such as amyotrophic lateral sclerosis (ALS) and strokes in the brain stem, also rob many patients of their ability to speak. Assistive technologies enable keyboard control for some of these individuals (like the famed late physicist Stephen Hawking), and brain-computer interfaces make it possible for others to control machines directly with their thoughts. But both types of devices are slow and impractical for people with locked-in syndrome and other communication impairments.

Now researchers are developing tools to eavesdrop on speech-related brain activity, decode it and convert it into words spoken by a machine. A recent study used state-of-the-art machine learning and speech-synthesis technology to yield some of the most impressive results to date.

Electrical engineer Nima Mesgarani of Columbia University's Zuckerman Institute and his colleagues studied five epilepsy patients who had electrodes implanted in or on their brain as part of their treatment. The electrodes covered regions involved in processing speech sounds. The patients listened to stories being read aloud as their brain activity was recorded. The team trained a "deep learning" neural network to match this activity with the corresponding audio. The test was then whether, given neural data it had not seen before, the system could reproduce the original speech.

When the patients heard the digits zero through nine spoken four times each, the system transformed the neural data into values needed to drive a vocoder, a special kind of speech synthesizer. A separate group of participants heard the synthesized words and identified them correctly 75 percent of the time, according to the study, published in January in *Scientific Reports*. Most previous efforts have not measured how well such reconstructed speech can be understood. "We show that it's intelligible," Mesgarani says.

Researchers already knew it was possible to reconstruct speech from brain activ-

SEISMOLOGY

Missing Earthquakes Found

Geologists fill in mysterious gap in Nepal's quake record

Aftermath of the 2015 Nepal earthquake in Sankhu.

TURJOY CHOWDHURY *Getty Images*

Like a slow-motion car crash, the Indian subcontinent is colliding with Eurasia. This impact, along a fault known as the Main Himalayan Thrust, is the force driving the rise of the Himalayas. In April 2015 it triggered Nepal's magnitude 7.8 Gorkha earthquake, which destroyed villages and parts of Kathmandu, killing thousands.

Nepal is no stranger to such temblors—but in the western part of the country, no significant earthquakes have been recorded since 1505. Such a "seismic gap" could be bad news: if the region's faults are not releasing their pent-up stress every so often, one or more very large and potentially catastrophic earthquakes could result. "With more than 500 years of waiting, the stored energy due to the convergence of India [and Eurasia] could be considerable," says Zakaria Ghazoui, a geologist at the Institute of Earth Sciences in Grenoble, France. The sudden release of this energy could devastate nearby places such as Pokhara, one of Nepal's largest cities.

To determine whether this seismic gap actually exists, Ghazoui and a team of researchers ventured onto Rara Lake in western Nepal's Himalayas and retrieved cores of sedimentary layers from the bottom. They suspected the cores might contain records of when any past earthquakes occurred because quakes can cause underwater avalanches that leave behind layers of what Ghazoui calls "disorganized" sediment.

The team found evidence of at least eight avalanches since 1505, corresponding to moderate to large quakes. "We were hoping to find the trace of the 1505 earthquake, but the discovery of the other earthquake-triggered avalanches was a real surprise," he says. This means that the area's faults may not be storing as much stress as has been thought. But it also

ity, but the new work is a step toward higher performance. "There's a lot of room for improvement, but we know the information is there," says neurosurgeon Edward Chang of the University of California, San Francisco, who was not involved in the study. "Over the next few years it's going to get even better—this is a field that's evolving quickly."

There are some limitations. Mesgarani's team recorded brain activity from speech-perception regions, not speech-production ones; the researchers also evaluated their system on only a small set of words instead of complete sentences drawing on a large vocabulary. (Other researchers, including Chang, are already working on these problems.) Perhaps most important, the study was designed to decode activity related to speech that was actually heard rather than merely imagined—the latter feat will be required to develop a practical device. "The challenge for all of us is actual versus imagined" speech, Mesgarani says. *—Simon Makin*

The western Nepal part of the Main Himalayan Thrust, a geologic fault at the junction of the Indian and Eurasian Plates, has not experienced a significant earthquake since 1505.

highlights the "almost permanent risk" that the area faces when it comes to earthquake hazards in general, explains Ghazoui, who led the new research, which will appear in *Nature Communications*.

This is the first time that researchers have used lake sediment records to peer into the Himalayas' earthquake history, according to Roger Bilham, a seismologist at the University of Colorado Boulder, who was not involved in the research—which, he says, "is just a teaser of what can be done." *—Lucas Joel*

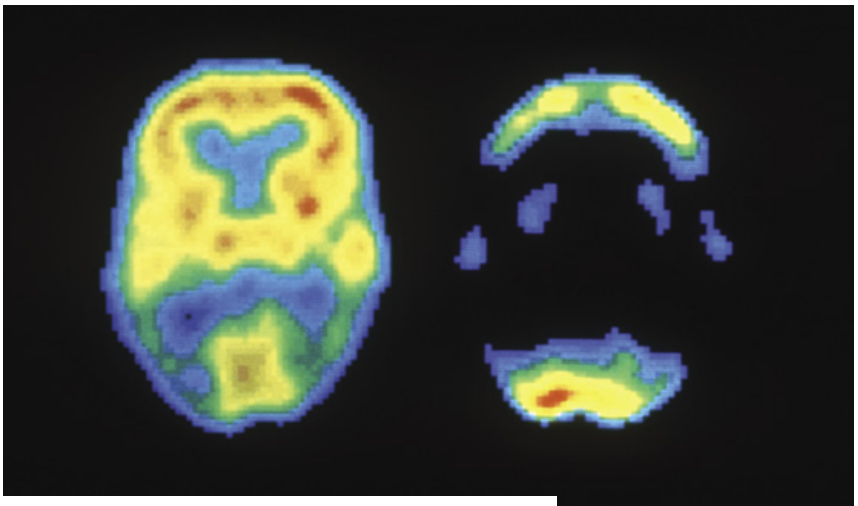
SOURCE: "BIMODAL SEISMICITY IN THE HIMALAYA CONTROLLED BY FAULT FRICTION AND GEOMETRY," BY LUCA DAL ZILIO ET AL., IN *NATURE COMMUNICATIONS*, VOL. 10, ARTICLE NO. 48; JANUARY 3, 2019

Map by Mapping Specialists

HEALTH TECH

Alzheimer's AI

Algorithm predicts eventual Alzheimer's diagnoses from brain scans



PET scans of normal (*left*) and Alzheimer's (*right*) brains.

SCIENCE SOURCE

An estimated 5.7 million people in the U.S. have Alzheimer's disease—the most common type of dementia—and that number is expected to more than double by 2050. Early diagnosis is crucial for patients to benefit from the few therapies available. But no single assay or scan can deliver a conclusive diagnosis while a person is alive; instead doctors have to conduct numerous clinical and neuropsychological tests. So there is growing interest in developing artificial intelligence to identify Alzheimer's based on brain imaging.

Researchers at the University of California, San Francisco, have now successfully trained an AI algorithm to recognize one of the early signs of Alzheimer's—a reduction in the brain's glucose consumption—in positron emission tomography (PET) imaging. The algorithm accurately predicted an eventual Alzheimer's diagnosis in nearly all the test cases, according to the study.

In PET imaging, trace amounts of a radioactive compound are ingested or injected into the body, producing three-dimensional images of metabolism, circulation and other cellular activity. PET is well suited for an AI diagnostic tool because Alzheimer's causes subtle changes in the brain's metabolism that begin years before neural tissue starts to degrade, says study co-author Jae Ho Sohn, a radiologist at U.C.S.F. These changes are "very hard for radiologists to pick up," he notes.

The algorithm was trained and tested on 2,100 PET brain images from about 1,000 people 55 years and older. The images came from a 12-year study that tracked people who would ultimately be diagnosed with Alzheimer's, as well as those with mild memory declines and healthy control subjects. The algorithm was trained on 90 percent of the data and tested on the remaining 10 percent. It was then retested on a second, independent data set from 40 patients monitored for 10 years. The algorithm was highly sensitive and was able to recognize 81 percent of the patients in the first test group and 100 percent in the second who would be diagnosed with Alzheimer's six years later, on average. The findings were published in February in *Radiology.*

The algorithm is based on "deep learning," a machine-learning technique that uses artificial neural networks programmed to learn from examples. "This is one of the first promising, preliminary applications of deep learning to the diagnosis of Alzheimer's," says Christian Salvatore, a physicist at Italy's National Research Council, who was not involved in the study. "The model performs very well when identifying patients with mild or late" diagnoses, he says, but catching it in the earliest stages "remains one of the most critical open issues in this field."

—Rod McCullom

ALEX MUSTARD Getty Images

ECOLOGY

Counting Salmon

DNA in floating fish slime could help monitor migrating salmon

The slime that sloughs off the skin of Alaskan salmon might become the latest tool for measuring their numbers and protecting populations—an effort that could be vital to keeping the wild fish on dinner plates for years to come. Researchers recently counted the number of salmon migrating through a narrowed waterway for fish, or weir, in southeastern Alaska by measuring DNA in the bodily waste they shed into a stream as they headed to spawning grounds.

Scientists have been developing this approach, which relies on eDNA (or environmental DNA), for years. They can determine a fish species' presence and get a general idea of its abundance by measuring the amount of its DNA in a sample of water. But to maintain salmon populations in a commercial fishery worth more than $500 million a year, managers need a more accurate way to count fish that return from the ocean to spawn. Salmon use thousands of streams throughout Alaska; biologists can count them only at a small subset because of the costs of traveling to remote locations, building weirs that funnel the fish for counting and paying biologists who can accurately identify salmon species.

In the new study, Taal Levi, an assistant professor of fisheries and wildlife at Oregon State University, and his colleagues collected daily eDNA samples at a counting station at Auke Creek and compared their results with human counts of sockeye and coho salmon. They also recorded streamflow, which affects how much eDNA is present. After accounting for the flow rate, Levi and his team accurately matched eDNA concentrations with numbers of salmon counted. They reported their findings online last December in *Molecular Ecology Resources*.

The effort was a proof of concept, but Levi hopes this approach can be applied to other streams and automated to provide more cost-effective monitoring. And eDNA is already helping scientists track the movement of salmon into the Canadian Arctic, as the climate changes, by documenting their presence in new locations.

Chris Habicht, a fisheries geneticist at the Alaska Department of Fish and Game, who was not involved in the work, is skeptical that this approach can be applied broadly. He notes that biologists would need to install streamflow sensors at each site sampled—a costly endeavor in remote parts of Alaska. Study co-author Scott Vulstek, a fisheries biologist at the National Marine Fisheries Service, admits there are challenges. But not every unmonitored stream is remote, he says, and eDNA could supplement data collected at monitored sites. Moreover, he adds, "this technology is only going to get better over time." —*Amy Mathews Amos*

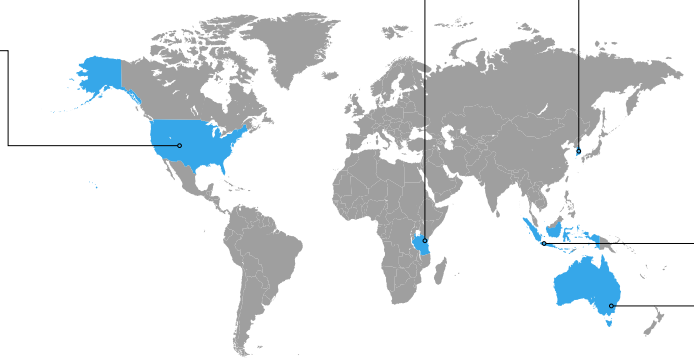
IN THE NEWS

Quick Hits

By Jim Daley

TANZANIA
A butterfly farming project in the country's East Usambara Mountains is providing an alternative to timber-harvesting jobs that threaten forest biodiversity. The project's 250 farmers—more than half of whom are women—raise caterpillars and sell pupae to zoos and butterfly parks in Europe and the U.S.

SOUTH KOREA
Paleontologists found 110-million-year-old fossilized spiders in South Korea's Jinju Formation. The well-preserved arachnids had remnants of a reflective layer called a tapetum behind their retinas, which would have given their eyes an eerie, catlike glow.



U.S.
The U.S. Nuclear Regulatory Commission shut down a research reactor in Denver after inspectors found it to be in violation of staffing and training regulations. The commission recommended imposing a $7,250 fine on the U.S. Geological Survey, which operates the reactor.

INDONESIA
Hundreds of scientists protested plans by the Indonesian Institute of Sciences to relocate more than 1,400 administrative and support jobs from research centers around the country to central hubs or the institute's Jakarta headquarters. Senior researchers say they were not consulted about the decision.

ANTARCTICA
A NASA-led study discovered a cavity two-thirds the size of Manhattan underneath one of Antarctica's largest and fastest-moving glaciers. The 1,000-foot-high, six-mile-long hole in the Thwaites Glacier used to contain some 14 billion tons of ice, most of which has melted away in the past three years.

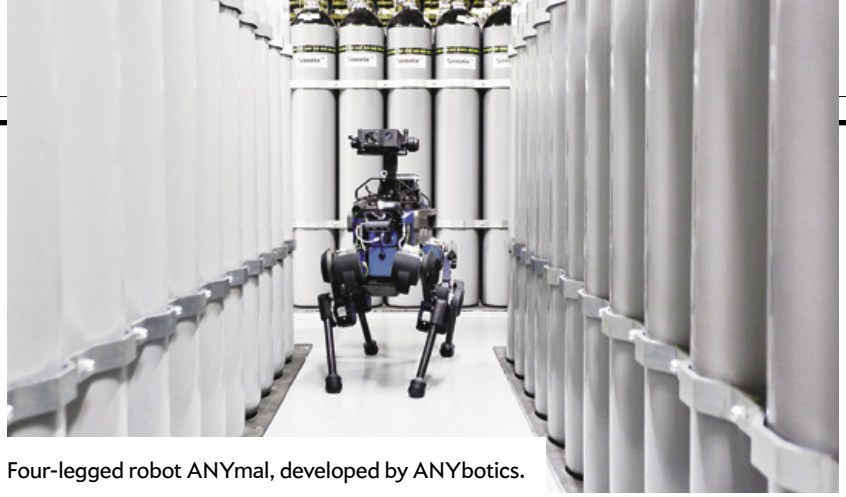
AUSTRALIA
A court in the state of New South Wales rejected an application to build a coal mine because of its potential to exacerbate climate change. This is the first time Australia has blocked building a coal mine over global warming concerns.

For more details, visit www.ScientificAmerican.com/may2019/advances

TECH

Good Bot

Doglike robots simulate their skills before entering the real world



Four-legged robot ANYmal, developed by ANYbotics.

Programming robots that can walk, run and grasp is laborious, so researchers would prefer that they learn on their own. To solve the problem of wear-and-tear on real robots learning by trial-and-error, groups of researchers are developing ways to simulate the bots and download the skills they learn to real hardware. A new method improves these simulations with data from the real robots, closing the feedback loop. The result is robots with boosted speed and agility.

Working with a robotic quadruped called ANYmal, roboticists at the Swiss Federal Institute of Technology Zurich (ETH Zurich) augmented its algorithms with neural networks (software inspired by the human brain). As the robot fumbles around in the real world, the neural networks learn the quirks of each of the bot's motors. That information feeds back into the simulation, helping it more accurately model the real bot and thus produce more effective skills for downloading. In experiments, ANYmal broke its previous trotting speed record by 25 percent, the researchers reported in January in *Science Robotics.* It could also regain its balance after being pushed and its footing after being flipped.

ANYmal is commercially available through the ETH Zurich spinoff ANYbotics. Motors in its joints have tendonlike springs that absorb shock, store energy and provide sensory feedback. Each leg has three motors, all interchangeable. Jemin Hwangbo, a roboticist who helped to develop the simulation-based training method, says it was created for rescue operations and oil rig inspections. It can climb stairs and crawl through tunnels while carrying its heavy digital brain inside its dustproof and watertight body. A Kevlar belly helps it survive half-meter falls.

Others are developing quadruped bots that rival ANYmal's abilities. In 2008 Boston Dynamics gained notice for comical (and creepy) footage of its noisy, gas-powered "BigDog" trudging up treacherous terrain. The newer "SpotMini" is its 25-kilogram electric cousin. Sangbae Kim, a mechanical engineer at the Massachusetts Institute of Technology, who is not affiliated with Boston Dynamics, says SpotMini has the world's most advanced algorithm for navigating around and over obstacles. The company plans to start selling it this year for jobs ranging from construction to home assistance. A top-mounted port allows users to attach tools, including a five-kilogram arm that can fetch drinks and load the dishwasher—truly a human's best friend.

Kim's team at M.I.T. has built a 40-kilogram bot named "Cheetah 3," which he says moves more efficiently than four-legged animals of similar weight. The robot also has the most powerful joints of any legged robot of its size, he adds—they were built from scratch and produce as much torque as a car engine. The joints also regenerate energy and handle impacts well. Cheetah 3 is not as fast as its predecessor, Cheetah 2, which can run at 23 kilometers an hour, Kim says. But it can perform backflips (at least in theory) as well as climb stairs and obstacles without relying on camera vision. It is built for research, however, so do not expect to adopt one soon. —*Matthew Hutson*

ANYBOTICS www.anybotics.com

GETTY IMAGES

SLEEP SCIENCE

Cuttlefish Dreams

The marine invertebrates appear to experience rapid eye movement sleep

Cuttlefish are known for their sophisticated camouflage, as well as their kaleidoscopic displays for attracting mates and mesmerizing prey. These close relatives of squid and octopuses achieve such feats via millions of chromatophores—tiny sacs of pigment under the skin attached to muscles that squeeze or relax to push colors to the surface. In a new study, researchers report they have observed resting cuttlefish cyclically changing color and twitching their limbs in phases that resemble rapid eye movement (REM) sleep.

Many animals experience REM, a sleep phase that may involve eye movements and loss of muscle tone; in humans and some other mammals, it is often linked to dreaming. Study co-author Teresa Iglesias, a biologist at the Okinawa Institute of Science and Technology, cannot yet say whether cuttlefish experience the same kind of sleep that we do, but the animals' active phase during rest is similar to the REM sleep observed in humans and other vertebrates. Although the lineage that includes cuttlefish diverged from vertebrates around 500 million years ago, the study findings hint at a common evolutionary origin for sleep, she says.

Iglesias and her colleagues filmed cuttlefish in laboratory tanks for 24 to 48 hours at a time. While resting, the animals would demonstrate REM-like behavior for periods lasting between two and three minutes. They made sporadic arm and eye movements, and the chromatophores around their eyes got darker. Such phenomena were not observed during waking activity or inactive parts of their "sleep" cycles. The findings were published in January in the *Journal of Experimental Biology*.

"Sleep is a neural phenomenon more than a behavioral one," says psychologist Jennifer Mather, a cephalopod expert at the University of Lethbridge in Alberta, who was not involved in the new research. Cycles of brain activity while an animal is quiescent, she explains, suggest sleep may play a role in stabilizing neural circuitry and processing newly acquired information. The REM-like behavior observed in cuttlefish could indicate a similar process is happening in their brain, she says.

But do cuttlefish dream? "We can speculate all we like," Mather says. "It's difficult because I don't [even] think we know why we dream." Iglesias says it is not impossible, but there is not enough evidence to answer this question. "For now," she says, "the biggest takeaway is that we need to dig deeper and keep an open mind." —*Jim Daley*

Troubled Sleep and Dementia

Could better nighttime rest help delay symptoms of Alzheimer's?

By Claudia Wallis

Among the many things that can shatter when Alzheimer's disease tightens its grip is the steady rhythm of the body's sleep-wake cycle. The problem is so common that one New York City nursing facility—the Hebrew Home at Riverdale—ran an all-night program for many years that took in afflicted community members for a dusk-to-dawn schedule of games, snacks, arts and crafts, and other activities so that their exhausted families could get some shut-eye.

Troubled sleep often begins long before dementia becomes apparent. In recent years research has been heating up on two key questions: Could disrupted sleep be a reliable early warning sign that the brain changes of Alzheimer's have begun? And even more exciting, though still speculative: Could the onset of the disease or its progression be slowed by treating sleep-related issues?

The brain pathology of Alzheimer's gets underway roughly 20 years before symptoms such as memory lapses and confusion become obvious. Scientists believe the fateful sequence goes something like this: beta-amyloid, a nerve cell waste product, starts to accumulate in the spaces around brain cells, eventually forming the telltale plaques of Alzheimer's. This is followed by a toxic buildup of tangles of tau protein inside nerve cells, first in the medial temporal lobe and then spreading to other regions. These changes lead to the death of neurons, loss of synapses and general atrophy seen in Alzheimer's-addled brains and the observable deterioration of cognition and behavior.

Sleep, as it turns out, impacts both beta-amyloid and tau. Studies in humans and mice indicate that levels of both proteins fall during sleep. People who sleep poorly have higher levels of beta-amyloid and tau in their cerebrospinal fluid—even after a single bad night. What is perhaps more significant is what happens over the long term. PET scans show older adults with chronic sleep problems have more beta-amyloid deposited in their brain. Research published earlier this year in *Science* revealed that in a mouse model of Alzheimer's, lack of sleep promotes the spread of abnormal tau across certain brain regions. "It suggests that if there's a sleep disturbance night after night for some prolonged period, it could expose an individual to higher concentrations of these proteins and increase the risk of Alzheimer's," says Brendan Lucey, one of the *Science* paper's authors and an assistant professor of neurology at Washington University in St. Louis.

A 2018 study provides evidence for this cumulative damage scenario. Using data on 124 older adults participating in a long-term National Institute on Aging (NIA) study, sleep researcher Adam Spira and his colleagues at Johns Hopkins University and the NIA found that people who complained of "excessive daytime sleepiness" at an average age of 60 were 2.75 times more likely to have beta-amyloid plaques in their brain some 16 years later.

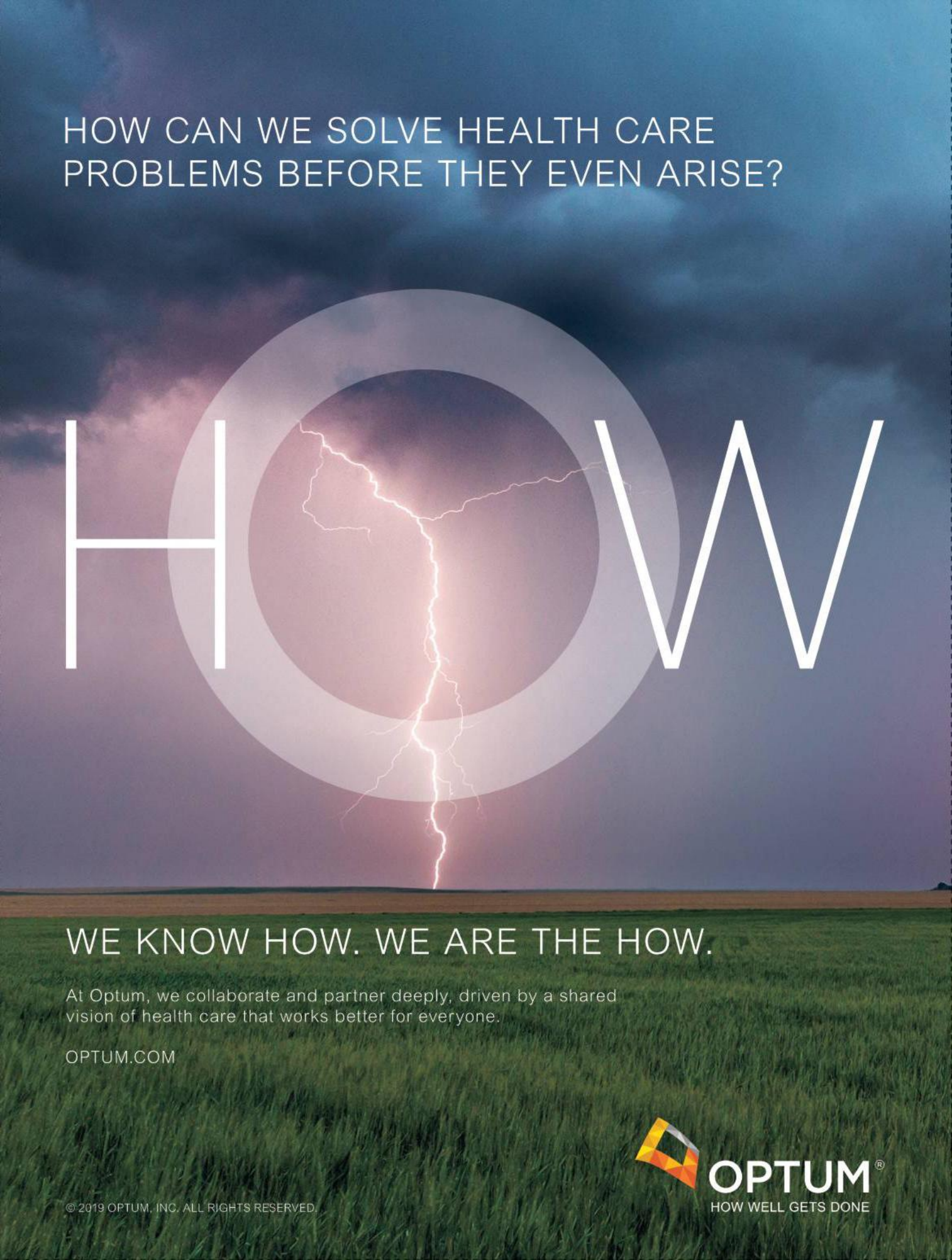
In another new study, published earlier this year in *Science Translational Medicine,* Lucey and his colleagues explored which part of sleep may be most relevant to Alzheimer's pathology. They found that having less of a very deep phase called slow-wave, non-rapid eye movement sleep, is associated with more accretion of tau and, to some degree, beta-amyloid. This part of sleep also happens to be important to memory consolidation.

No one knows for sure what comes first: Do excess beta-amyloid and tau impair sleep, or does impaired sleep lead to a build-up of these proteins? The leading hypothesis is that it goes both ways in a kind of vicious cycle. For example, Lucey proposes, let's say someone "develops sleep apnea, sleeps poorly, increasing Alzheimer's pathology, which then worsens their sleep further and accelerates their pathology."

Could disrupting this cycle help stave off dementia? It's too early to say, but as Spira notes, "there's a growing interest in coming up with ways to attack poor sleep as a possible way to prevent Alzheimer's." A small study published earlier this year by a team at the University of California, San Francisco, offers a glimmer of hope. It looked at 50 older adults with Alzheimer's, mild cognitive impairment or normal cognition and found that the 25 who used the drug trazodone as a sleep aid had a significantly slower cognitive decline than the 25 who did not use the it. Trazodone, intriguingly, is known to increase slow-wave sleep. Alas, the road to an Alzheimer's treatment is littered with disappointment. Working the sleep angle may prove to be yet another pipe dream, but it's hard to imagine it could do much harm. SA

Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic.* She was science editor at *Time* and managing editor of *Scientific American Mind.*

Illustration by Celia Krampien



Turning Off the Emotion Pump

Are there better social technologies than Facebook?

By Wade Roush

Strip away the baby pictures, the cat GIFs and the high school reunion invitations, and what is lurking underneath your Facebook news feed is one of history's most effective targeted advertising platforms.

Facebook watches to learn what pleases you and what angers you, and it uses that information to auction ads to companies that want to reach consumers with your specific profile. It also watches what everyone else likes, then shows you more of whatever is most engaging that day—the better to keep you scrolling, so that you'll encounter more ads. If the "whatever" happens to be an Islamophobic graphic posted by state-sponsored trolls in Russia saying, "Type Amen if you want Texas to stay Christian," that's what the algorithms will show. Think of it as an emotion pump. You finish reading a post. Before you can close the app or click to another browser tab, you scroll some more, almost by reflex. In that moment, Facebook injects another post optimized to make you laugh or get you angry, and the cycle continues. Polarizing content keeps the pump constantly primed by riling users up.

The side effects of this strategy have become plain in nations such as Myanmar, the Philippines and the U.S., where misinformation shared on Facebook has fueled division and social unrest.

Wade Roush is the host and producer of Soonish, a podcast about technology, culture, curiosity and the future. He is a co-founder of the podcast collective Hub & Spoke and a freelance reporter for print, online and radio outlets, such as *MIT Technology Review*, Xconomy, WBUR and WHYY.

Kathleen Hall Jamieson, a professor of communications at the University of Pennsylvania, concluded in her 2018 book *Cyberwar* that Russian-sponsored Facebook ads and posts swayed the outcome of the 2016 presidential election. Nobody at Facebook anticipated these effects. But they can't be swept under the rug—and they can't be solved through minor algorithmic adjustments, because this *is* Facebook. The emotion pump is at the core of its business model.

Are there other ways to design social media networks? Yes and no. For years I enjoyed a smartphone-based social network called Path, which was conceived in 2010 by Facebook alumnus Dave Morin as a kind of un-Facebook and a home for smaller groups (it initially limited users' networks to just 50 people). Path had an enchanting interface, but it never found a solid source of revenue, and it shut down in 2018. The Diaspora project raised $200,000 on Kickstarter in 2010; its vision was to build a decentralized network where users would run their own servers, or "pods," and control their own data. It still exists as an open-source project, but the difficulty of setting up a Diaspora pod has kept its user base small. The failure of these small-scale networks doesn't bode well for Mark Zuckerberg's plan, announced in March, to remake Facebook around messaging within small, private groups.

Without revenue from emotion-pumped advertising, Facebook would wither, and there could never be another social-networking company that reaches its planetary scale. But I believe those would be *good* things. Facebook does only one thing well: it keeps you from falling out of touch with people you don't see very often. There are smaller-scale services that serve the same end, however, without the risk of blowing up our democracies.

For instance, after I decided to leave Facebook, my family began using GroupMe, a free group-texting app owned by Microsoft. It's simple, but for the photos and updates that we formerly shared on Facebook, it's fine. To share news with people who've asked to follow my writing or podcast projects, I've used platforms such as Google Groups and Mailchimp. I even send out an occasional personal e-mail or (gasp!) handwritten note.

I was interested to hear about the finding by University of Oxford evolutionary psychologist Robin Dunbar that Facebook hasn't actually enhanced our capacities as networkers. In a 2016 study of 2,000 users, respondents told Dunbar that only 28 percent of their Facebook friends could be considered "genuine" or close friends. That fits with my experience. The other 72 percent—let's be honest here—aren't worth a big cognitive investment, and they wouldn't be in our circles at all unless the technology made it so easy.

In the past year I've lost two dear friends from former workplaces. They both died after brief, sudden, shocking illnesses. I did not learn about their deaths from my Facebook news feed. Friends, colleagues and family members reached out to me directly, and we shared our memories and grief through e-mail, calls and visits.

That's how society functioned before Facebook. And these skills can resurface—but not until we reclaim some of the energy captured by the emotion pump. SA

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Illustration by Jay Bendt

FERTIL GROU

When the discussion of reproductive health is dominated by the political will to control it, gaps in medical research get overshadowed

FEMALE REPRODUCTIVE HEALTH has frequently been wrapped up in politics and patriarchy. In 2019 millions of women globally are still ostracized for menstrual bleeding. American lawmakers are trying to roll back the legal right to abortions and have cut off funding for contraception and sex education. The contraceptive devices known as IUDs are being promoted as a "set it and forget it" solution to poverty. This uneasy dance between science and society has a long history, as evidenced in a 1933 article in *Scientific American*. In "Birth Control and Bigotry," C. C. Little embraces "contraceptive clinics" but then explains his motivation: "Unwanted and uncared for children spreading misery and disease have produced a flood of criminals and have disturbed the progressive development of a sane social structure," he writes. When eugenics gets conflated with reproductive freedom, it is not surprising that the science itself is warped and incomplete.

Today a sustained assault on women's reproductive agency is still a force in much of the world, and scientists struggle to balance research and public education in the onslaught of political resistance. "Many people in the reproductive health field are exhausted," says Carolyn Westhoff, editor of the journal *Contraception*. Understanding how we got to this point goes back, in part, to age-old taboos and myths about female menstruation, a number of which still exist.

FEMALE REPRODUCTIVE HEALTH

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Having periods is not a disease. But when they go wrong, they offer clues into disorders that require intervention. The medical field has largely done a poor job of identifying and treating them with precision. Clinicians tend to wield synthetic hormones like a hammer, liberally prescribing the birth-control pill for all kinds of pain—which is partly why serious diseases of the female organs such as endometriosis take an average of eight years to be diagnosed. That women's symptoms are often dismissed does not help.

In this special report, *Scientific American* examines the consequences to these gaps in understanding. What might be different if researchers had investigated the evolutionary purpose of periods *before* they developed a pill to shut down a woman's cycle? Why are women expected to shoulder health trade-offs in exchange for avoiding pregnancy? We also illuminate the dangers of giving birth in America—particularly for black women, who die at a rate up to four times higher than the rest of the population. And amid a global fertility crisis affecting both sexes, we ask whether the promises of assisted reproductive technologies are overblown.

Going forward, rigorous, collaborative and innovative research in reproductive health could lead to better birth control, safer clinical protocols and more personalized care. Filling these gaps is vital not just for the well-being of women but for the health of society.

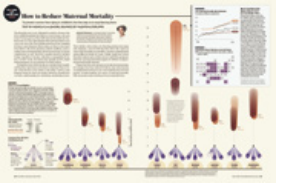
—Clara Moskowitz and Jen Schwartz

THE POINT OF A PERIOD

Squeamishness about female menstruation has led to limited research on how periods work and why they go wrong. pg. 32

SET IT AND FORGET IT?

There is more to contraceptives than their effectiveness. Why women—and men—need better birth control. pg. 40



MATERNAL MORTALITY

Too many U.S. women are dying in pregnancy and childbirth—and then getting blamed for it. pg. 48

EGGS ON ICE

Scientific and social forces invite people to pause their fertility. But what will happen when the eggs thaw? pg. 52

THE POINT OF A PERIOD

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Age-old taboos against menstruation have led to a lack of research on how women's cycles work, with serious consequences for their health

By Virginia Sole-Smith

Photographs by Jamie Chung

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IN 2007 SUSAN BROWN ENCOUNTERED THE REPELLING POWER OF PERIOD BLOOD. While studying what menstrual fluid might reveal about a woman's health, she wanted data from a cross section of subjects beyond the student volunteers at the University of Hawaii at Hilo, where she worked as an evolutionary psychologist. Brown's team members set up a booth near the entrance of a Walmart in downtown Hilo and hung a sign that said, "Menstrual Cycle Research." Then they waited. All afternoon women and men would spot the sign, then gingerly skirt past without making eye contact.

About six months later Brown and her Hilo colleague Lynn Morrison presented their findings at the annual meeting of the American Association of Physical Anthropologists. A wave of "nervous twittering" broke out when Morrison described carrying menstrual blood samples down the hallway of their laboratory to analyze hormone levels and other biomarkers. "The audience was fine discussing a woman's cycle in the abstract," Brown explains, "but not menstrual blood itself."

That aversion has influenced women's relationships to their own bodies as well as how the medical establishment manages women when things go wrong with their reproductive health. "Our menstrual taboo is at the core of how this science is getting done," Brown says of research on menstruation.

Or not getting done, as the case may be. It is hard to measure how much money is spent on period research, but experts agree the subject is underfunded. "It's a chicken-and-egg situation, where there's not much funding for research, so there's also not much quantifying of that lack of research," says Elizabeth Yuko, a bioethicist at Fordham University.

Yet period disorders are incredibly common. When Saudi Arabian researchers surveyed 738 female college students in a 2018 study, they found that 91 percent reported at least one menstrual problem: some got their periods irregularly or not at all; others reported excessive levels of bleeding and pain. Different studies show that as many as one in five women experiences menstrual cramps severe enough to limit her daily life. About one in 16 worldwide suffers from endometriosis, a disease where menstrual blood and tissue migrate outside a woman's uterus and form painful lesions in her pelvic cavity. And one in 10 women has polycystic ovarian syndrome, a hormonal imbalance that disrupts a woman's cycle and is a leading cause of infertility. "You can argue we need to put our resources toward researching the life-and-death stuff," Yuko says. "But that argument falls apart because we've had no problem funding erectile dysfunction research."

Menstruation, of course, is essential to human reproduction and therefore survival. It is also one of the biological processes that makes us special because humans, chimpanzees, bats and elephant shrews are among the only animals on earth that go through it. The vast majority of mammals signal fertility through estrus, the period when females are ovulating and display their sexual receptivity via genital swelling, behavioral changes or pronounced alterations in body odor. The female human body, however, conceals this critical window. Instead our most visible sign of potential fertility is menstrual blood, which, ironically, appears after the fertile period has closed. The endometrial lining of the uterus thickens over the course of a woman's cycle as her estrogen level rises. If none of the eggs she releases at ovulation joins with a sperm and implants in that lining as a fertilized zygote, then levels of estrogen and another hormone called progesterone drop, triggering the uterus to shed the thickened endometrium so it can start fresh in the next cycle.

But beyond this basic picture, scientists are still struggling to understand fairly fundamental questions: Why do we share this process with at least six species of bats, for example, but not monkeys? And just what is menstrual blood, exactly? "It's quite different from regular blood," Brown notes. "We know it

Virginia Sole-Smith is a journalist who writes about feminism, body image and health for the *New York Times Magazine*, *Harper's Magazine*, *Elle* and many other publications. She is author of *The Eating Instinct: Food Culture, Body Image, and Guilt in America* (Henry Holt, 2018).

can't clot and is full of immune agents, but we don't know much about what they do." It is also unclear why we shed this biological tissue so dramatically when most mammals that experience estrus appear to reabsorb their endometrial linings at the end of each cycle. Even less is known about why so many women—up to 80 percent by some estimates—experience cramps, bloating, fatigue, anger or other symptoms just before the onset of menstruation. "We know so little about menstruation," says Tomi-Ann Roberts, president of the Society for Menstrual Cycle Research and a professor of psychology at Colorado College, and what scientists do know is often badly communicated with the public. "Because of this, our attitudes toward menstruation are overwhelmingly negative. This has real consequences for how we can begin to understand healthy menstruation, as well as menstruation-related disorders and the treatment options available."

MASKING MENSTRUATION

THE TABOO has taken many forms. In 1920 a Hungarian-born pediatrician working in Vienna named Béla Schick published a collection of anecdotal observations: When he asked a menstruating woman to handle flowers, they wilted within minutes. When he compared the bread dough made by several women, the loaf made by the one having her period rose 22 percent less. Schick concluded that menstrual blood contained a kind of poison. By the early 1950s Harvard University scientists were referring to "menotoxins" and injecting menstrual blood into animals to observe the effects. Some of those animals died, most likely because the blood samples carried bacteria and other contaminants. Not much came of these experiments in terms of useful data, but the notion that menstrual blood contains mysterious and even dangerous properties has persisted in the scientific literature and our cultural imagination.

By the late 1950s research around menstruation had shifted to center almost entirely on preventing unplanned pregnancies at a time when maternal and infant mortality was troublingly high, especially in poor communities. In 1923 Margaret Sanger, the activist, nurse and founder of the organizations that would later become Planned Parenthood, wrote that "Birth Control means liberation for women and for men." In 1951 she met a physiologist named Gregory Pincus, who had performed what was considered at the time to be the first in vitro fertilization of rabbits. With Sanger securing funding, Pincus set up a lab to test formulations of synthetic versions of hormones that regulate the menstrual cycle and teamed up with John Rock, a Boston obstetrician-gynecologist, to run clinical trials of the drug.

After a study of almost 60 women in and around Boston, Pincus and Rock turned to Puerto Rico to run the first large-scale trial of the drug that the U.S. Food and Drug Administration would approve in 1960 as the first oral contraceptive. They recruited 265 Puerto Rican women, many of them poor, to the study without the level of "informed consent" required today. Twenty-two percent of the participants dropped out after reporting side effects such as nausea, dizziness, headaches and vomiting. The study's medical director argued that the pill "caused too many side reactions to be generally acceptable." Nevertheless, it went to market.

MENSTRUAL CUPS can be a reusable, environmentally friendly alternative to tampons and pads.

The pill was, of course, celebrated as a huge breakthrough. "It was the first form of birth control separate from sex that women could completely control," notes Elizabeth Kissling, a professor of women and gender studies at Eastern Washington University. It is impossible to overstate the freedom the pill represented for women, whose reproductive lives were otherwise largely under male control. But liberation came with a price. By the late 1960s patients across the U.S. were reporting the same symptoms documented during the Puerto Rican trial. Despite many reformulations over the ensuing decades, side effects remain a problem for many women on the pill; risks for breast cancer, blood clots and stroke may also be higher. In their quest to bring reproductive freedom to women, Sanger, Pincus and Rock appear to have ignored the implications of shutting down a woman's natural cycle, Kissling explains. In other words, scientists figured out how to supplant periods long before they began

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trying to understand why they work the way they do.

It was not until the late 1980s that scientists really began to grapple with the larger question of why menstruation happens at all. As an undergraduate, evolutionary biologist Beverly I. Strassmann wrote a paper on how concealing ovulation could entice more paternal partners. (Because a woman's fertile window is more or less invisible, it encourages what researchers call pair-bonding: human males invest in fewer sexual relationships and protect and care for the resulting offspring as a way to ensure their paternity.) Strassmann, now a professor of anthropology at the University of Michigan, wanted to explore human attitudes toward menstruation by collecting data in a community where women spend five nights of their period sleeping in huts that are separate from the rest of the tribe.

In 1986 Strassmann moved to Mali to conduct field research on the Dogon, an ethnic group of millet farmers that hew to their traditions. Dogon people who continue to practice their indigenous religion believe that a menstruating woman's presence would desecrate the religious objects in the family compounds. Researchers had not previously considered that these religious beliefs were rooted in any kind of reproductive agenda. But, as Strassmann explains, she hypothesized that this was "a cultural pattern embedded in religion that did directly serve reproduction." Although research on modern indigenous communities can offer only clues about how humans lived thousands of years ago, Strassmann hoped to show that long-standing cultural taboos around menstruation had developed to support our larger evolutionary goals.

In their quest to bring reproductive freedom to women, scientists figured out how to supplant periods long before they tried to understand why they work the way they do.

During her initial fieldwork, Strassmann studied the community's use of menstrual huts for almost three years, collecting urine samples from 93 women to test hormone levels and prove that their use of the huts correlated with actual menstruation patterns. She also observed how quickly most of the women got pregnant again after their visits to the huts. Although the practice was ostensibly about keeping menstruation sequestered, the huts themselves were located in full view of a shade shelter used by men in the community. So the huts made a woman's fertility status clear to her husband and his family whether she liked it or not. (As noted earlier, women enter their "fertile window" after their period.)

Other religious practices around menstruation, such as the Orthodox Jewish purification ritual of sending menstruating women to mikvah baths, can also be traced to men's need to track female fertility and schedule sexual activity accordingly. And although the advent of the pill means that many women can now control their reproductive life in ways that render the purpose of such practices moot, the taboos still persist, Roberts says. "We still think of menstruation as something that women have to keep hidden and separate."

PERIOD EVOLUTION

ALTHOUGH STRASSMANN'S WORK was primarily about understanding the biological underpinnings of menstrual taboos, her data also revealed important characteristics about the process of menstruation itself. Perhaps her most oft-cited finding was published in 1997 in *Current Anthropology:* across human history, menstruation has been a rather infrequent event. That is because women tend to get pregnant earlier, have more babies and spend more time breastfeeding in communities where birth control is unavailable or difficult to access than they do in communities with high rates of birth-control usage. "We think of periods as happening 12 times a year, but if you're pregnant and then nursing for extended time frames, that's a stretch of two or three years for each child when you're not menstruating," Strassmann explains. Her data showed that in the 1980s the average Dogon woman menstruated only around 100 times in her life, compared with the average American woman's experience of as many as 400 periods in her lifetime. And Dogon women's experience is closer to what all women would have experienced throughout history before the development of the pill.

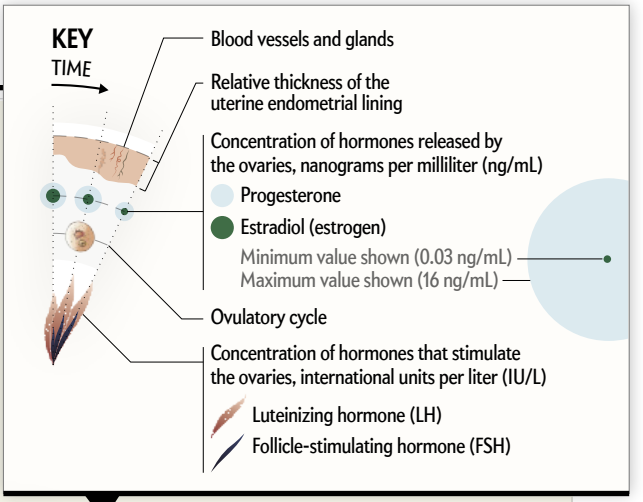
This historical infrequency of menstruation helps to explain why humans evolved to do something as potentially disadvantageous as releasing blood—losing iron, protein and other nutrients and probably attracting predators in the process. It could also help explain why periods and the week before their onset can be so unpleasant for many women. Michael Gillings, a professor of molecular evolution at Macquarie University in Australia, became interested in women's experiences of premenstrual symptoms (PMS) when premenstrual dysphoric disorder (PMDD) was added to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* in 2013.

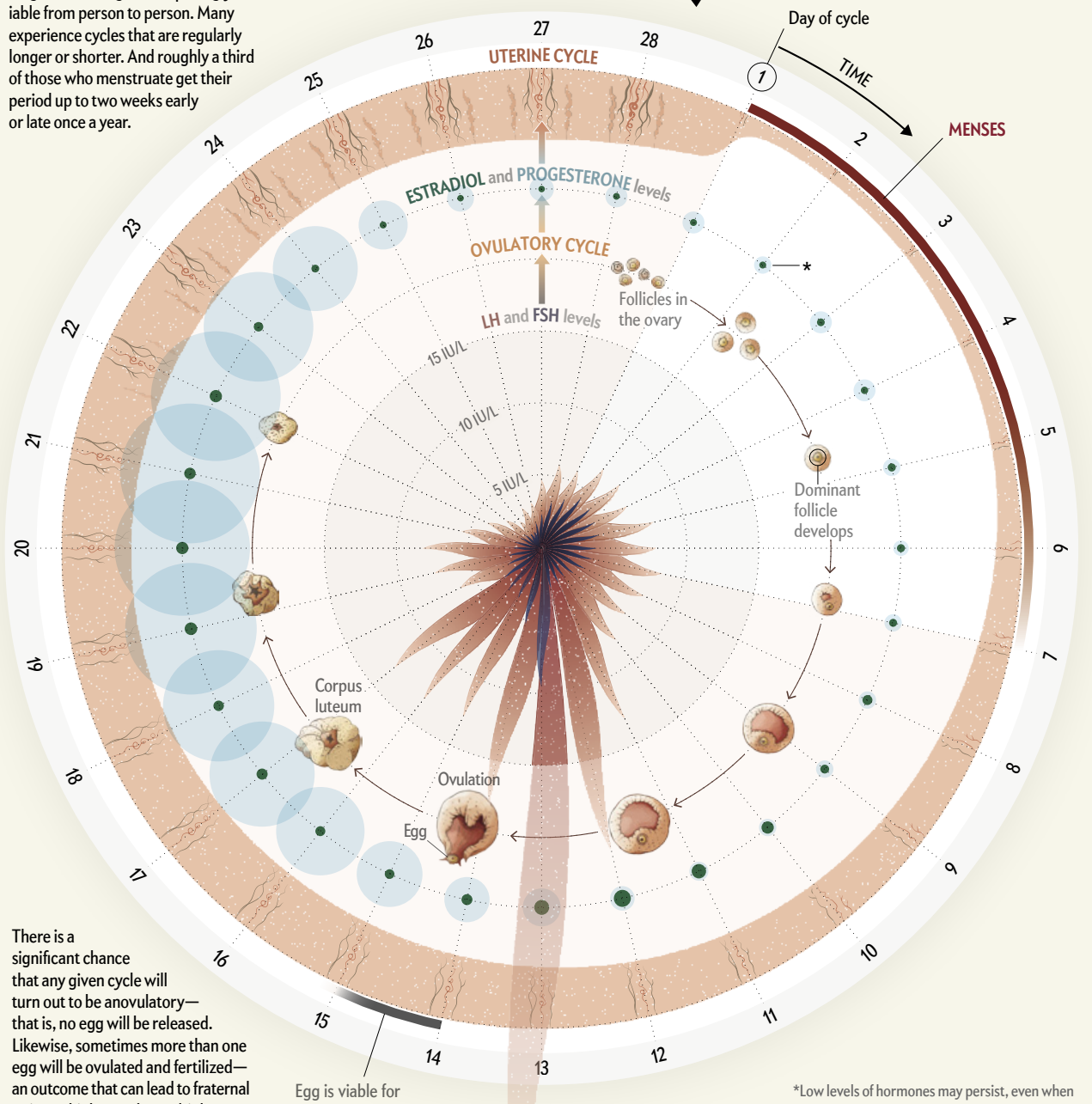
PMDD is defined as severe irritability, depression or anxiety in the week or two prior to menstruation, with symptoms easing two or three days after menstruation begins. But Gillings, along with many feminist scholars, balked at the characterization of mood swings as disordered. "Up to 80 percent of women re-

The Menstrual Cycle

Humans are among the very few species to experience a period. The menstrual cycle starts in the brain, which sends signals to the pituitary gland (*not shown*) to produce hormones that stimulate the ovaries. The ovaries house egg-containing follicles that release an egg during ovulation. The ovaries also secrete hormones to help prepare the uterus to host an embryo, which results if the egg is fertilized by a sperm. If no embryo implants, the uterus disposes of its lining, and the cycle begins again.

The average menstrual cycle is 28 days long, but the length is surprisingly variable from person to person. Many experience cycles that are regularly longer or shorter. And roughly a third of those who menstruate get their period up to two weeks early or late once a year.





There is a significant chance that any given cycle will turn out to be anovulatory—that is, no egg will be released. Likewise, sometimes more than one egg will be ovulated and fertilized—an outcome that can lead to fraternal twins or higher-order multiples.

SOURCE: "CIRCULATING IMMUNOREACTIVE INHIBIN LEVELS DURING THE NORMAL HUMAN MENSTRUAL CYCLE" BY R. I. McCLACHLAN ET AL., IN *JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM*, VOL. 65, NO. 5; NOVEMBER 1, 1987 (*hormone level data*); JERILYNN C. PRIOR *University of British Columbia, Center for Menstrual Cycle and Ovulation Research (consultant)*

Graphic by Federica Fragapane

Why Are Girls Getting Their Periods So Young?

Female puberty is starting earlier and earlier, with worrying consequences for women's health

Three weeks before her eighth birthday, Josie got her period at school. Magen, her mother, stopped at a drugstore for supplies before picking up her daughter. In the tampon aisle, she found a shelf of "tween" menstrual pads promising to "fit smaller bodies." She remembers thinking, "How does this even exist as a product?"

Magen was heartbroken that her seven-year-old was menstruating but not completely surprised. She had begun to notice her daughter's body odor when Josie was six. By the time Josie turned seven, she was getting blackheads on her nose, slamming doors and sleeping late. She developed breast buds the summer before second grade. "That was traumatizing for both of us," Magen says.

Magen showed Josie how to put a pad in her underwear and then called the pediatrician, expecting to be referred for some kind of hormonal testing. Instead, Magen recalls, "he said, 'Yes, this happens. She likely won't be regular for a while, but she's very clearly in puberty at eight years old.'"

Josie's mom found a shelf of "tween" menstrual pads promising to "fit smaller bodies." She remembers thinking, "How does this even exist as a product?"

The average age of menarche, or a girl's first period, in the U.S. is now 12, according to the most recent data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, down from 14 a century ago and as much as six months earlier than 20 or 30 years ago. But puberty does not start with menstruation. The onset of breast development, or thelarche, tends to come first, just as Josie experienced. "We're now seeing thelarche occur 18 months to two years earlier than we did a few decades ago," says Frank Biro, who studies problems related to pubertal maturation at Cincinnati Children's Hospital Medical Center. His research, published in 2013 in the journal *Pediatrics,* put the average age of breast development at 8.8 years old for African-American girls, 9.3 for Hispanic girls, 9.7 for Caucasians and 9.7 for Asian-Americans. "The age of breast development has clearly dropped, while the age of menarche has drifted down. They are both concerning," he says.

One popular misconception about menarche is that it represents the onset of ovulation; in fact, most girls do not begin ovulating regularly for up to two years after their first period, which is why early ones can be light and irregular. Menarche is instead triggered by changes in a girl's estrogen levels. The most probable explanation for why periods and breast development might be happening younger is that girls tend to weigh more today than they did a generation ago—and this higher body fat percentage is leading to earlier activation of the pituitary gland, which produces the hormones responsible for puberty.

In Biro's study, a higher body mass index (BMI) was the strongest predictor of early breast development across all racial groups, although the relation was correlative, not causal. "What we need to ask is, Why has BMI gone up?" he says. "Decreased physical activity and a more calorically dense diet are probably part of the puzzle. But I think another critical piece is our ubiquitous environmental exposure to endocrine-disrupting chemicals," or EDCs. This class of chemicals (including phthalates, bisphenol A and others) is used in many consumer products (shower curtains, plastic bottles, couch cushions) and has been shown to mimic estrogen and other naturally occurring hormones in the human body. Biro theorizes that some of these chemicals may promote weight gain or contribute to early puberty by influencing how cells and the body regulate metabolism, which then affects estrogen production. He is currently leading a study tracking the growth and development of 379 girls from age six onward that has been examining relations between their pubertal development and environmental exposures. Trauma could be another explanation: "Stress can also change your estrogen levels," Biro says.

To Magen, the more pressing question is not why Josie started puberty so early but rather what this means for her daughter's immediate and long-term health. The data Biro is collecting now show that girls who start puberty early tend to stay in the stage longer, meaning they spend more time in a "window of susceptibility"—a time when the human body is in a particularly critical stage of development, such that environmental exposures and other experiences are more likely to have an impact on their later health. When it comes to future risk of breast cancer, for example, fetal development and infancy are one window, and puberty is the other. "We know that for every year you delay menarche, you decrease the risk of premenopausal and postmenopausal breast cancer by 4 to 8 percent," Biro says. "On a population basis, that's really important."

Other researchers are looking at how early puberty affects girls socially and emotionally. "We know that early reproductive development is not matched by early cognitive development," says Marcia Herman-Giddens, an adjunct professor of maternal and child health at the University of North Carolina's Gillings School of Global Public Health. "So how do we teach children to manage sexual urges and other realities of puberty? And of course, these girls have to deal with sexual advances from older boys and even men long before they are ready to navigate that."

Magen is trying to figure out how to introduce these issues to Josie in an age-appropriate way without overburdening her already anxious daughter. "I've had to tell her, 'At some point, you're going to feel interested in relationships and sex, and when you are, you need to tell me right away,'" she says. "But am I really going to have to put a 12-year-old on birth control to make sure she's safe?" —*V.S.-S.*

port these symptoms; that makes PMS normal, not a psychological disorder," he says. "So we have to ask, Was there, at some point in history, an advantage to having these symptoms?" In 2014 he published a paper in the journal *Evolutionary Applications* arguing that PMS offered a selective advantage because it caused tension between pair-bonds and therefore might help women dissolve relationships with infertile men. "It is difficult to prove a hypothesis like this," he acknowledges. And the media response characterized him as insensitive to the suffering of women. "I was burned in effigy on five continents," he says. Some researchers counter Gillings's claim that PMS is a product of evolution—and contend that its roots are more cultural than biological because it manifests differently around the world. Roberts sees the concept mostly as one influenced by the menstrual taboo and a way to dismiss women's emotions.

Scientists are also divided over whether the act of bleeding itself serves an evolutionary purpose. "It's never made sense to me that we have this free-flowing blood, while other animals reabsorb it," Brown argues. Many evolutionary biologists now think that the essential feature of women's cycles is not the bleeding but rather the ability of the uterus to thicken its lining in preparation for implantation and then dispose of the endometrium when it is not needed. "A healthy endometrium requires constant metabolic support, so it is less energy-intensive for the female body to tear down and rebuild it each cycle than it is to maintain it in a constant state of readiness for embryo implantation," Strassmann explains. Human circulation happens to result in a particularly bloody endometrium. "Our physiology doesn't permit reabsorption, so much of the blood gets discharged as menstruation," she says. Bleeding may therefore be an insignificant byproduct of evolution rather than an advantage.

PHONE APPS, such as Clue (*shown*), help women to keep track of their monthly cycles.

A WORLD WITHOUT PERIODS?

IF THE ACT OF SHEDDING menstrual blood poses no clear health benefit or evolutionary advantage and if, historically, women have not even done it all that often, then why, in this postpill era, do women continue to do it all? The answer: some do not. In January the Royal College of Obstetricians and Gynecologists in London released new guidelines that approved skipping the placebo pills in birth control to reduce the frequency of periods or avoid them altogether.

Although this formal acknowledgment is new, the practice is not. Medical menstrual suppression has long been embraced by clinicians, the media and women frustrated by the pain, mood swings or inconvenience of their menstrual cycle. The pharmaceutical industry also took notice: as the researcher who first measured and quantified the frequency of human menstruation, Strassmann has been asked to present her data to drug manufacturers, who have offered several versions of the pill and other forms of contraception that are formulated to let women skip their periods more often, if not avoid them altogether.

Skipping that monthly ordeal can mean avoiding debilitating pain, prolonged heavy bleeding, migraines and other symptoms that can dramatically impair a woman's quality of life. The approximately 25 percent of reproductive-age women and girls who struggle with additional kinds of severe menstrual pain may be at increased risk for developing other chronic pain conditions. "We suspect the cyclical experience of monthly menstrual pain somehow alters how some women process all kinds of pain," explains Laura Payne, who directs pain research for a pediatric program at the David Geffen School of Medicine at the University of California, Los Angeles.

To many doctors faced with patients whose periods cause problems, "the pill is the closest thing we have to a panacea in women's health," says Jonathan Schaffir, an associate professor of obstetrics and gynecology at the Ohio State University. But is it? "The pill isn't a treatment for these conditions," Kissling says. "It's a way of refusing to treat them." It can take up to a decade or longer from disease onset for a woman to be diagnosed with endometriosis, for example, in part because doctors are so quick to prescribe the drug to teenagers reporting bad cramps without investigating to see if there is an underlying cause, says endocrinologist Jerilynn Prior of the University of British Columbia. And where one version of the pill may succeed in masking a woman's symptoms, another may exacerbate them. "You can spend years jumping from one

pill to another, not finding relief," notes Kissling, who published a paper on how women end up "treating each other," for better or worse, in online forums, where they share alternative medicine remedies and other tips out of frustration with their doctors' limited repertoire.

Strassmann and many others are skeptical about the health effects of medically induced menstrual suppression, which may expose women to hormone levels higher than what they would have experienced in the evolutionary past or even now, when regularly cycling on the pill. "It's true a monthly menstrual period is not necessary," she says. "But taking more progestin to skip your period is not living like our ancestors did 500 or 1,000 years ago." Research shows taking the pill reduces the risk for endometrial and ovarian cancers but slightly raises the risk for breast cancer, stroke and blood clots.

In 2017 Strassmann and her colleagues published a paper in *Evolution, Medicine, & Public Health* tracking how exposure to synthetic hormones varied depending on the type of birth-control pills used. "We know that American women experience more periods than the Dogon because they start menstruating earlier and have fewer children, and we know that having more periods is associated with a higher breast cancer risk," she explains, noting that the relation is likely because of the additional hormone exposures accrued from those extra periods. "But we don't really know how that risk squares with the hormone exposure women are also getting from long-term use of birth-control pills." After analyzing data from 12 studies, as well as the information on birth-control package inserts, Strassmann's team concluded that some types of the pill exposed women to a quadruple dose of progestin (a synthetic form of progesterone contained in the pill), relative to the progesterone their naturally cycling body would produce.

Nobody knows for sure what that exposure to synthetic hormones will mean long term for women using the pill to suppress their cycles indefinitely. This knowledge gap speaks to broader concerns about our ignorance around menstruation. If Rock and Pincus had begun their work with a deeper understanding of menstruation's evolution and purpose, how might that have affected the pill's development? Would women today have more—and more targeted—options to manage their menstrual pain and associated disorders?

In this latest iteration of our menstrual taboo, dispatching with the period instead of researching its complexity might have unforeseen health consequences, Prior says. "Our data on the pill come from generations of women who followed the schedule for 28-day cycles and didn't stay on it for nearly as long as women do today," Kissling says. "What we have now" with women using birth control for long-term suppression "is the largest uncontrolled medical experiment on women in history." SA

FUTURE OF MEDICINE 2019

SET IT AND FORGET IT?

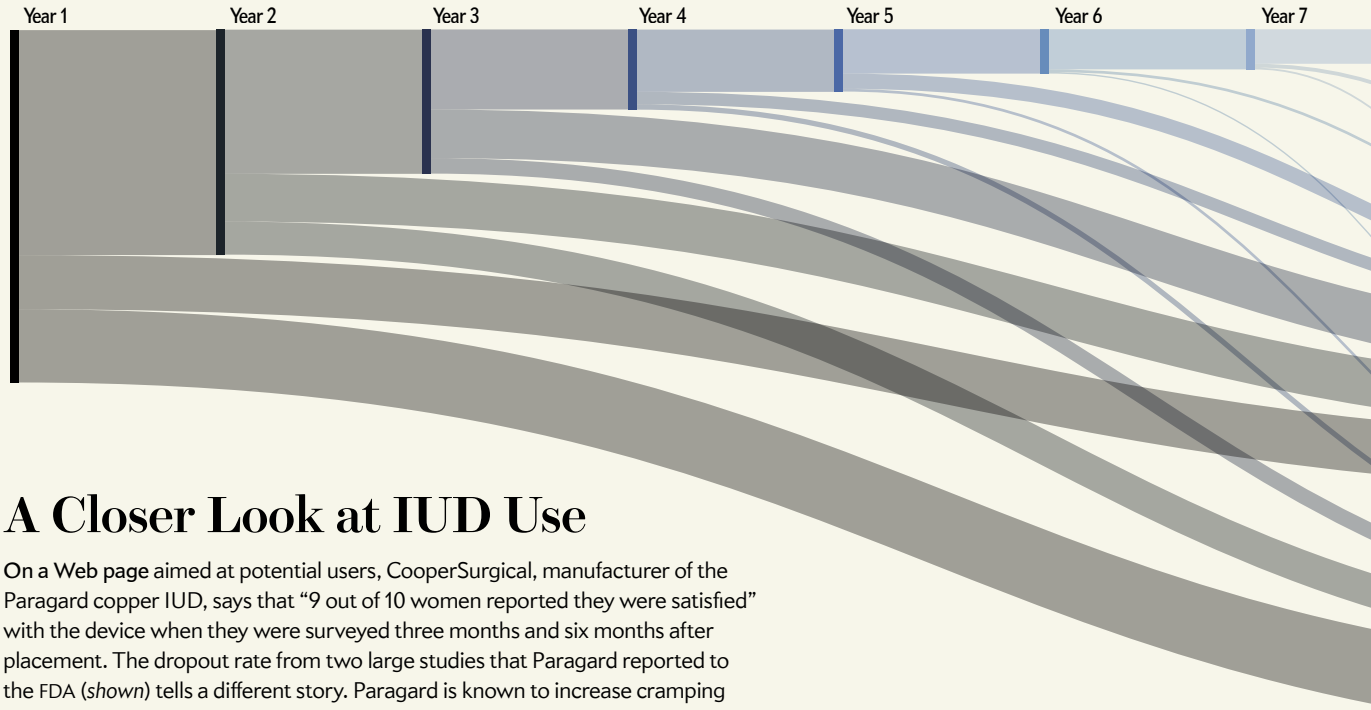
The IUD is held up as the gold standard of birth control. That says a lot about the slothful pace of innovation

By Maya Dusenbery

EVEN BEFORE THE RESULTS of the 2016 presidential election were official, women on social media began offering a tip for surviving the next four years: get an IUD tomorrow.

Small, plastic T-shaped devices loaded with synthetic hormones or wrapped with copper coil, IUDs—or intrauterine devices—are inserted into the uterus to offer pregnancy prevention for years. Along with less frequently used hormonal implants that go in the arm, they are known in the reproductive health field as

Photographs by Jamie Chung



A Closer Look at IUD Use

On a Web page aimed at potential users, CooperSurgical, manufacturer of the Paragard copper IUD, says that "9 out of 10 women reported they were satisfied" with the device when they were surveyed three months and six months after placement. The dropout rate from two large studies that Paragard reported to the FDA (*shown*) tells a different story. Paragard is known to increase cramping and bleeding in many users; a few months may be too short to judge the effects of a device that women live with for years. A 2017 retrospective study of "real world" IUD discontinuation rates found the number to be even higher.

long-acting reversible contraception, or LARC. And with a new leader who pledged to repeal the Affordable Care Act, along with its mandate to cover contraception with no co-pays, many women figured they should seize the chance to secure long-lasting birth control while they still could.

Plenty heeded this advice. Shortly after the election, the president of Planned Parenthood said the organization had seen a "900 percent increase" in IUD-insertion appointments at its clinics nationwide. In March a study published in *JAMA Internal Medicine* confirmed that the number of women receiving LARC rose by 21.6 percent in the month after Donald Trump won the presidency.

While this so-called Trump bump was significant, the comeback of IUDs began several years earlier. In 2002 just 2 percent of U.S. women using contraception chose them. In 2014 that number rose to 11.8 percent, an all-time high that matches the average prevalence among other developed nations. For decades IUDs had a bad image after the Dalkon Shield, a poorly designed device from the 1970s, caused infections, infertility and even death in tens of thousands of women. Today's models are much safer, and younger women don't have the same negative associations with IUDs as prior generations. Before 2010 the high up-front cost of such a device—up to several hundred dollars—was often a non-starter. But under the still intact Affordable Care Act, insertion is free with private health insurance.

IUDs have also benefited from a concerted advocacy effort to eliminate barriers to their use. A Colorado outreach initiative to provide low-income women with no-cost IUDs and implants, which was launched in 2009, led to significant declines in the state's teen birth and abortion rates and drew national attention. Since 2014 a nonprofit called Upstream has offered training and technical assistance to health centers to increase same-day access to all forms of birth control, particularly LARC. Upstream currently partners with state governments in Delaware, Massachusetts, Washington State and North Carolina. Under the program, use of IUDs and implants among low-income women in Delaware more than doubled in three years. Forty states have now changed their Medicaid policies to reimburse hospitals for inserting IUDs in the delivery room immediately postpartum.

The rising popularity of the IUD represents the largest shift in American contraceptive trends in recent decades. Researchers at the Guttmacher Institute say it has contributed to an 18 percent decrease in the unintended pregnancy rate between 2008 and 2011: a "historic" low after a long period of stagnation. Both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics

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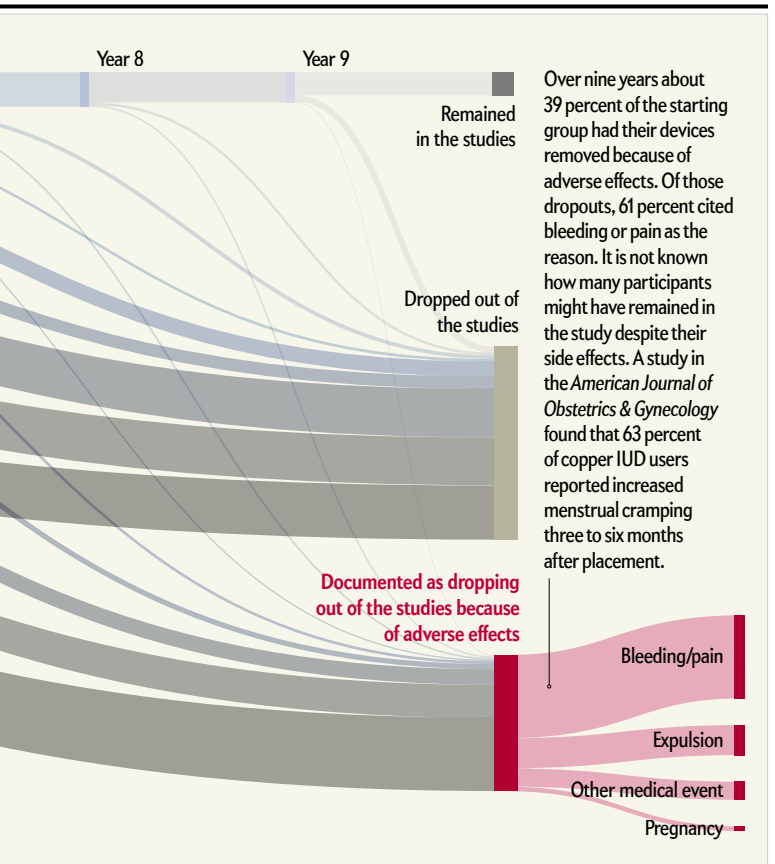
SOURCE: PARAGARD® T380A INTRAUTERINE COPPER CONTRACEPTIVE. PRESCRIBING INFORMATION. TEVA WOMEN'S HEALTH. SUBMITTED TO FOOD AND DRUG ADMINISTRATION ON JUNE 11, 2013

Graphic by Amanda Montañez



now recommend IUDs as a top birth-control option for all women, including adolescents.

It's easy to see why IUDs are so appealing: less than 1 percent of users will get pregnant in a year, making the devices just as effective as sterilization, and they last between three and 12 years. What gives IUDs the most compelling edge over other methods is that they are practically immune to human error. Once inserted, you don't have to do anything else—interrupt sex to put on a condom or remember to take a pill at the same time every day—to get reliable pregnancy prevention. It is this feature in particular that has led to a common refrain in the reproductive health field: "Set it and forget it," an Upstream trainer recently told the *New York Times,* borrowing the advertising tagline of a rotisserie chicken oven to describe the IUD.

On the surface, this highly effective, long-acting, difficult-to-mess-up form of birth control seems to be well liked. ACOG's guidelines point out that IUDs have the highest continuation rates and user satisfaction of all reversible birth-control methods. Diana Blithe, program director for contraception development at the National Institutes of Health's National Institute of Child Health and Human Development (NICHD), says the introduction of the first hormonal IUD in 2000, in particular, "has been a bit of a game changer in that women like it." Three fourths of IUD users in the U.S. choose a hormonal IUD (as opposed to the nonhormonal copper IUD), which tends to make menstrual periods lighter or disappear altogether. "It's really effective and popular—it's all good," Blithe says.

There are plenty of self-described IUD evangelists. But that's not the whole picture. Although IUDs do work well for many women, a significant number experience side effects and sometimes debilitating ones. As medical devices, IUDs have drawbacks that other contraceptive methods do not. Without easy access to a health care provider—and one who takes a patient's symptoms seriously—"set it and forget it" can start to sound less like convenience and more like coercion.

The IUD cheerleading obscures a broader illusion of choice. Nearly 60 years after the first oral contraceptive pill was sold, most prescription birth-control methods are variations on the same synthetic hormones that have always been used. The first IUDs date back even further, to a time when inert devices made of silkworm gut or metal stopped pregnancy by creating sustained inflammation. At a time when lawmakers are constantly threatening to roll back access to all aspects of reproductive health care, it can feel risky to criticize birth-control methods. After all, ultraconservative foes of birth control tend to manipulate concerns about side effects and risks into a reason women should forgo contraception entirely. But in 2019 it is worth asking: Why don't we have more innovative birth-control options? When it comes to preventing pregnancy, is a device that works in part by irritating the uterus really the best science can provide?

MEASURING DISSATISFACTION

MUCH OF THE RECENT ENTHUSIASM over IUDs can be traced back to a single study called the Contraceptive CHOICE research project. Funded in part by a then anonymous donor now known to be the Susan Thompson Buffett Foundation and facilitated by Washington University in St. Louis, the project had the explicit goal of increasing the use of LARC among women at high risk of unintended pregnancy.

Between 2007 and 2011 a cohort of 9,256 women and adolescent girls were offered their choice of a contraceptive method free of charge. Participants received "tiered contraceptive counseling," in which they were presented with the risks and benefits of each method in order of most effective to least effective, meaning that they heard about IUDs and implants first. Three quarters of the participants chose to use those LARC

methods, and those who did were 20 times less likely to have an unintended pregnancy than those who chose other prescription methods such as the pill.

In addition to this dramatic effect on unintended pregnancy rates, the reproductive health field was excited by the discontinuation rates found in the CHOICE study. The number of women who had their IUD or implant removed early was much lower, relative to the study participants who had abandoned their non-LARC methods. Remarkably, 69 percent of the women who had chosen oral contraceptives, injection, the vaginal ring or the skin patch had given up on them after three years—more than twice the dropout rate of the IUD users. As such, the IUD was held up as the form of birth control that users liked the most.

But what is often underdiscussed are the IUD discontinuation rates themselves. After one year nearly 20 percent of copper IUD users and about 14 percent of hormonal IUD users reported they were "not satisfied" with the device; 12.5 and 16 percent, respectively, had had it removed. Around the five-year mark, 44.1 percent of copper IUD—and 48.3 percent of hormonal IUD—users had discontinued the device. About two thirds of those who had done so by the end reported that the reason was because of pain, bleeding changes or other side effects or because the foreign object had been expelled from their body. In other words, the IUD dropout rate linked to side effects looks low largely in the context of other methods.

The CHOICE findings, which have been reported in nearly 70 published papers and more than 500 media outlets, helped to spur a shift in the field from "options-based" contraceptive counseling, in which a range of methods are presented, to the "LARC-first" counseling used in the CHOICE study. Even the ACOG guidelines cite the CHOICE study as evidence of the "superiority of LARC methods over short-acting methods." Manufacturer brochures for IUDs, such as from CooperSurgical, manufacturer of Paragard, also use CHOICE data to promote their devices to women.

Other studies have reported markedly higher discontinuation rates. In the original Food and Drug Administration clinical trials, the five-year rates for the copper Paragard and hormonal Mirena were 60 percent and 55 percent, respectively. Then, in 2017, a retrospective study at Harvard Medical School of more than 1,000 American women found that at five years, 71.9 and 76.2 percent, respectively, had removed their device. The researchers suggested that these results might better reflect "real-world" rates in the clinical setting, "outside of the structured setting of a randomized controlled trial," or the CHOICE study, which was trying to increase uptake of LARC and offered subjects "extensive counseling."

That IUDs are comparatively well liked might say less about how popular they are and more about how dissatisfied women are with birth control in general. Perhaps the IUD is just the least onerous option out of an unimpressive field. According to an analysis of data from the 2006–2010 National Survey of Family Growth, women in the U.S. have tried a median of three contraceptive methods. Whereas many women eventually find one that works well for them—often after years of trial and error—some simply settle on one out of sheer frustration: nearly two fifths of women surveyed in 2004 by the Guttmacher Institute said they chose their current method mostly because they didn't like any other available options.

It is hard to know what self-reported "satisfaction" is even measuring when it comes to contraception. "Many women tolerate negative side effects because their sense of the risk of pregnancy is higher or their anticipation of the consequence of a pregnancy is worse," says Diana Greene Foster, director of research at Advancing New Standards in Reproductive Health (ANSIRH) at the University of California, San Francisco. Nearly 40 percent of women in the Guttmacher survey said they were not satisfied with the method they were currently using. And that makes them less likely to use it consistently. For example, 48 percent of dissatisfied oral contraceptive users skipped at least one pill in the past three months as compared with 35 percent of satisfied users.

Just how far we are from having a variety of options that truly meet women's needs becomes clear when you ask them what they actually *want* in a contraception method, which Foster and her colleagues did in a 2012 study. The three features deemed "extremely important" by the largest proportions of women were effectiveness (84 percent), lack of side effects (78 percent) and affordability (76 percent). Then they determined how many of the currently available methods met the women's criteria and found that "for 91 percent of women, no contraceptive method has all the features they think are extremely important." Perhaps unsurprisingly, what women really want is a highly effective method with few or no side effects. And as the researchers explain in the study, "that combination does not exist."

The IUD discontinuation rates seem more notable after considering how much harder it is to stop using a device that is lodged in your uterus than it is to stop taking a pill. The process of removing an IUD is often no more complicated than pulling on the exposed strings, and some researchers have begun to explore how to make self-removal more feasible. But for now IUD extraction requires an appointment with a health care provider—an appointment that some women struggle to access or afford. Even then, several qualitative studies have found that many women who want to stop using their IUD because of side effects face resistance from their doctor.

In a pair of recent studies, Jennifer R. Amico, an assistant professor at Rutgers Robert Wood Johnson Medical School, and her colleagues interviewed providers and women seeking "early" IUD removal—within nine months of insertion—at two clinics in New York City. Many of the women said their providers minimized their side effects and were reluctant to grant their request for removal. The providers, many

BARRIERS don't have side effects, but hormones are more effective. This variety of choice is really a study in trade-offs.

of whom admitted they had negative feelings about early removals, said they usually encouraged patients to stick with the device for at least three to six months.

The belief that side effects will improve for most IUD users after an "adjustment period" is widely held by providers. But most studies claiming to show such a decline in side effects over time have not accounted for the dropping out of dissatisfied users. In other words, it could be an illusion produced by the fact that those who do continue to have side effects eventually remove the device, leaving only satisfied users at the end. In a 2009 prospective analysis of copper IUD users that sought to correct this bias in prior studies, researchers found that while some problems improved, others did not; women reported that the number of days they experienced spotting and pain between periods actually became *more* frequent over time.

"There is a long, terrible history of discounting what women report as contraceptive side effects," Foster says. In the 1950s, when the first large human trials of the original birth-control pill—which contained astronomical levels of hormones by today's standards—were conducted on Puerto Rican women, their complaints of severe side effects were brushed off as hypochondria. Today, Foster says, "there is a belief that if a clinician tells a woman about side effects, that she is more likely to experience them." Indeed, a number of published articles in recent years claim that "nonspecific" side effects to oral contraceptives are the result of the "nocebo" effect—a negative placebo effect—and so providers should offer "optimistic" counseling that downplays their likelihood.

THE ILLUSION OF CHOICE

THE "LARC-FIRST" MOVEMENT is based on the assumption that effectiveness should be the only factor to consider in a contraceptive method. "Folks will often say, 'I wouldn't give you a statin that is 91 percent effective versus one that is 99 percent, so why would I give a contraceptive that has that difference in efficacy?'" says Anu Manchikanti Gomez, director of the University of California, Berkeley's Sexual Health and Reproductive Equity Program. But there are many factors—from side effects to health risks to control over starting and stopping the method—that women weigh when choosing among imperfect options.

Gomez, who co-authored a critique of the LARC zeal in a 2014 article entitled "Women or LARC First?" now says that the reproductive health field has begun to see a "pendulum shift toward a patient-centered approach and recognition that what health care providers and policy makers consider to be the 'best method' is often misaligned with what women want." In 2016 the advocacy groups National Women's Health Network and SisterSong released a statement of principles for IUDs and implants that rejected "efforts to di-

rect women toward any particular method" while supporting greater access to LARC devices. It also emphasized the right of all women to opt against LARC or discontinue using one without judgment from their provider. More than 250 advocates and organizations, including ACOG, have signed on to it.

The reality is that most women who are shopping for birth control likely won't choose these devices anyway. In a 2015 study, Foster and her team surveyed about 100 experts who had published research on LARC and asked them to estimate how many women would use it if all the current barriers were eliminated. The median estimate was 25 percent. "The idea that LARCs are going to solve all our problems is problematic on a lot of fronts," Foster says. "It's also just not realistic." The solution to better birth control, she adds, lies in soliciting and respecting women's preferences when it comes to contraception and then using science to develop methods that meet their needs.

That is certainly not the approach we have taken so far. Although investment in research and development by pharmaceutical companies in the 1990s and 2000s yielded new products, such as the patch, ring and hormonal IUD, it has cooled in the past decade. These days "they think that there are enough products for female contraception," says Régine Sitruk-Ware, a scientist at the Population Council's Center for Biomedical Research.

That IUDs are comparatively well liked might say less about how popular they are and more about how dissatisfied women are with birth control in general.

Anyway, recent contraception advances have largely been tweaks to the formulations or modes of delivery of the same basic synthetic hormones that have always been used. And projects in the pipeline are similarly focused on making existing contraceptives easier or safer. For example, a self-administered injectable, recently approved in other countries, could hit the market in the U.S. A "pericoital" pill, similar to emergency contraception, that needs to be taken only when someone has sex is under development. So is a ring that uses natural estradiol—bioidentical to the estrogen in the human body—instead of a synthetic estrogen, which may be a safer option for women put at an increased risk of blood clots by many existing hormonal contraceptives.

Experts say the focus has been on improving existing hormonal methods largely because they are well understood at this point. Efforts to develop brand-new ones will face a long and expensive path to reach the market. But all the scientific progress since the pill was developed could yield much more imaginative strategies.

TOWARD INNOVATIVE BIRTH CONTROL

RECENT ADVANCES in genomics have identified many proteins, enzymes and genes involved in the reproductive process that could be targeted to prevent pregnancy in both women and men—and potentially do so in more precise ways. Sitruk-Ware says her group is exploring a molecule that, by acting on a particular protein, would prevent sperm from maturing, making them unable to fertilize an egg. Another research team has been testing a compound in nonhuman primates that binds to different protein and turns off sperm's ability to swim. "There may be as many as 1,000 possible targets," Blithe says, including some "very exciting possibilities" when it comes to inhibiting ovulation that are at the basic research stage.

None of these compounds has made it through preclinical toxicology studies to get into a human trial yet. "We are expecting that they would be safer because we are targeting and blocking only one specific protein, and there will be no other action on any other cells in the human body," Sitruk-Ware says. "But it's unknown—any molecule may bring other effects."

Genomic approaches could someday bring a precision medicine approach to prescribing contraception as well. Genetic variations may explain why the side effects of contraceptive methods vary widely among individuals—and genetic testing might help predict which method is best for a particular woman. For example, although such testing is not available in routine practice, doctors already have the ability to test for specific mutations that put women at higher risk of blood clots on estrogen-based contraceptives. And genetic variations may explain why no birth control is 100 percent foolproof. A study published online in March in *Obstetrics & Gynecology* found that about 5 percent of women possess a genetic mutation that makes them more likely to produce an extra hormone-dismantling enzyme that makes birth control less effective. Previously, women who got pregnant on the pill were blamed for not using it correctly.

Technological advances are also bringing more precision to one of the oldest contraceptive methods: fertility awareness. A couple can only fertilize an egg up to about five days before and two days after ovulation because of the combined viability of sperm and egg in the female body. So the goal of fertility awareness–based methods, or FABMs, is to predict—and then confirm—when ovulation occurs. Many FABMs do so by tracking physical signs of hormonal shifts, including changes in cervical fluid and a spike in basal body temperature. When done right, some are 95 to 99 percent effective.

FABMs are one of the only contraceptive methods besides LARC whose popularity is on the rise. An estimated 3.2 percent of women using contraception use a FABM today, a figure that doubled between 2008 and 2014. The interest is likely being driven in part by the variety of fertility- and period-tracking apps now available. Some just provide a digital platform to chart one's cycle, whereas others utilize predictive algorithms. "There's machine learning going on in the app that helps it adapt to the woman's cycle," explains Victoria Jennings, director of the Institute for Reproductive Health at Georgetown University Medical Center.

Jennings doubts the new algorithm-based apps are *more* effective than old-school FABMs that require a woman to chart her cycle with paper and pencil, but "they're so much easier to use that, in my opinion, people may be more likely to use them correctly." So far few apps have undergone rigorous efficacy testing. She and her colleagues recently completed a first-of-its-kind prospective study of one such app called Dot. The results, published online in March in the *European Journal of Contraception and Reproductive Healthcare,* found a perfect-use failure rate of 1 percent and a typical-use failure rate of 5 percent.

Even with an app, FABMs are as far from "set it and forget it" as you can get. Because a woman's cycle is affected by factors such as stress, lack of sleep and illness, algorithms cannot confidently predict the exact day of ovulation for each cycle based on historical patterns alone. That is where scientific advances could help. Current at-home urine tests can anticipate ovulation by a couple of days at most. But that won't cut it if a couple is trying to avoid pregnancy instead of achieve it. "I would love to see some kind of a hormonal test that could accurately predict ovulation far enough in advance for people to be able to rely on it for pregnancy prevention at a cost that they could afford," Jennings says. That would achieve the same goal as FABMs at a fraction of the effort.

Of course, one way to relieve some of the burden on women to prevent pregnancy is to share it with their male partners. Hormonal birth control for men is much further along in development than nonhormonal approaches for either sex. "We have a lot of small studies that demonstrate it works and in a similar way to female methods," Blithe says. Late last year the second phase of a clinical trial of 420 couples to test the safety and efficacy of a male contraceptive gel, developed by the Population Council and NICHD, got underway. But the oft-repeated joke in the field is that male contraception has been 10 years away for 30 years. "I'm not promising anything in the next five years for men," Blithe says.

Among the barriers to developing a male contraceptive has been that the regulatory pathway is uncertain. When the FDA evaluates the safety of a female contraceptive method, any health risks are compared with the risks the woman could experience from pregnancy to calculate the risk-benefit ratio. But in the case of a male contraceptive, "the FDA is going to have a very high bar, I'm sure, when it comes to getting approval for a drug that will be taken by the person who is not at risk of pregnancy," Blithe says. The pharmaceutical industry has also yet to be convinced there is a big market. A 2005 survey of men in nine countries found that 55 percent would be willing to use a male hormonal contraceptive. (Their current options are only condoms and vasectomy.) More recent market research by the Male Contraceptive Initiative found almost four in 10 men in the U.S. would be interested, but they also reported "little tolerance for side effects," especially depression, reduced libido or acne.

Researchers acknowledge that a male contraceptive may need to meet a higher standard than its female counterparts. To many women, the benefit of pregnancy prevention is great enough that they're willing to put up with nausea, mood swings or heavier periods as the trade-off. "But men? Not necessarily," says Sitruk-Ware, who co-founded the International Consortium of Male Contraception. "If they make this effort of taking the burden of the couple's contraceptive method, they would expect that there are absolutely no side effects."

Female contraceptives should have to clear that high bar, too. Birth control, in general, presents a more complicated risk-benefit analysis than other medications. In exchange for treatment for a life-threatening illness, people may accept considerable side effects and health risks. But "contraceptives are not designed to treat a disease, and the users are typically young and healthy," Sitruk-Ware says. "Zero side effects should be the rule."

This push for contraceptive innovation is not universally evident. Many investors believe that to reduce unintended pregnancies, we simply need to ensure that women have access to existing methods. But dissatisfaction is also a reason people use contraception inconsistently or forgo it entirely. Safeguarding and expanding access, though vital, need not crowd out the pursuit of better birth control—a truly diverse range of options that meet the differing needs of both women and men at various stages in their reproductive lives. "Adolescents may not want the same method as a woman who is spacing her pregnancies or a woman who has completed her family," Sitruk-Ware says. Likewise, whereas many women in a committed relationship may consider a male contraceptive a welcome relief, for others, maintaining control themselves over the use of the method is paramount.

It is hoped that researchers—and funders—will develop targeted ways of preventing pregnancy, along with the ability to more precisely match formulations to individuals' unique physiology. For now a more personalized approach is critical to help women choose among the current lineup of choices, which force too many of us to trade well-being for effectiveness. Finding a contraceptive method that best fits someone's body, way of life and priorities is a complex task—and shouldn't be compared to setting a chicken in an oven and walking away. SA

FUTURE OF MEDICINE 2019

How to Reduce Maternal Mortality

To prevent women from dying in childbirth, the first step is to stop blaming them

TEXT BY MONICA R. McLEMORE, GRAPHICS BY VALENTINA D'EFILIPPO

Monica R. McLemore is an assistant professor in the family health care nursing department and a clinician-scientist at Advancing New Standards in Reproductive Health at the University of California, San Francisco. She maintains a clinical practice at Zuckerberg San Francisco General.

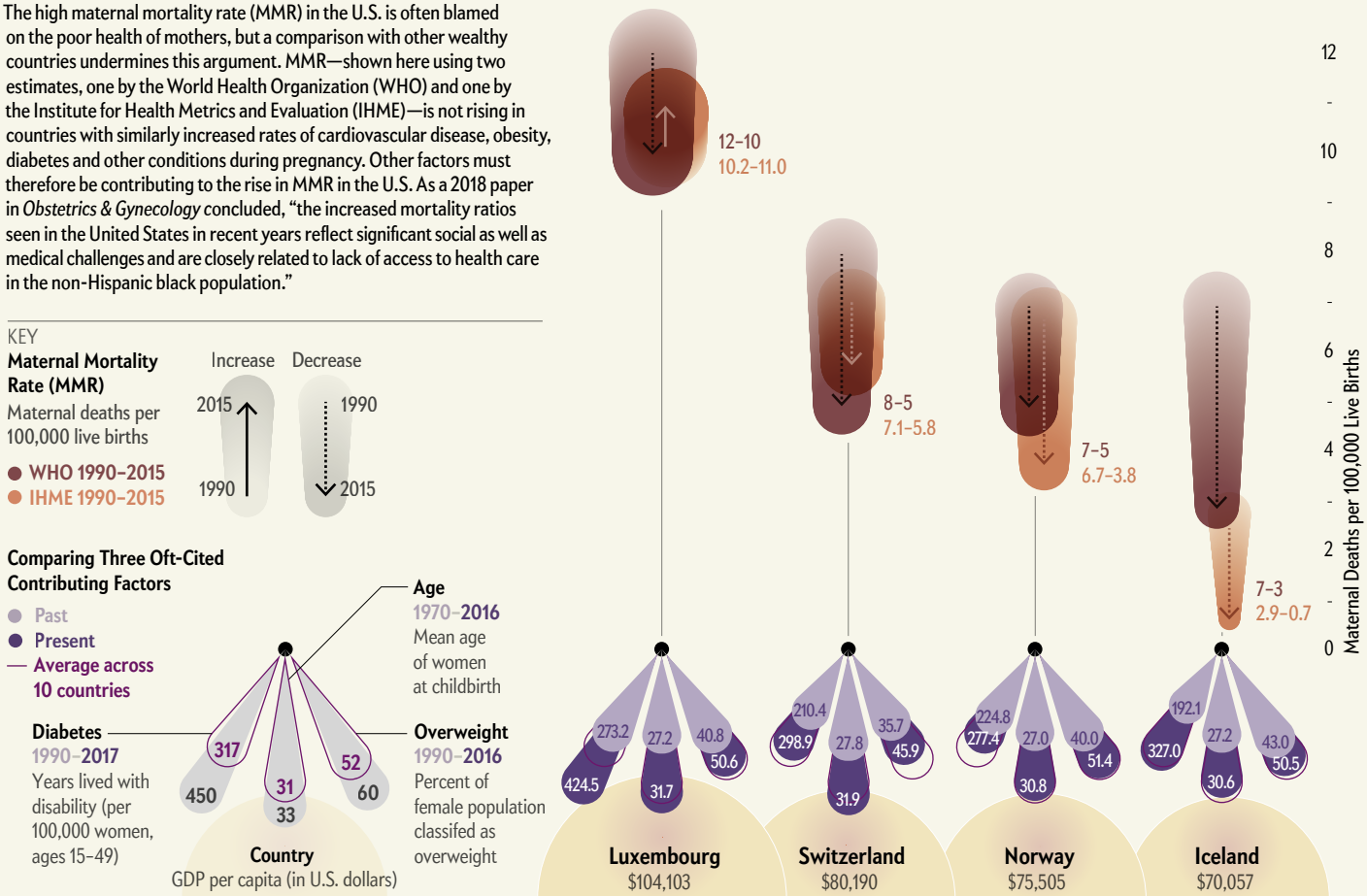
The shameful secret is out: Although the number of women who die in childbirth globally has fallen in recent decades, the rates in the U.S. have gone up. Since 1987 maternal mortality has doubled in the U.S. Now approximately 800 maternal deaths occur every year. One of the most striking takeaways from examining the data is racial disparity: Black women are three to four times more likely to die from pregnancy-related conditions such as cardiac issues and hemorrhage and to bear the brunt of serious complications as well. That risk is equally shared by all black women regardless of income, education or geographical location. In other words, the factors that typically protect people during pregnancy are not protective for black women.

Fortunately, most of these deaths are considered preventable, and therefore, much more can be done to stop them. First, everyone—from doctors to the media to the public—needs to stop blaming women for their own deaths. Instead we should focus on better understanding the underlying contributing factors. These include a lack of data; not educating patients about signs and symptoms—and not believing them when they speak up; errors made by health care providers; and poor communication among different health care teams. Finally, studies have shown that interventions such as wider access to midwifery, group prenatal care, and social and doula support are effective in improving maternal health outcomes.

Progress has been slow and uneven. Deaths from hemorrhage, for example, have been reduced by half in some states because of standardized tool kits for care. And California has led in the pursuit of understanding root causes of maternal mortality. Still, structural racism is proving to be an intractable force.

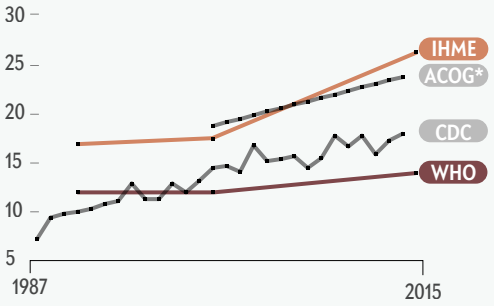
The U.S. Is an Outlier

The high maternal mortality rate (MMR) in the U.S. is often blamed on the poor health of mothers, but a comparison with other wealthy countries undermines this argument. MMR—shown here using two estimates, one by the World Health Organization (WHO) and one by the Institute for Health Metrics and Evaluation (IHME)—is not rising in countries with similarly increased rates of cardiovascular disease, obesity, diabetes and other conditions during pregnancy. Other factors must therefore be contributing to the rise in MMR in the U.S. As a 2018 paper in *Obstetrics & Gynecology* concluded, "the increased mortality ratios seen in the United States in recent years reflect significant social as well as medical challenges and are closely related to lack of access to health care in the non-Hispanic black population."



U.S. Maternal Mortality Rate Estimates

According to different organizations



Inconsistent Data Collection across the States

Pregnancy question included in state death certificate (status in 2014)

										ME	
AK					WI				VT	NH	
WA	ID	MT	**ND**	**MN**	**IL**	MI		**NY**	MA		
OR	NV	WY	SD	**IA**	**IN**	OH	PA	**NJ**	CT	RI	
CA	UT	CO	**NE**	**MO**	**KY**	WV	**VA**	**MD**	DE		
	AZ	**NM**	KS	AR	TN	NC	SC	DC			
			OK	**LA**	**MS**	**AL**	GA				
HI			**TX**					**FL**			

Maternal Mortality Data in the U.S. Is an Unreliable Mess

As bad as the numbers sound, the U.S. MMR is widely considered to be an underestimate. That is because different methods are used to count deaths related to pregnancy, and reporting is inconsistent. The World Health Organization, for instance, defines maternal deaths as the death of a woman while pregnant or within 42 days of the end of a pregnancy. But the Centers for Disease Control and Prevention defines maternal mortality as "the death of a woman while pregnant or within one year of the end of a pregnancy." Both these definitions exclude accidental or incidental causes of death. The difference in time frame for maternal mortality is further complicated at the state level, where data collection from death certificates is not comparable because of different definitions of the cause and time of death. States could fix this problem by creating standardized maternal mortality review committees, which comprehensively evaluate each maternal death and discuss the factors that contributed to the outcome.

*As published in *Obstetrics & Gynecology*, a publication of the American College of Obstetricians and Gynecologists (ACOG).

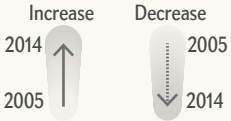
SOURCES: GLOBAL HEALTH OBSERVATORY DATA REPOSITORY, WORLD HEALTH ORGANIZATION (*WHO MMR data*); MATERNAL MORTALITY 1990–2015 TABLES IN *GLOBAL BURDEN OF DISEASE STUDY 2015*. GLOBAL BURDEN OF DISEASE COLLABORATIVE NETWORK. INSTITUTE FOR HEALTH METRICS AND EVALUATION, 2016 (*IHME MMR data*); IHME (*diabetes*); ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (*age*); WHO (*weight*); WORLD BANK (*GDP*); "RECENT INCREASES IN THE U.S. MATERNAL MORTALITY RATE: DISENTANGLING TRENDS FROM MEASUREMENT ISSUES," BY MARIAN MACDORMAN ET AL., IN *OBSTETRICS & GYNECOLOGY*, VOL. 128, NO. 3; SEPTEMBER 2016 (*ACOG data and map*)

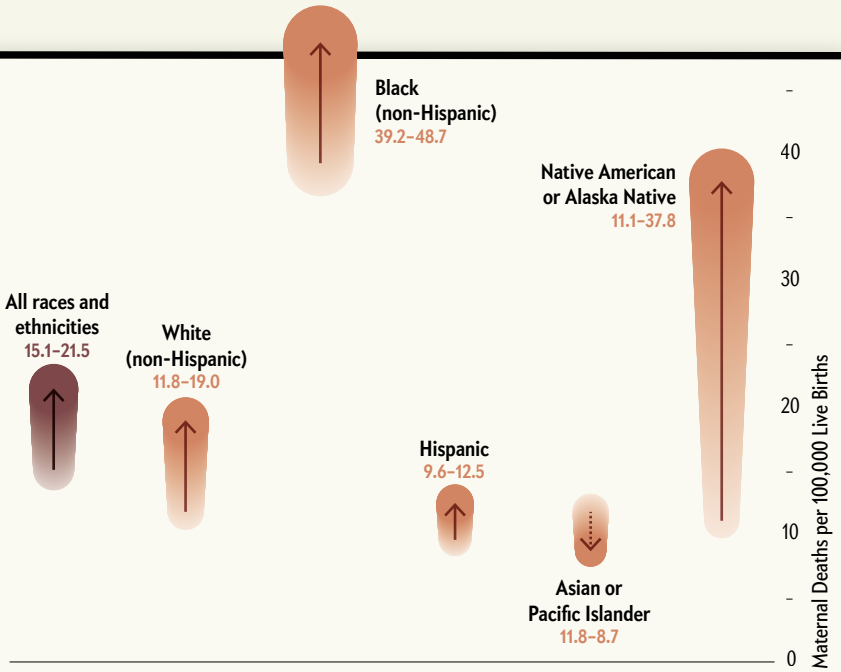
Who Is Dying?

It's common to blame women for their own deaths. Many scientific publications have cited that women are coming to pregnancy older (called advanced maternal age, or geriatric pregnancy), sicker (with hypertension, diabetes or other chronic illnesses) and fatter (that is, suffering from obesity). But even in studies that control for age, chronic disease and obesity, the MMR in the U.S. still far exceeds rates in similarly wealthy nations. In a 2016 report that looked at pregnancy-related death disparities among states, the authors wrote that "excellent care is apparently available but is not reaching all the people."

U.S. Maternal Mortality Rate over Time, by Race and Ethnicity

2005–2014

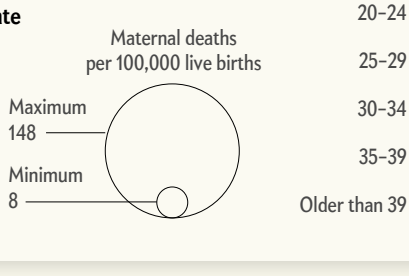


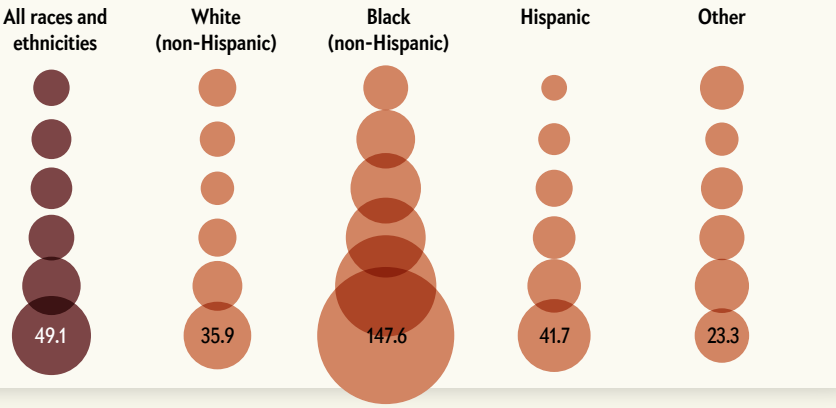


In all racial categories, maternal mortality is worse among older women, but the burden is concentrated among black women, who are more likely to experience structural determinants of health that worsen over time.

U.S. Maternal Mortality Rate across Age Groups

2006–2010



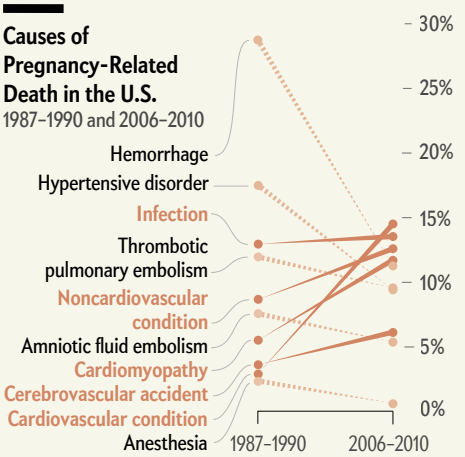


Why Are Mothers Dying—and How Many Causes Are Preventable?

Pregnancy exacerbates existing clinical conditions such as cardiovascular disease (including high blood pressure), enlarged heart and an irregular heartbeat. Black women are more likely to have these conditions before, during and after pregnancy. Chronic, toxic stress—the way that experiences of discrimination are embodied—has been shown to make these conditions worse. But in the U.K., for example, there were only two deaths from preeclampsia and eclampsia over a three-year period, according to a 2018 study, suggesting deaths from these hypertensive disorders of pregnancy are highly preventable. Life-threatening heavy bleeding, or hemorrhage, is also one of the major risk factors for death and is easily preventable. One way this can be done is to develop checklists that document bleeding over time and interventions to address it; these checklists must be accessible to all members of a health care team.

Causes of Pregnancy-Related Death in the U.S.

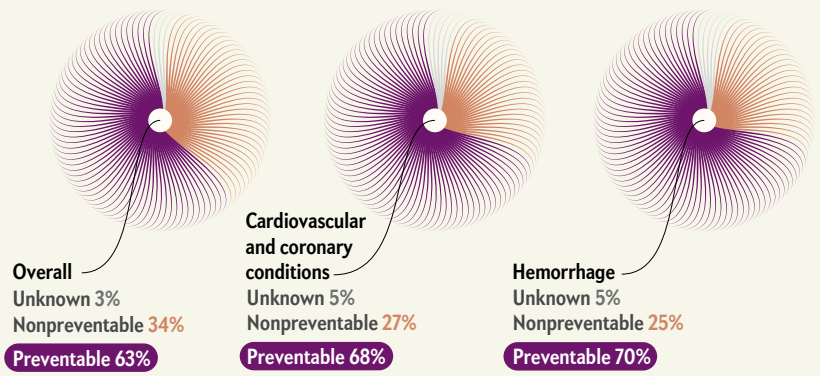
1987–1990 and 2006–2010



There have been significant reductions in pregnancy-related deaths in hypertensive disorders and hemorrhage. MMR rates are dynamic and shift over time.

Distribution of Preventability among Pregnancy-Related Deaths

Per a 2018 report including data from nine states, spanning 2008–2017



About a third of all maternal deaths are considered to be nonpreventable. But the most common conditions associated with maternal mortality, such as heart disease and hemorrhage, can be better handled to avoid poor outcomes.

FUTURE OF MEDICINE 2019

How the U.S. Is Tackling the Problem—Or Not

Recently several groups, including the World Health Organization, have called for a more respectful approach to maternal care. This would be helped by diversification of the health care workforce so that clinical teams reflect the populations they serve. It also means better communication of knowledge between patients and their health care teams. One program that embraces these features is called the Alliance for Innovation on Maternal Health (AIM). Funded through the federal Maternal and Child Health Bureau, AIM is a national alliance to promote consistent and safe maternity care, with the initial goal of reducing maternal mortality by 1,000 instances—and severe maternal morbidity by 100,000 instances—between 2014 and 2018. Many states are currently participating. The efforts involved in AIM include hospital-based interventions whereby health care teams—from obstetricians to emergency room staff—practice simulations of emergencies. The alliance also advocates for increased access to doulas and midwives, as well as a reclamation of normal physiological birth—that is, not treating birth as a disease to be managed.

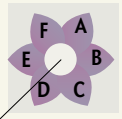
Which States Are Taking Action?

Alliance for Innovation on Maternal Health

KEY

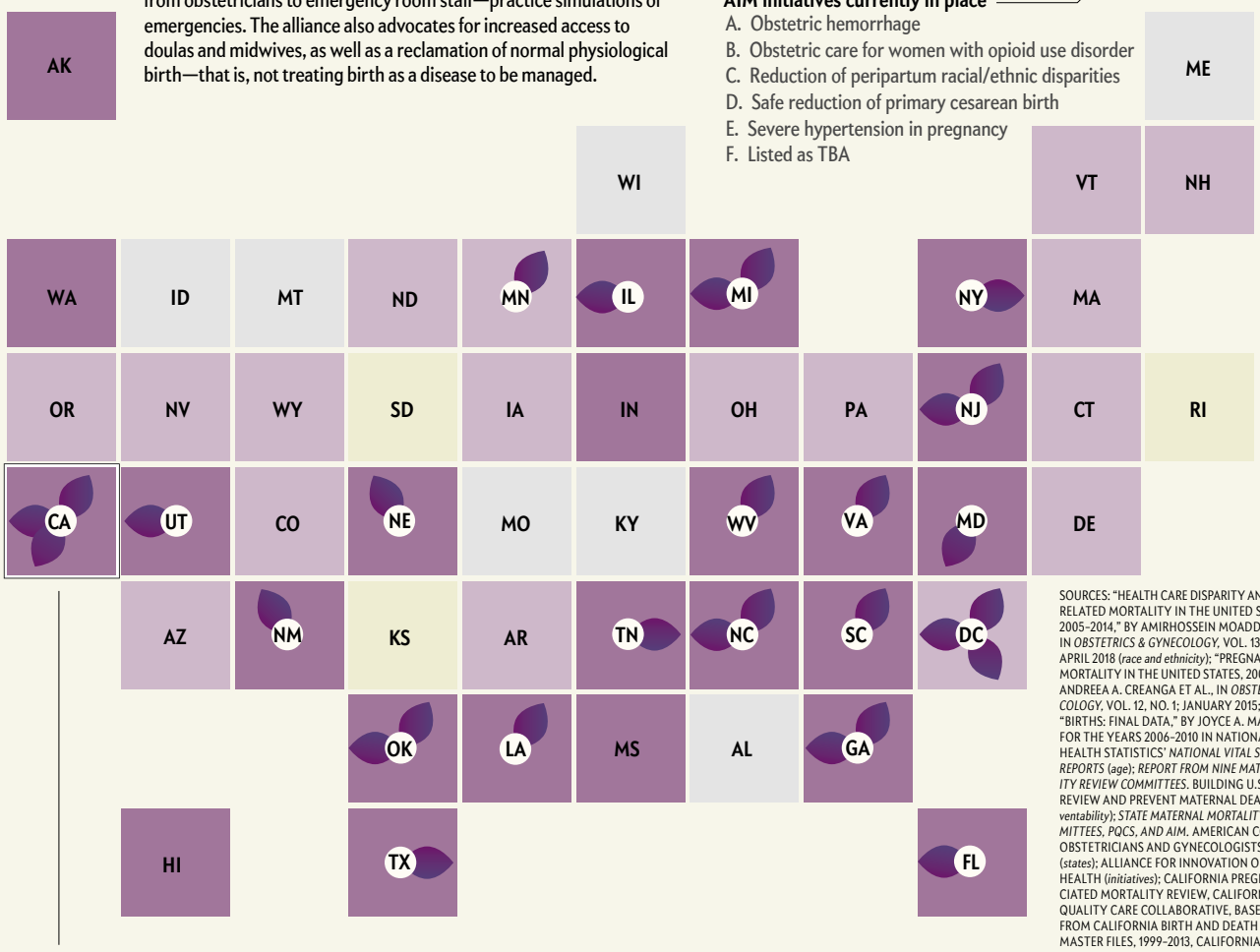
AIM states

- Current AIM states
- States with intent to apply
- States exploring engagement
- No data



AIM initiatives currently in place

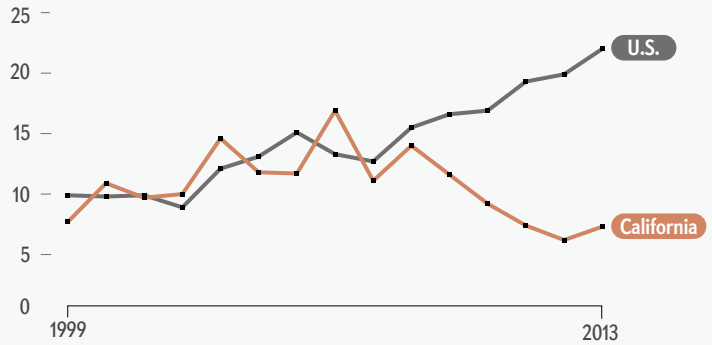
A. Obstetric hemorrhage
B. Obstetric care for women with opioid use disorder
C. Reduction of peripartum racial/ethnic disparities
D. Safe reduction of primary cesarean birth
E. Severe hypertension in pregnancy
F. Listed as TBA



SOURCES: "HEALTH CARE DISPARITY AND PREGNANCY-RELATED MORTALITY IN THE UNITED STATES, 2005–2014," BY AMIRHOSSEIN MOADDAB ET AL., IN *OBSTETRICS & GYNECOLOGY*, VOL. 131, NO. 4; APRIL 2018 (*race and ethnicity*); "PREGNANCY-RELATED MORTALITY IN THE UNITED STATES, 2006–2010," BY ANDREEA A. CREANGA ET AL., IN *OBSTETRICS & GYNECOLOGY*, VOL. 12, NO. 1; JANUARY 2015; REPORTS ON "BIRTHS: FINAL DATA," BY JOYCE A. MARTIN ET AL., FOR THE YEARS 2006–2010 IN NATIONAL CENTER FOR HEALTH STATISTICS' *NATIONAL VITAL STATISTICS REPORTS* (*age*); *REPORT FROM NINE MATERNAL MORTALITY REVIEW COMMITTEES*. BUILDING U.S. CAPACITY TO REVIEW AND PREVENT MATERNAL DEATHS, 2018 (*preventability*); *STATE MATERNAL MORTALITY REVIEW COMMITTEES, PQCS, AND AIM*. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, MARCH 2019 (*states*); ALLIANCE FOR INNOVATION ON MATERNAL HEALTH (*initiatives*); CALIFORNIA PREGNANCY-ASSOCIATED MORTALITY REVIEW, CALIFORNIA MATERNAL QUALITY CARE COLLABORATIVE, BASED ON DATA FROM CALIFORNIA BIRTH AND DEATH STATISTICAL MASTER FILES, 1999–2013, CALIFORNIA DEPARTMENT OF PUBLIC HEALTH (*California vs. U.S. MMR*)

California vs. U.S. Maternal Mortality Rate

Maternal deaths per 100,000 live births (1999–2013)



California Leads the Way

Established in 2006, the California Maternal Quality Care Collaborative (CMQCC) has used data-driven approaches in an attempt to understand the root causes of maternal mortality. A few of their tactics include distributing plain-language tool kits, conducting mock emergencies, making quality improvements in hospital settings and training staff to work more collaboratively. So far the program has reduced the MMR from 16.9 per 100,000 people to 7.3. In addition to tapping into the latest research at its Maternal Data Center, the CMQCC does outreach partnerships to improve health outcomes for mothers and infants. Parsing its successes more closely has shown that much work still needs to be done. Despite admirable reductions in overall maternal mortality in California, significant racial disparities remain and align with the demographics represented in the national data sets. Keeping black women alive before, during and after birth is the focus of an innovative new CMQCC program—a hospital-based racial equity pilot. In several communities, organizations led by black women are working with CMQCC to redesign obstetric practices. Data from the pilot should be available in 2020.

FUTURE OF MEDICINE 2019

EGGS ON ICE

Technical advances are driving a boom in egg freezing, which promises to let women put off pregnancy indefinitely. But will the science live up to the hype?

By Liza Mundy

Photographs by Jamie Chung

EQUIPMENT for in vitro fertilization includes syringes for injectable medications, petri dishes, sperm vials, and more.

FUTURE OF MEDICINE 2019

SPRIGHTLY YELLOW SEEMS TO BE THE HUE OF CHOICE FOR CORPORATE wellness chains designing a logo to attract health-minded women. There is the cleansing grapefruit of SoulCycle, the happy buttercup of Drybar. And last year vans started materializing at busy pedestrian spots in Manhattan and Los Angeles that sported the shade of sunflowers. These vans are mobile fertility clinics, inviting women to pop in and learn how to safeguard their reproductive germ line by freezing their eggs. "Own your future," the ads on the side promise. "Your fertility, understood."

The vehicles are emissaries of Kindbody, a boutique fertility practice that courts the same clientele that frequents spin classes and blow-dry bars. It is one of a small but growing number of outfits that offer fertility services, including retrieving a woman's eggs, or oocytes, to be frozen for later use. Because eggs are one of the most important factors in female fertility, and both their quality and quantity declines with age, banking eggs promises to lengthen a woman's window of fertility and postpone the decision of whether to have kids. As a rival service, Extend Fertility, puts it, "Women have more options today than ever before. And we're giving you one more—the option to start your family when you're ready."

The appearance of boutique egg-freezing outfits is one of the most high-profile—but not the only—recent developments in assisted reproductive technology, which is the science (and commerce) of helping people have the babies they want. These stand-alone clinics exist thanks to a convergence of female financial empowerment, venture capital backing and real medical progress. And it is not just mobile clinics behind the push. Egg freezing is on the rise at gold-standard fertility clinics, such as the one at the University of Southern California. There, according to clinic director Richard Paulson, it accounts for almost 40 percent of egg-retrieval cycles—in which women inject themselves with hormones to stimulate their ovaries to release multiple eggs, and doctors then collect those eggs while the women are under anesthesia. (The other 60 percent of cycles at the clinic involve women undergoing infertility treatment who intend to use the eggs soon.)

Ultimately these providers are making the case that egg freezing has come far enough to justify the $10,000-plus bet women place by investing in the procedure and medications not covered by insurance (that price tag does not include the storage fees women must pay yearly to keep the eggs on ice). This confidence stems from significant breakthroughs in the science of fertility and conception made over the past decade, notably a process that allows doctors to flash-freeze eggs. Physicians have also come a long way in the science of in vitro fertilization (IVF)—the process that comes after egg freezing—which unites a thawed egg (or a fresh one) with a sperm for conception in a petri dish and then grows the resulting embryo to the point where it can be put back inside a woman's uterus to implant.

All this amounts to a sea change in the science of making babies, one that suggests, in theory, that women are not bound by the traditional notion of the ticking biological clock. Yet in practice, the reality is more complicated. Women must consider other factors besides their eggs, such as their overall health and the health of the sperm they plan to use, in deciding when to get pregnant. And just how good of a bet these new technologies truly are remains to be determined: the vast majority of frozen eggs at clinics have yet to be thawed. The question remains: Will they all be viable? Can science really safeguard fertility for later?

THE FREEZING BOOM

IN SOME PLACES, such as the San Francisco Bay Area, the rise in egg freezing is linked in part to nearby tech companies such as Facebook and Google, which now (and with some fanfare) cover the procedure for employees. In Silicon Valley, egg freezing has become part of the benefits package a prudent career woman may consider availing herself of, a kind of 401(k) for future family formation. The boom also stems from other converging trends. One is the millennial generation's comfort with social media; boutique clinics have strong presences on Instagram and Twitter, as do a growing number of traditional clinics. Even online dating—which has sold the hope that much messiness of the human heart can be solved by downloading an app—has an impact. "Women have said to me, instead of looking at every date as 'Is this someone I could marry?' they can set that aside," says Marcelle Cedars, director of the University of California, San Francisco's Center for Reproductive Health.

The rise in freezing also bespeaks a public inured to paying a monthly fee for products. What egg freezing is—among other things—is one more paid-subscription service, like Netflix or Zipcar. Oocytes, once frozen, must be

Liza Mundy is a journalist, a senior fellow at the New America foundation and a former staff writer for the *Washington Post*. She is author of four books, most recently the *New York Times* best seller *Code Girls: The Untold Story of the American Women Code Breakers of World War II* (Hachette Books, 2017).

VITRIFICATION DEVICES such as the S-Cryolock (*shown*) help to freeze eggs and embryos almost instantly to prevent damage.

kept frozen until used. After a woman goes through the not easy or cheap process of having eggs retrieved, she will be powerfully motivated to continue paying the storage fee, which can be as much as $500 or $1,000 a year. Every batch of eggs in liquid nitrogen represents an income stream for years, for the clinic and its investors.

But the freezing trend is also the outcome of science. Asked to reflect on stages of progress in the field, Paulson casts his mind back to when in vitro was in its infancy. The first IVF baby was Louise Brown, born in 1978, now a mother herself. The technology for the scheme was nonexistent to the point where doctors had to fashion their own utensils to retrieve eggs and incubate embryos; when the late gynecologist Patrick Steptoe and the late physiologist Robert Edwards were performing the experiments that would result in Brown's birth, they kept embryos warm in a pouch created in the skin of a living rabbit.

Into the 1980s IVF patients could expect, at best, a 10 to 15 percent delivery rate. "We were able to help a handful of people," says Alan Penzias, an associate professor at Harvard Medical School and a doctor at Boston IVF. "But not the majority. Most people failed."

The retrieval of eggs—the well-protected female germ line—has always been hard. The 1980s saw basic techniques developed and refined; at first, doctors had to perform laparoscopic surgery to extract a single egg the instant it was ovulated. They learned to administer hormones that could cause eggs to ovulate in greater quantity and at a more predictable time and to retrieve them vaginally, with a needle that pokes through to the ovaries. The 1990s were—unexpectedly—the decade of the man. Male-factor infertility—slow or misshapen sperm or low sperm count—is a common reason couples

INSTEAD of growing embryos in incubators in the lab, the INVOcell device can be inserted into a patient's vagina to incubate them there.

may be unable to conceive. For a long time the only "cure" for male-factor infertility was sperm donation. Then, in 1992, scientists in Belgium announced the first live birth after using ICSI—intracytoplasmic sperm injection—in which a single sperm is injected into the egg. ICSI was a disruptive technology that cured male-factor infertility, for couples who can afford it.

For more than half a century it has been almost ridiculously easy to freeze sperm, which are stripped-down DNA missiles. The first reported human birth from frozen sperm occurred back in 1953. Not so for the egg, which is among the largest cells in the body and difficult to freeze well. Eggs are mostly water, meaning ice crystals can form, with sharp edges that damage organelles and other delicate structures. For years freezing an egg entailed dehydrating it to the fullest extent possible, then introducing tiny amounts of cryoprotectant, a kind of antifreeze that aims to prevent crystals from forming. Everything was done very slowly. "It would be this painful process that would take about two to three hours," says Amy Sparks, an embryologist at the University of Iowa, who remembers the agony of ratcheting down the temperature bit by bit. This technology enabled the first human birth from a frozen embryo in 1984; the first birth from a frozen oocyte was reported two years later, in 1986. But for eggs, freezing remained both difficult and damaging: the upshot often was like what happens when you thaw ice cream and refreeze it: icy granulation. "When it thaws, all of a sudden the water from those crystals has nowhere to go and causes damage to the cell," Sparks says.

Then, about 10 years ago, came the most important recent scientific breakthrough in assisted reproductive technology. Vitrification—from *vitrum,* Latin for "glass"—is the ability to freeze eggs (and embryos) breathtakingly fast. The procedure involves larger quantities of cryoprotectant than earlier methods and a direct plunge into liquid nitrogen, which triggers "ultrarapid cooling," minimizes the formation of ice crystals and almost instantly transforms the egg into a glasslike state. "In the past 10 years the impact of vitrification … has really transformed the field in ways that we could not have foreseen," says Serena Chen, director of the clinic at Saint Barnabas Medical Center in New Jersey.

Vitrification is akin to pushing the "pause" button, Chen says; when the time comes, the laboratory pushes "play" and commences rapid thawing. The results are so show-stopping that in 2018, the ethics committee of the American Society for Reproductive Medicine (ASRM)—which up to that point had declined to recommend social use of the technology—issued a paper saying egg freezing "for women attempting to safeguard their reproductive potential for the future" could now be considered "ethically permissible." In short: egg freezing has gone mainstream. Clinics disagree over whether frozen eggs are as viable as fresh, but most experts, including Paulson and Sparks, say they are very, very close. And there is no question that eggs frozen when a woman is 32 are better than fresh eggs retrieved from the same woman at 42.

But even great eggs, just like sex, do not always make a baby. Cedars explains to patients that they should not wait to use frozen eggs until their early 40s, because if they do not work, the old-fashioned method might not either. Yet here lies a quandary—if women cannot wait until their fresh eggs have declined, what is the point of freezing in the first place?

IVF STRIDES

VITRIFICATION is not the only advance helping to buoy the promise of egg freezing. Other elements of IVF have seen major improvements, such as the new standard of growing an embryo for five days in the lab before transferring it back to a woman. A decade ago embryos were often transferred at the three-day stage, when they consisted of just eight cells. Human embryos now arrive in the uterus as "blastocysts," with roughly 100 cells, which are more mature and robust and have a much greater chance of success. According to CDC data from 2016, for women younger than 35, nearly 50 percent of fresh embryos transferred at day five resulted in a live birth as compared with 34.4 percent of embryos transferred at day three. For women between 35 and 37, the percentages were 42.1 for day five versus 28.6 for day three.

Success rates are also getting better because labs can now closely replicate the chemical environment of the fallopian tube, where embryos spend their first five or so days when pregnancy happens naturally. Labs have gotten much better at regulating the amounts and concentrations of nitrogen, oxygen and carbon dioxide. Current incubators also feature more solid-state technology that requires less opening and closing of doors so that embryos can rest undisturbed.

The ability to develop embryos to the blastocyst

stage means embryologists can more easily recognize the best of the batch before deciding which to try to implant. These judgment calls are also improved by a process called preimplantation genetic selection. Back in the three-day-embryo era, if scientists wanted to gauge the genetic health of an embryo, they had to pry one cell from an eight-cell mass, a lab procedure so harrowing that Sparks still has "nightmares" about it. Now it is much easier to use lasers to grab a couple of cells from the part of the blastocyst that will create the placenta—the less vital section than the one that is destined for the fetus.

All in all, embryologists' improved ability to freeze and test embryos amounts to "a huge change," Penzias says. About 10 years ago, frozen embryos had a 10 percent lower success rate than fresh. "Now we're talking about parity," he says. The improved odds mean, in theory, that whether women are using embryos created from eggs retrieved the same month or from those frozen years before, clinics can transfer just one embryo at a time rather than the two or three that used to be the norm. For 14 years it has been the University of Iowa's policy that if a woman is younger than 38, has no prior failed transfers at the clinic and has at least a single good-looking blastocyst (a five-day-old embryo), then one is "all they get," Sparks says. These trends have reduced the prevalence of twins, and especially of triplets and higher-order multiples, which are much riskier pregnancies than carrying singletons, for both babies and moms. At the University of Iowa, the rate of twin birth used to be 40 percent in 2001; now it is under 5 percent. Industrywide, according to the CDC, the portion of transfers involving a single embryo has more than tripled, from 12 percent in 2007 to 40 percent in 2016. Equally important: the percentage of fresh single-embryo transfers resulting in a live birth increased from 21 percent in 2007 to 37 percent in 2016.

These innovations are just the beginning. A new invention allows a woman to incubate embryos inside a device inserted in her vagina rather than an incubator in the lab. And even more radical technologies are on the horizon: Mitochondrial replacement therapy, for instance, is a controversial procedure that can eliminate the risk of genetic mitochondrial disease by injecting the nucleus of a mother's egg into an egg from a woman without the disease whose nucleus has been removed but whose mitochondria remain. The procedure is banned in the U.S., out of concerns about mixing the DNA of two women, but is being developed in England. The day is also coming, Paulson says, when it will be possible to use stem cell technology to manufacture sperm and eggs from normal body cells, such as skin cells. Although it sounds like science fiction, the procedure would involve no changes to a cell's DNA, so that part, at least, is less worrisome than mitochondrial transfer. With this technology, women would no longer need to bank eggs. "At 45, you can still have an egg made out of your skin cells," Paulson says. It sounds wild, but so did IVF 40 years ago. "It's going to happen."

TICKING CLOCKS

IT IS A FACT THAT A woman is born with all the oocytes she will have; over time her ovarian reserve diminishes, as does the quality of her eggs.

Talking about this subject has always been fraught. Back in 2001, when the ASRM launched an ad campaign partly about age-related infertility, the National Organization for Women attacked it as coercive and antifeminist. Chen says this reaction does women a major disservice; older eggs are more likely to be chromosomally abnormal, with a higher risk for miscarriage and the grief that follows. She adds that egg freezing is often depicted as elective and narcissistic, "kind of like plastic surgery or getting a cute Mini Cooper." But women face many pressures, particularly in their mid-30s, when each year of delayed childbearing means an increase in earning power. "It's not about women just being selfish and trying to work on their careers," Chen says. "The truth is, a lot of people just haven't found the right partner."

Still, Chen shares concerns about the commercialization of a technology that originally aimed to help cancer patients preserve fertility during treatment. Jake Anderson-Bialis, co-founder of the consumer education Web site FertilityIQ, worries that women do not realize taking hormones and then undergoing retrieval is not a minor lunch-hour-type procedure. And there is still no guarantee the eggs will result in a live birth. The backlash could be huge if many of the women now freezing their eggs later attempt to use them, only to find out their investment failed. The dirty secret of the fertility industry, up to now, has been multiple births; going forward, Anderson-Bialis says, "if there's going to be a black eye, it's egg freezing." By this, he means the danger that the eggs, once thawed, will not be viable—a potentially devastating outcome to women sold on the promise of egg freezing. Cedars agrees that some women are too bullish on what technology can accomplish. "We have to repeatedly say to patients, 'There's not a baby in the freezer,'" she says. "'There is the *potential* for a baby.'" SA

MORE TO EXPLORE

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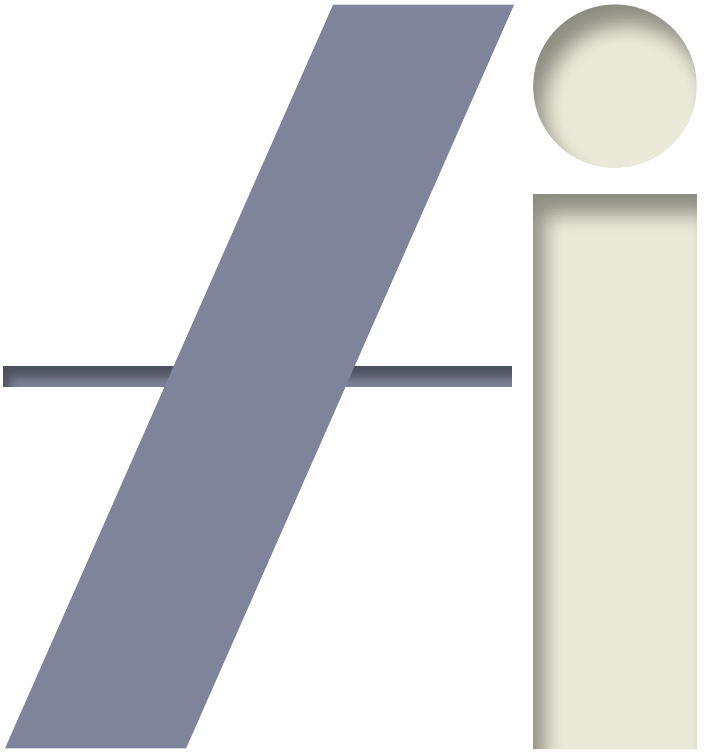


ARTIFICIAL IMAGINATION

How machines could learn creativity and common sense, among other human qualities

By George Musser

IF YOU EVER FEEL CYNICAL ABOUT HUMAN BEINGS, A GOOD ANTIDOTE IS TO TALK to artificial-intelligence researchers. You might expect them to be triumphalist now that AI systems match or beat humans at recognizing faces, translating languages, playing board and arcade games, and remembering to use the turn signal. To the contrary, they're always talking about how marvelous the human brain is, how adaptable, how efficient, how infinite in faculty. Machines still lack these qualities. They're inflexible, they're opaque and they're slow learners, requiring extensive training. Even their well-publicized successes are very narrow.

IN BRIEF

Several emerging methods endow artificial-intelligence systems, such as neural networks, with features that were once considered to be quintessentially human. **Meta-learning primes a network** to adapt quickly so that it can pick up new tasks without requiring reams of data. **So-called generative adversarial networks** provide a form of imagination, letting machines reproduce the statistical features of data sets. **Disentanglement sensitizes** neural networks to the underlying structure of data, making their inner workings more understandable in human terms.

Illustration by Gabriel Silveira

Many AI researchers got into the field because they want to understand, reproduce and ultimately surpass human intelligence. Yet even those with more practical interests think that machine systems should be more like us. A social media company training its image recognizers, for example, will have no trouble finding cat or celebrity pictures. But other categories of data are harder to come by, and machines could solve a wider range of problems if they were quicker-witted. Data are especially limited if they involve the physical world. If a robot has to learn to manipulate blocks on a table, it can't realistically be shown every single arrangement it might encounter. Like a human, it needs to acquire general skills rather than memorizing by rote.

In getting by with less input, machines also need to be more forthcoming with output. Just the answer isn't enough; people also want to know the reasoning, especially when algorithms pass judgment on bank loans or jail sentences. You can interrogate human bureaucrats about their biases and conflicts of interest; good luck doing that with today's AI systems. In 2018 the European Union gave its citizens a limited right to an explanation for any judgment made by automated processing. In the U.S., the Defense Advanced Research Projects Agency funds an "Explainable AI" research program because military commanders would rather not send soldiers into battle without knowing why.

A huge research community tackles these problems. Ideas abound, and people debate whether a more humanlike intelligence will require radical retooling. Yet it's remarkable how far researchers have gone with fairly incremental improvements. Self-improvement, imagination, common sense: these seemingly quintessential human qualities are being incorporated into machines, at least in a limited way. The key is clever coaching. Guided by human trainers, the machines take the biggest steps themselves.

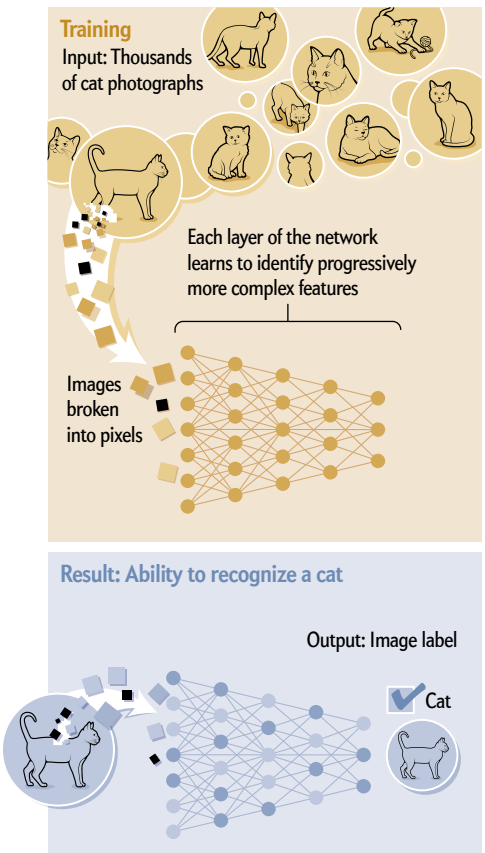
George Musser is a contributing editor to *Scientific American* and author of *Spooky Action at a Distance* (Farrar, Straus and Giroux, 2015) and *The Complete Idiot's Guide to String Theory* (Alpha, 2008).

DEEP NETWORKS

MORE THAN MOST FIELDS of science and engineering, AI is highly cyclical. It goes through waves of infatuation and neglect, and methods come in and out of fashion. Neural networks are the ascendant technology. Such a network is a web of basic computing units: "neurons." Each can be as simple as a switch that toggles on or off depending on the state of the neurons it is connected to. The neurons typically are arrayed in layers. An initial layer accepts the input (such as image pixels), a final layer produces the output (such as a high-level description of image content), and the intermediate, or "hidden," layers create arithmetic combinations of the input. Some networks, especially those used for problems that unfold over time, such as language recognition, have loops that reconnect the output or the hidden layers to the input.

Network Effects

For all their immense power, neural networks still have frustrating limitations. For classifying images, the network takes in the image pixels, processes them through multiple stages, and outputs the probabilities of the various labels the image might be given. Fine-tuning the interconnections typically takes thousands of sample images. How exactly the network performs the classifications is lost in the tangle of wiring. Several new techniques fix these shortcomings



Meta-Learning

To reduce the amount of training data, researchers can prime the network by giving it practice exercises of the same general type. The network does not retain any of the information but gradually gets better at solving whatever new tasks it is given. It learns how to learn.

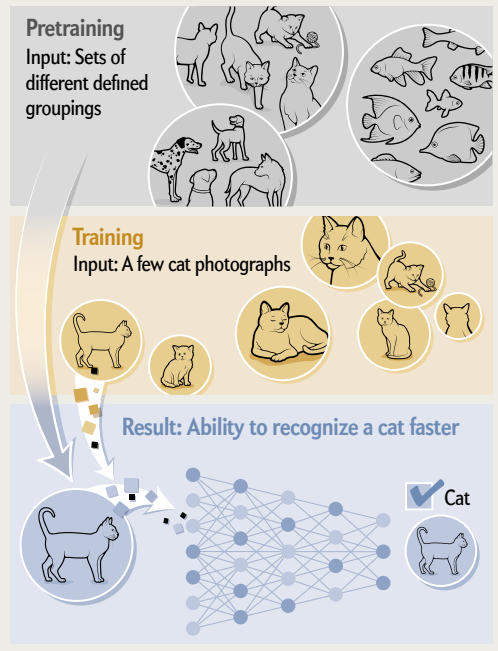


Illustration by Brown Bird Design

A so-called deep network has tens or hundreds of hidden layers. They might represent midlevel structures such as edges and geometric shapes, although it is not always obvious what they are doing. With thousands of neurons and millions of interconnections, there is no simple logical path through the system. And that is by design. Neural networks are masters at problems not amenable to explicit logical rules, such as pattern recognition.

Crucially, the neuronal connections are not fixed in advance but adapt in a process of trial and error. You feed the network images labeled "dog" or "cat." For each image, it guesses a label. If it is wrong, you adjust the strength of the connections that contributed to the erroneous result, which is a straightforward exercise in calculus. Starting from complete scratch, without knowing what an image is, let alone an animal, the network does no better than a coin toss. But after perhaps 10,000 examples, it does as well as a human presented with the same images. In other training methods, the network responds to vaguer cues or even discerns the categories entirely on its own.

Remarkably, a network can sort images it has never seen before. Theorists are still not entirely sure how it does that, but one factor is that the humans using the network must tolerate errors or even deliberately introduce them. A network that classifies its initial batch of cats and dogs perfectly might be fudging: basing its judgment on unreliable cues and variations rather than on essential features.

This ability of networks to sculpt themselves means they can solve problems that their human designers have no idea how to solve. And that includes the problem of making the networks even better at what they do.

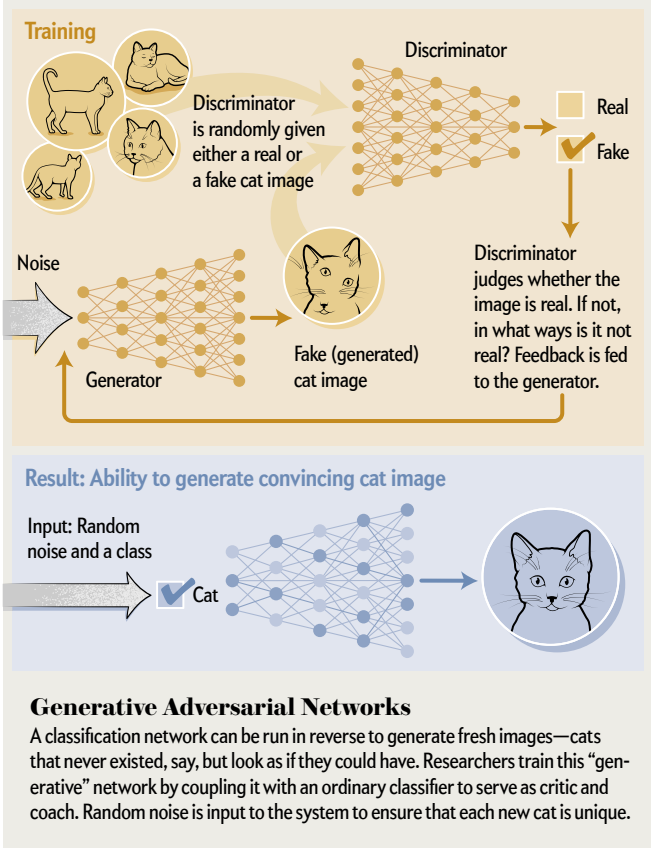
GOING META

TEACHERS OFTEN COMPLAIN that students forget everything over the summer. In lieu of making vacations shorter, they have taken to loading them up with summer homework. But psychologists such as Robert Bjork of the University of California, Los Angeles, have found that forgetting is not inimical to learning but essential to it. That principle applies to machine learning, too.

If a machine learns a task, then forgets it, then learns another task and forgets it, and so on, it can be coached to grasp the common features of those tasks, and it will pick up new variants faster. It won't have learned anything specific, but it will have learned *how* to learn—what researchers call meta-learning. When you do want it to retain information, it'll be ready. "After you've learned to do 1,000 tasks, the 1,001st is much easier," says Sanjeev Arora, a machine-learning theorist at Princeton University. Forgetting is what puts the meta into meta-learning. Without it, the tasks all blur together, and the machine can't see their overall structure.

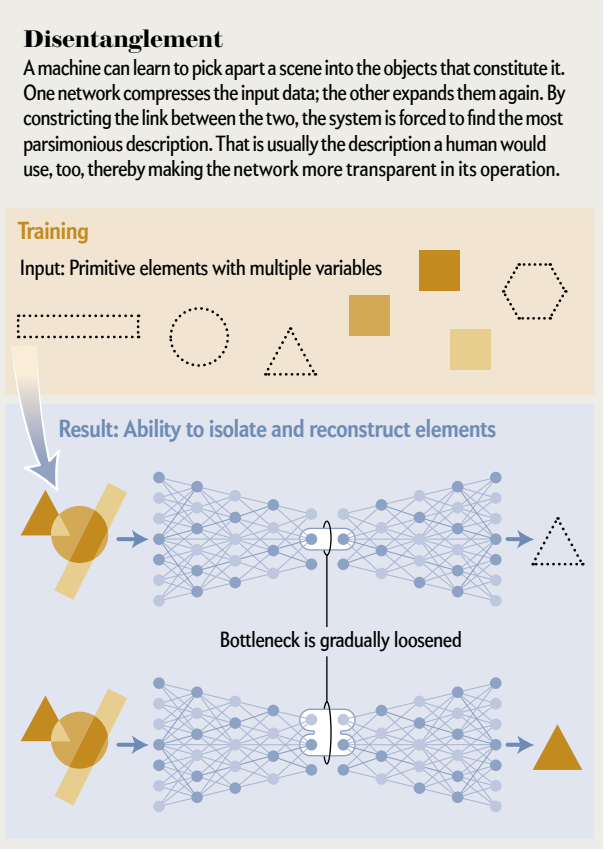
Meta-learning gives machines some of our mental agility. "It will probably be key to achieving AI that can perform with human-level intelligence," says Jane Wang, a computational neuroscientist at Google's DeepMind in London. Conversely, she thinks that computer meta-learning will help scientists figure out what happens inside our own head.

In nature, the ultimate meta-learning algorithm is Darwinian



Generative Adversarial Networks

A classification network can be run in reverse to generate fresh images—cats that never existed, say, but look as if they could have. Researchers train this "generative" network by coupling it with an ordinary classifier to serve as critic and coach. Random noise is input to the system to ensure that each new cat is unique.



evolution. In a protean environment, species are driven to develop the ability to learn rather than rely solely on fixed instincts. In the 1980s AI researchers used simulated evolution to optimize software agents for learning. But evolution is a random search that goes down any number of dead ends, and in the early 2000s researchers found ways to be more systematic and therefore faster. In fact, with the right training regimen, any neural network can learn to learn. As with much else in machine learning, the trick is to be very specific about what you want. If you want a network to learn faces, you should present it with a series of faces. By analogy, if you want a network to learn how to learn, you should present it with a series of learning exercises.

In 2017 Chelsea Finn of the University of California, Berkeley, and her colleagues developed a method they called model-agnostic meta-learning. Suppose you want to teach your neural network to classify images into one of five categories, be it dog breeds, cat breeds, car makes, hat colors, or what have you. In normal learning, without the "meta," you feed in thousands of dog images and tweak the network to sort them. Then you feed in thousands of cats. That has the unfortunate side effect of overriding the dogs; taught this way, the machine can perform only one classification task at a time.

In model-agnostic meta-learning, you interleave the categories. You show the network just five dog images, one of each breed.

Forgetting is not inimical to learning but essential to it. That principle applies to machine learning, too.

Then you give it a test image and see how well it classifies that dog—probably not very well after five examples. You reset the network to its starting point, wiping out whatever modest knowledge of dogs it may have gained. But—this is the key step—you tweak this starting point to do better next time. You switch to cats—again, just one sample of each breed. You continue for cars, hats, and so on, randomly cycling among them. Rotate tasks and quiz often.

The network does not master dogs, cats, cars or hats but gradually learns the initial state that gives it the best head start on classifying anything that comes in fives. By the end, it is a quick study. You might show it five bird species: it gets them right away.

Finn says the network achieves this acuity by developing a bias, which, in this context, is a good thing. It expects its input data to take the form of an image and prepares accordingly. "If you have a representation that's able to pick out the shapes of objects, the colors of objects and the textures and is able to represent that in a very concise way, then when you see a new object, you should be able to very quickly recognize that," she says.

Finn and her colleagues also applied their technique to robots, both real and virtual. In one experiment, they gave a four-legged robot a series of tasks to run in various directions. Going through meta-learning, the robot surmised that the common feature of those tasks was to run, and the only question was: Which way? So the machine prepared by running in place. "If you're running in place, it's going to be easier to very quickly be adapted to running forward or running backward because you're already running," Finn says.

This technique, like related approaches by Wang and others, does have its limitations. Although it reduces the amount of sample data needed for a given task, it still requires a lot of data overall. "Current meta-learning methods require a very large amount of background training," says Brenden Lake, a cognitive scientist at New York University, who has become a leading advocate for more humanlike AI. Meta-learning is also computationally demanding because it leverages what can be very subtle differences among tasks. If the problems are not sufficiently well defined mathematically, researchers must go back to slower evolutionary algorithms. "Neural networks have made progress but are still far from achieving humanlike concept learning," Lake says.

THINGS THAT NEVER WERE

JUST WHAT THE INTERNET NEEDED: more celebrity pictures. Over the past couple of years a new and strange variety of them has flooded the ether: images of people who never actually existed. They are the product of a new AI technology with an astute form of imagination. "It's trying to imagine photos of new people who look like they could plausibly be a celebrity in our society," says Ian J. Goodfellow of Google Brain in Mountain View, Calif. "You get these very realistic photos of conventionally attractive people."

Imagination is fairly easy to automate. You can basically take an image-recognition, or "discriminative," neural network and run it backward, whereupon it becomes an image-production, or "generative," network. A discriminator, given data, returns a label such as a dog's breed. A generator, given a label, returns data. The hard part is to ensure the data are meaningful. If you enter "Shih Tzu," the network should return an archetypal Shih Tzu. It needs to develop a built-in concept of dogs if it is to produce one on demand. Tuning a network to do so is computationally challenging.

In 2014 Goodfellow, then finishing his Ph.D., hit on the idea of partnering the two types of network. A generator creates an image, a discriminator compares it with data and the discriminator's nitpicking coaches the generator. "We set up a game between two players," Goodfellow says. "One of them is a generator network that creates images, and the other one is a discriminator network that looks at images and tries to guess whether they're real or fake." The technique is known as generative adversarial networks.

Initially the generator produces random noise—clearly not an image of anything, much less the training data. But the discriminator isn't very discriminating at the outset. As it refines its taste, the generator has to up its game. So the two egg each other on. In a victory of artist over critic, the generator eventually reproduces the data in enough verisimilitude that the discriminator is reduced to guessing at random whether its output is real or not.

The procedure is fiddly, and the networks can get stuck creating unrealistic images or failing to capture the full diversity of the data. The generator, doing the minimum necessary to fool the discriminator, might always place faces against the same pink background, for example. "We don't have a great mathematical theory of why some models nonetheless perform well, and others perform poorly," Goodfellow says.

Be that as it may, few other techniques in AI have found so many uses so quickly, from analyzing cosmological data to designing dental crowns. Anytime you need to imbibe a data set and produce simulated data with the same statistics, you can call on a

generative adversarial network. "You just give it a big bunch of pictures, and you say, 'Can you make me some more pictures like them?'" says Kyle Cranmer, an N.Y.U. physicist, who has used the technique to simulate particle collisions more quickly than solving all the quantum equations.

One of the most remarkable applications is Pix2Pix, which does almost any kind of image processing you can dream of. For instance, a graphics app such as Photoshop can readily reduce a color image to gray scale or even to a line drawing. Going the other way takes a lot more work—colorizing an image or drawing requires making creative choices. But Pix2Pix can do that. You give it some sample pairs of color images and line drawings, and it learns to relate the two. At that point, you can give it a line drawing, and it will fill in an image, even for things that you didn't originally train it on.

Other projects replace competition with cooperation. In 2017 Nicholas Guttenberg and Olaf Witkowski, both at the Earth-Life Science Institute in Tokyo, set up a pair of networks and showed them some mini paintings they had created in various artistic styles. The networks had to ascertain the style, with the twist that each saw a different portion of the artwork. So they had to work together, and to do that, they had to develop a private language—a simple one, to be sure, but expressive enough for the task at hand. "They would find a common set of things to discuss," Guttenberg says.

Networks that teach themselves to communicate open up new possibilities. "The hope is to see a society of networks develop language and teach skills to one another," Guttenberg says. And if a network can communicate what it does to another of its own kind, maybe it can learn to explain itself to a human, making its reasoning less inscrutable.

LEARNING COMMON SENSE

THE MOST FUN PART of an AI conference is when a researcher shows the silly errors that neural networks make, such as mistaking random static for an armadillo or a school bus for an ostrich. Their knowledge is clearly very shallow. The patterns they discern may have nothing to do with the physical objects that compose a scene. "They lack grounded compositional object understanding that even animals like rats possess," says Irina Higgins, an AI researcher at DeepMind.

In 2009 Yoshua Bengio of the University of Montreal suggested that neural networks would achieve some genuine understanding if their internal representations could be disentangled—that is, if each of their variables corresponded to some independent feature of the world. For instance, the network should have a position variable for each object. If an object moves, but everything else stays the same, just that one variable should change, even if hundreds or thousands of pixels are altered in its wake.

In 2016 Higgins and her colleagues devised a method to do that. It works on the principle that the real set of variables—the set that aligns with the actual structure of the world—is also the most economical. The millions of pixels of an image are generated by a relatively few variables combined in multitudinous ways. "The world has redundancy—this is the sort of redundancy that the brain can compress and exploit," Higgins says. To reach a parsimonious description, her technique does the computational equivalent of squinting—deliberately constricting the network's capacity to represent the world, so it is forced to select only the most important factors. She gradually loosens the constriction and allows it to include lesser factors.

In one demonstration, Higgins and her colleagues constructed a simple "world" for the network to dissect. It consisted of heart, square and oval shapes on a grid. Each could be one of six different sizes and oriented at one of 20 different angles. The researchers presented all these permutations to the network, whose goal was to isolate the five underlying factors: shape, position along the two axes, orientation and size. At first, they allowed the network just a single factor. It chose position as most important, the one variable without which none of the others would make much sense. In succession, the network added the other factors.

To be sure, in this demonstration the researchers knew the rules of this world because they had made it themselves. In real life, it may not be so obvious whether disentanglement is working or not. For now that assessment still takes a human's subjective judgment.

Like meta-learning and generative adversarial networks, disentanglement has lots of applications. For starters, it makes neural networks more understandable. You can directly see their reasoning, and it is very similar to human reasoning. A robot can also use disentanglement to map its environment and plan its moves rather than bumbling around by trial and error. Combined with what researchers call intrinsic motivation—in essence, curiosity—disentanglement guides a robot to explore systematically.

Furthermore, disentanglement helps networks to learn new data sets without losing what they already know. For instance, suppose you show the network dogs. It will develop a disentangled representation specific to the canine species. If you switch to cats, the new images will fall outside the range of that representation—the type of whiskers will be a giveaway—and the network will notice the change. "We can actually look at how the neurons are responding, and if they start to act atypically, then we should probably start learning about a new data set," Higgins says. At that point, the network might adapt by, for example, adding extra neurons to store the new information, so it won't overwrite the old.

Many of the qualities that AI researchers are giving their machines are associated, in humans, with consciousness. No one is sure what consciousness is or why we have a vivid mental life, but it has something to do with our ability to construct models of the world and of ourselves. AI systems need that ability, too. A conscious machine seems far off, but could today's technologies be the baby steps toward one? SA

MORE TO EXPLORE

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SOCIAL NEUROSCIENCE

THE ROOTS OF HUMAN AGGRESSION

Experiments in humans and animals have started to identify how violent behaviors begin in the brain

By R. Douglas Fields

Illustration by Scott Bakal

R. Douglas Fields is a neuroscientist and author of *Why We Snap*, about the neuroscience of sudden aggression, and the soon-to-be-published *Electric Brain*, about brain waves and brain-stimulation research. Fields is an adjunct professor at the University of Maryland, College Park, in the neuroscience and cognitive science program and chief of the nervous system development and plasticity section at the National Institute of Child Health and Human Development.

FROM HIS SNIPER'S PERCH ON THE 32ND FLOOR OF THE MANDALAY BAY HOTEL IN LAS VEGAS, a lone gunman fired 1,000 bullets from high-powered rifles into a crowd of concertgoers in 2017, murdering 58 innocent people and injuring 869 others. After he committed suicide at the crime scene, the mass murderer's brain was shipped to Stanford University to seek a possible biological explanation for this depraved incident.

What could the scientists possibly find during such an inspection? Quite a lot, in fact. No genetic test for homicidal behavior is in the offing. But this type of investigation can add insight into how violence is controlled by the brain. Using the same experimental methods that have enabled the tracing of brain circuits responsible for other complex human activities—including walking, speech and reading—neuroscientists now can pinpoint pathways that underlie aggressive behaviors. These new findings help to expose the underlying mechanisms at work in acts of extreme violence, such as the Las Vegas atrocity, but they also help to explain the more commonplace road rage and even a mother's instantaneous response to any threat to her child.

IN BRIEF

Humans and other animals sometimes use violence to obtain food or protect themselves.
Decisions to take aggressive action are risky and bring into play specific neural circuits.
Separate pathways respond to immediate threats versus ones requiring deliberation.
Brain abnormalities appear more often in violent offenders than in those without a history of violence.

Physical, sometimes deadly violence is the hub of nature's survival-of-the fittest struggle, and all animals have evolved specialized neural circuitry to execute—and control—aggressive behavior. In pioneering experiments on cats beginning in the late 1920s, Walter Hess discovered a locus deep within the hypothalamus, a brain area that unleashes violent aggression. It turns out that this is the same spot where other powerful compulsive urges and behaviors are activated, including sex, eating and drinking. When Hess stimulated this knot of neurons using a wire electrode inserted into the brain of a docile cat, the feline instantly launched into a hissing rage, attacking and killing another animal in its cage. The human brain has this same neural structure, labeled the hypothalamic attack area.

This discovery sparked the widely popularized "lizard brain" concept, the assertion that primitive urges in humans spring from an evolutionarily ancient neural core that, in the right circumstance, provokes beastly behavior. Since Hess's discovery, the vital question confronting scientists for nearly a century has centered on what circuits feed into the brain's hypothalamic attack region to activate or squelch an attack. Relatively new techniques—optogenetics (an experimental method to switch neural circuits on or off) and fiber-optic cameras threaded into the brains of experimental animals to observe neurons firing during a violent attack—enable some of these questions to be answered. In fact, it is now possible to identify rage and aggression circuits.

For ethical reasons, much of the research tracing the neurocircuitry of violent behavior comes from animal research. Care must be taken in applying terminology used in animal studies to human behaviors and emotions, but clear parallels exist between violence in humans and in other vertebrates. Engaging in physical aggression is potentially life-threatening in any animal, so this behavior is tightly regulated and exhibited only in response to specific types of perceived threats.

Humans and other animals use violent, even dead-

ly aggression instinctively to obtain food, protect their young or defend themselves against bodily injury. But for any of these violent actions—killing prey as opposed to protecting one's young, for example—separate neural connections come into play.

In addition, many animals are highly social species, and aggression is how social order is established and maintained—picture rams butting heads to determine which one gets to breed with the females. For humans, capital punishment, imprisonment and forced removal of resources (fines and revoking privileges) are all codified forms of aggression to maintain social order. Defending territory, protecting group members and competition are other parallels that enable scientists to extrapolate from studies on experimental animals to find neural circuits in humans for each distinct type of aggression.

From a psychological perspective, human aggression can be sparked by a seemingly endless range of provocations and motives, but from the viewpoint of neuroscience, only a few specific neural circuits in the brain are responsible for this behavior. Identifying them and understanding how they function is still a work in progress, but undertaking this task is critically important. The capability for violent aggression engraved in our brain by eons of tooth-and-nail struggle for survival too often malfunctions in response to disease, drugs or psychiatric impairments and can lead to tragic consequences.

The Neuroanatomy of Aggression

AMYGDALA—Deep in the temporal lobe, this structure responds to emotionally charged events and is involved in threat detection, fear, aggression and anxiety.

BRAIN STEM—Nerve fibers from all over the brain and spinal cord pass through this nexus. During a fight, it controls reflexive head movements.

HYPOTHALAMUS—This relay point for information shuttling between the brain and spinal cord regulates release of hormones from the pituitary gland, maintaining vital bodily functions such as temperature regulation, eating, sexual behavior and aggression.

LIMBIC SYSTEM—The middle-of-the-brain network interconnects the amygdala, hypothalamus, hippocampus and cerebral cortex, melding emotion, learning, memory and threat detection.

PITUITARY GLAND—An unpaired structure situated at the top of the brain stem releases hormones into the bloodstream that control the fight-or-flight response and reproduction.

PREFRONTAL CORTEX—The cerebral cortex region at the front of the brain (under the forehead) integrates information to make complex decisions, focus attention and regulate impulses.

NEURAL CIRCUITS OF AGGRESSION

THE DECISION to use violent force is fraught with risk, and before a person lashes out, a set of intricate neural circuits extending widely across the brain's expanse become active. To understand the anatomy of aggression, visualize the human brain as if it had the structure of a mushroom. The thin skin covering the bell of the mushroom equates to the cerebral cortex. A mere three millimeters thick, the cortex is a center of higher cognitive functions—the essence of what makes us human. It is also involved with sensorimotor integration (perception that triggers an action) and even consciousness itself—and it plays a key role in an animal's deciding whether to exhibit aggressive behavior.

The amygdala, a neural structure located deep underneath the cerebral cortex, which rapidly assesses sensory inputs for possible threats, would be situated at the top of the mushroom stalk, where the rafterlike gills radiate out to support the cap. The amygdala has widely branching ingoing and outgoing links that span from the cerebral cortex to the hypothalamus. The almond-shaped structure acts as a central relay point for sensory information coming into the brain, as well as inputs descending from the cerebral cortex, which convey the results of decision-making and other high-level information processing.

The hypothalamus, also situated at the top of the stalk, is the core brain region that unconsciously controls automatic bodily functions, including heart rate, temperature, breathing, sleep cycles, attention and the release of hormones from the pituitary gland. It is where the emotional drive is generated to initiate an attack. The human brain stem, analogous to the mushroom stalk, is where information is transmitted into and out of the brain through the spinal cord. To depict this analogy accurately, it is important to remember that the human brain is a paired structure, with separate left and right hemispheres. An amygdala, for instance, is found on both the left and right sides of the brain.

Multiple regions controlling aggressive behaviors allow the brain to think fast or slow in response to a threat. The latter more deliberative reaction, however, is the most complex of the two, and the prefrontal cortex is critical for such decision-making. Neuroscientist Simone Motta and colleagues working in the laboratory of Newton Sabino Canteras at the University of São Paulo captured in a 2013 study the biological details of the familiar "momma bear" response, which is by no means solely confined to ursine mothers.

The researchers looked through a microscope at the hypothalamus of a mother rat just after a male intruder entered the cage with the mother and her newborn pups, causing her to attack. After staining the postmortem brain tissue, they identified a protein called Fos in the tiny hypothalamic attack region. Through the microscope, it seemed as if the area had been stippled with a black ink pen. The sudden appearance of Fos, represented by the black staining, resulted from rapid synthesis of the protein as a consequence of neurons in the attack region firing bursts of electrical impulses when the mother was provoked into an assault on the intruder. Other research groups have confirmed a link to aggressive behavior by inserting a fiber-optic camera into the hypothalamic at-

tack region in mice genetically engineered to make neurons emit flashes of light when they fire.

When this cluster of neurons, referred to as the ventral premammillary nucleus, was removed from the hypothalamic attack region before the entry of an intruder, Motta's group found that a mother was much less likely to respond with a defensive attack. But destroying these neurons did not affect the mother's responses to a predator cat or other threats. Hess's electrodes from nearly a century ago were too blunt to reveal fine-level subcircuitry for aggression embedded inside the hypothalamic attack region. New methods of analysis are providing a far more detailed picture.

For this area to be activated by the male intruder, sensory information about the attacker had to be received, processed and relayed through the hypothalamus. All major senses enter the brain via separate neural pathways: visual inputs arrive by way of the optic nerve, the sense of smell via the olfactory nerve. Incoming sensory information reaches the cerebral cortex, where it is analyzed to extract detailed features of a stimulus, and a corresponding signal for each respective sense is sent to another more specialized cortical region. The visual cortex at the back of the head, for example, will extract the shape, color and movement of an object set against the broader visual field and then pass on that information to other cortical regions that bring the perception to our conscious mind—allowing, say, the recognition of a familiar face.

But this complex form of information processing, engaging several different cortical regions in sequence as if building an automobile on an assembly line, takes time. Faced with a sudden threat, a clenched fist thrown toward your chin, the time required to process the visual input and consciously perceive it would be far too slow to dodge the blow. For this reason, a high-speed subcortical pathway that recruits the amygdala has evolved to transmit incoming sensory inputs rapidly to the brain's threat-detection circuitry. The inflow from the senses reaches the amygdala before it arrives at our cerebral cortex and conscious awareness—the reason why we duck and bat away an errant basketball that suddenly streaks into our visual field and then ask later, "What was that?" The object suddenly intruding into our personal space is perceived as a threat, even though we cannot form an accurate image of it. Similar to a motion detector in a security system, the amygdala has detected an object that should not be there, and it rapidly activates an aggressive response to deal with the threat.

Humans rely heavily on vision, but the sense of smell is more important for many animals. In the Motta experiments, odor most likely alerted the mother rat's threat-detection mechanism to the male intruder, and this information may have been relayed rapidly to the hypothalamic attack area. Searching the amygdala under a microscope, the scientists saw two spots there that were clearly stained for Fos in response to the intruder's attack. Both these locations in the amygdala—within the medial amygdala nucleus—receive input from the olfactory region. The premammillary nucleus region of the hypothalamus, where the maternal aggression response is centered, has neurons in it that are known to respond to odors only from the opposite sex.

Another part of the amygdala, the posterior nucleus, also showed ample evidence of Fos staining. Neurons there have hormone detectors (mineralocorticoid receptors) to link stress to a trigger for aggression. In other studies on aggressive male rats, the animals become docile when these receptors are blocked. This observation explains in part how diverse aspects of a given situation, whether stress or other factors, can lower the threshold for inducing aggression.

HUMAN EXPERIMENTS

THE INTENTION OF ANY OF THESE STUDIES is to determine whether activating or switching off a particular brain area produces a specific behavior. Animal studies, however, cannot reveal much about what constitutes the actual sensations involved in any of the resulting behaviors. Stimulating the rat brain with an electrode might induce pain that then provokes a violent reaction, giving no hint about whether the reaction resulted directly from the activation of a brain center linked to aggression.

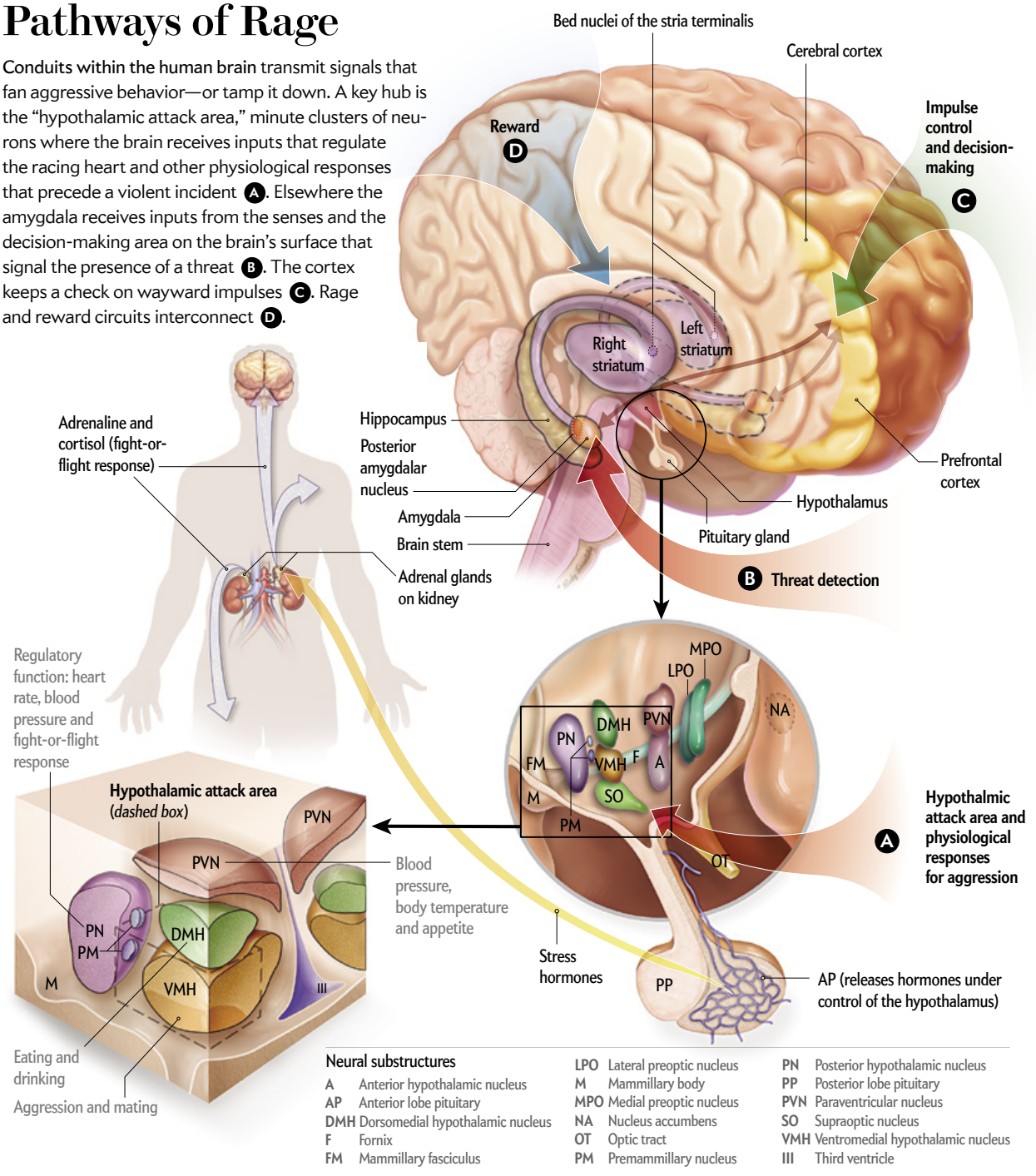
Some experiments, though, have been performed on human subjects, leaving no doubt that the amygdala unleashes intensely violent emotions. In the 1960s, when the late Spanish neuroscientist José Manuel Rodríguez Delgado stimulated an electrode in a woman's right amygdala as she was peacefully playing guitar, she stopped strumming and singing, threw the instrument away in a fit of rage and started to attack a nearby wall. Such powerful emotions unleashing violent behavior must override competing impulses. The risk of deciding to launch an attack could lead to retaliation that puts the aggressor at risk of severe injury—or death—or otherwise provoke the shame that results after fleeing in fear from a threat.

The neural seats of blind rage in both rats and humans are part of an expansive neural network that reaches beyond the amygdala to unleash violent behavior. Researchers have discovered a locus in the septal region, part of what is called the subcortical limbic system, that switches on after a rat fights off an intruder to protect her young. The septal area drives intense emotional responses, such as explosive rage, and is also active during sex and other rewarding activities. In the 1950s James Olds and Peter Milner showed that rats with electrodes implanted in the septal region would press a bar to deliver an electrical stimulus to neurons there to the point of exhaustion—up to 5,000 times per hour.

A counterpart to these experiments has been performed with human involvement. When Delgado stimulated patients' septal regions, they were suddenly overcome with strong sexual feelings that ultimately

Pathways of Rage

Conduits within the human brain transmit signals that fan aggressive behavior—or tamp it down. A key hub is the "hypothalamic attack area," minute clusters of neurons where the brain receives inputs that regulate the racing heart and other physiological responses that precede a violent incident **A**. Elsewhere the amygdala receives inputs from the senses and the decision-making area on the brain's surface that signal the presence of a threat **B**. The cortex keeps a check on wayward impulses **C**. Rage and reward circuits interconnect **D**.



built to an orgasm. One patient became flirtatious and even offered to marry the therapist.

In what are now recognized as unethical studies published in 1972, psychiatrist Robert G. Heath of Tulane University attempted to "cure" a young man of homosexuality. He implanted electrodes into the septal region of the man's brain to enable the physicians or the patient himself to provide neural stimulation that delivered sexual pleasure while watching heterosexual pornographic films and while having sex with a female prostitute. Heath reported that the subject stimulated himself to the point of euphoria. (His sexual orientation remained unchanged, however.)

Neurons in this part of the septal area (the bed nuclei of the stria terminalis, or BNST), which in animal studies were activated during maternal aggression,

Illustration by Body Scientific

also display receptors for norepinephrine, a neurotransmitter involved in stress responses. This brain region connects to the hypothalamus for the control of autonomic responses and release of hormones, such as oxytocin or the neurotransmitter dopamine, that regulate stress, mood and anxiety: it also receives input from the cerebral cortex.

The circuitry of aggression goes both high and low. The prefrontal cortex can inhibit or stimulate the limbic system, squelching an impulse or initiating a violent action based on the deliberation that takes place in high-level cognitive processing areas. This "top-down" control from the prefrontal cortex contrasts with its "bottom-up" counterpart, the rapid, reflexive response to a sudden environmental stimulus, as when the errantly thrown basketball is deflected without any conscious thought. Animals and people with weaker connections from the prefrontal cortex to the limbic system encounter difficulties with impulse control.

The rewarding aspect of aggression, including feelings of superiority and dominance, underlies the hedonistic component of bullying, as well as psychopathic and brutal criminal violence.

The brain's reward centers, including the striatum and nucleus accumbens, where the neurotransmitter dopamine acts, are another component of the aggression circuitry. Many drugs of abuse and addiction—methamphetamine and cocaine, for example—increase the reward-modulating dopamine to trip this circuitry. When a male rat succeeds in defeating a trespasser entering its cage, the animal will repeatedly activate a lever to open the passageway to admit the intruder to fight it again. If dopamine signaling is blocked with a drug, the male rat will cease to initiate another battle.

The rewarding aspect of aggression, including feelings of superiority and dominance, underlies several forms of this behavior, but in particular, the hedonistic component of bullying, as well as psychopathic and brutal criminal violence. In modern society, where our food needs are supplied by supermarkets, the missing sense of reward that comes from a successful kill can be satisfied through recreational activities such as hunting and fishing.

SEX DIFFERENCES

THE SINGLE MOST IMPORTANT FACTOR in predicting aggressive behavior is one's sex. According to 2018 statistics from the Federal Bureau of Prisons, 93 percent of inmates are male. The association between aggression and being male is prominent in the animal kingdom, demonstrating that the relation between violence and sex has a strong biological basis. Hormonal influences on neural circuits controlling aggressive behavior are a large contributor, but the selective pressure on males, especially in social mammals, including most primates, has promoted attributes that increase the probability of aggressive behavior in the quest to find a mate, achieve elevated social status, acquire food, and defend territory and tribe.

Neuroscientist David Anderson of the California Institute of Technology and his colleagues have investigated the neural circuitry that explains the perplexing association between sex and violence. Their research has uncovered part of the mechanism for how the same brain circuitry could be involved in extreme opposites such as love and hate. From a physiological perspective, several common features tie aggression to mating. Both behaviors evoke intense states of arousal and, when successful, potent feelings of reward. In the natural world, aggression and mating are often interrelated, and both are regulated by similar environmental influences and internal body states. Male animals, for example, are more aggressive during mating season.

It has been known for some time that mating is also controlled by the hypothalamic attack area and that stimulation from electrodes placed there can induce copulation or aggression. Using Fos staining to identify highly active neurons, the researchers found that cells in the hypothalamus became active immediately after mice engaged in either an aggressive encounter or mating. Dayu Lin, while working in Anderson's lab before becoming a professor at New York University, implanted microelectrodes into the hypothalamus of mice and found that neurons were buzzing during fighting and mating—some individual neurons fired during one behavior and not in the other, but some turned on during both activities. By threading in a fiber-optic strand to shine a laser beam that made genetically modified neurons generate electrical impulses in response to light, Lin and her colleagues spurred the mouse to initiate an attack or copulate. They used the laser to drive neuron firing at different frequencies and switch between behaviors.

LOSING IT

USING THESE NEW FINDINGS from the lab to help explain a mass killing is still an aspirational goal. But an incident that occurred more than 50 years ago may have set in motion a process of inquiry that could one day

fend off horrific headlines. On August 1, 1966, Charles Whitman, a troubled former U.S. Marine, stabbed and shot his mother to death and killed his wife with a knife in their respective homes before going to a tower on the University of Texas at Austin, campus with a footlocker packed with three knives, 700 rounds of ammunition and seven guns. Whitman killed 14 people from his sniper's perch and injured more than 30 others. He left a note requesting that his brain be studied after his death to determine if he was mentally ill.

Forensic analysis of the killer's brain found a small tumor, glioblastoma multiforme, near the amygdala. The team of experts conceded in its written report: "The highly malignant brain tumor conceivably could have contributed to his inability to control his emotions and actions," but the experts were unable to make a conclusive determination that the cancer had anything to do with Whitman's mass murders or his apparent mental illness. After all, many people suffer brain injuries and tumors, but they do not become violent killers; Senator Ted Kennedy and Senator John McCain, for example, were both stricken with glioblastoma multiforme.

Thus far no abnormality has been reported in the brain of the Las Vegas mass murderer Stephen Paddock—and one may never be found. If pathology does turn up, it will still be impossible to find a cause-and effect relation between the brain tumor and the heinous crime. Moreover, statistics from the MacArthur Violence Risk Assessment Study indicate that people with mental disorders are no more likely than others to be violent.

The odds are that no neurological abnormality will be found in the brain of the Mandalay Bay sniper. The major risk factors that predict violent behavior are youth, male sex, substance abuse and lower socioeconomic status. One third of self-reported violent acts committed by people without diagnosed mental illness and seven out of 10 violent crimes among the mentally ill are associated with substance abuse, according to a 2003 review by Heather Stuart of Queen's University in Ontario. Our knowledge of how alcohol or cocaine impairs the brain's neural circuitry for aggression leaves little doubt about the connection between substance abuse and violence.

NEW UNDERSTANDING

THE COMMITTEE OF EXPERTS who examined Whitman's brain articulated a larger reason for its inability to link the brain tumor to the crime—quite simply, it had to do with the basic lack of a scientific grasp of the brain in 1966. "The application of existing knowledge of organic brain function does not enable us to explain the actions of Whitman on August first," the report notes. "This case is a dramatic indication of the urgent need for further understanding of brain function related to behavior, and particularly to violent and aggressive behavior."

The MRI machine did not exist in 1966, and the entire field of neuroscience was in its infancy. More recent research using modern techniques to explore the new neuroscience underlying aggression is now yielding knowledge that might have helped Whitman's search for closure.

Psychiatrist Bernhard Bogerts of Otto von Guericke University Magdeburg in Germany and his colleagues used MRI and CT scans to examine the brains of violent and nonviolent prisoners. The research found significantly higher incidence of brain abnormalities in violent offenders than in nonviolent ones or a control group. For instance, 42 percent of the 162 violent prisoners had at least one abnormal area versus 26 percent of the 125 nonviolent inmates and 8 percent of the 52 individuals in the control group. The pathology showed up in the prefrontal cortex, the amygdala and other regions responsible for control of the amygdala and hypothalamus.

Information uncovered about the neurocircuits of aggression may provide a path to new answers, but it may also raise fresh questions. Both genes and experience guide the development of neural circuits differently in every individual, an explanation for the varying intensity and types of aggression exhibited in humans or experimental rodents. The prefrontal cortex does not fully develop until the early 20s in humans, pointing to why juveniles should not be held criminally responsible as adults in the U.S.

This sluggish neurodevelopment process provides some degree of biological insight into the seemingly incomprehensible waves of tragic school shootings rocking the country. Ultimately interventions to reduce violent behavior may be possible by regulating neural circuits of aggression with drugs, precision surgery, brain stimulation or other methods.

The emerging evidence of neurological abnormalities in people incarcerated for violent behavior raises ethical questions of legal culpability and whether psychiatric assessment of mental health patients should include EEG and brain-scanning assessments to look for signs of pathology. That may be what Whitman was seeking as he packed his footlocker and wrote out his suicide note asking that his brain be examined after the bloodbath he was about to commit. SA

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FUEL RODS stand ready at the Czech Republic's Dukovany nuclear power plant. Rods are often cylindrical elsewhere.

ENERGY

REACTOR MODEL

Rod McCullum is senior director of decommissioning and used fuel at the Nuclear Energy Institute in Washington, D.C. He has worked at the Stone & Webster engineering firm, the U.S. Department of Energy and three nuclear power plants.

IN BRIEF

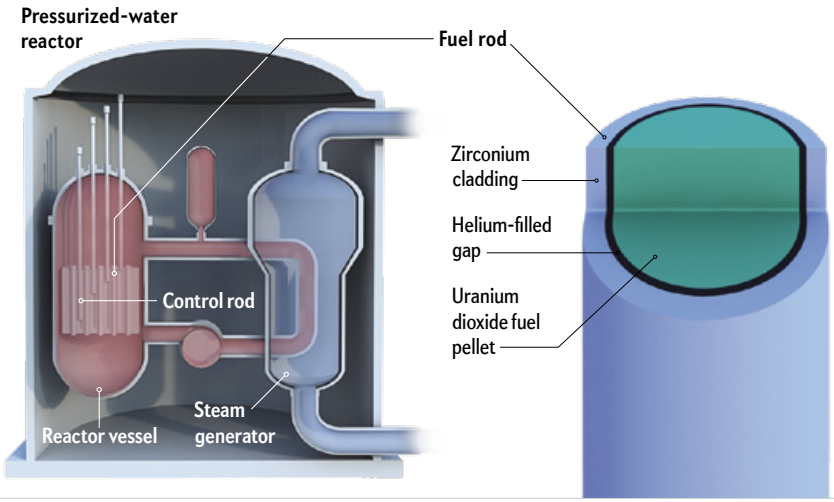
Fuel for nuclear reactors has remained virtually the same worldwide for decades.
Four new designs could make reactor cores safer and more efficient.
Companies are testing novel materials, and regulators are considering rules for use.

Advanced fuels could improve the safety and economics of nuclear power plants

By Rod McCullum

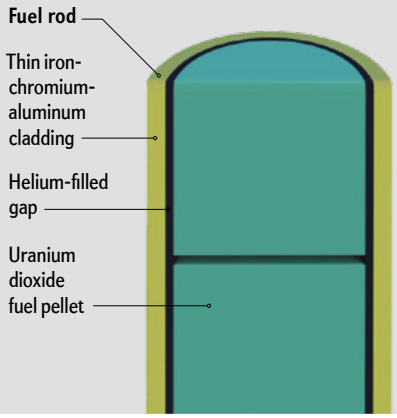
New Fuels for Reactors

Manufacturers are testing so-called accident-tolerant fuels. If overheated, they are far less likely to create conditions similar to the ones that led to explosions and the release of radiation in the 2011 Fukushima disaster. Almost all nuclear power plants use pressurized-water (*shown*) or boiling-water reactors. Fission occurs in fuel pellets stacked inside fuel rods made of cladding, separated by a gap that allows for thermal expansion during operation. Four examples of accident-tolerant fuels are depicted, in order of increasing departure from current design. Different manufacturers are each working on several varieties.



Reinvent the Wrapper

Inside a reactor, hot fuel rods turn water into steam to generate electricity. The standard rod around a fuel pellet, made of zirconium alloy cladding, allows neutrons from fission in the pellet to pass through, supporting a self-sustaining nuclear reaction. But if the zirconium overheats, it can react with the water or steam and produce hydrogen gas, which can build up and explode. Cladding made of iron, chromium and aluminum will not react. It tends to block some neutrons but can be made thinner, allowing enough neutrons to pass. (Design: GE Hitachi Nuclear Energy)



ENGINEERS ARE REDESIGNING the uranium fuel used in almost all nuclear reactors worldwide to reduce both the chance of a hydrogen explosion and the release of radiation during an accident—which is what happened in 2011 at Japan's Fukushima Daiichi power plant. The new fuels, which must still be perfected, are already being tested.

In a reactor core, uranium atoms are split, releasing neutrons and heat. Systems in and around the reactor keep the core from getting too hot. Improving the fuel so it is less likely to melt or crack under high heat, and less likely to lead to hydrogen production, can reduce the risk of radioactive material being released during an accident. The same enhancements could allow power plant operations to run more efficiently and generate electricity more competitively.

All 98 power reactors running in the U.S., regardless of their design, use uranium fuel pressed into cylindrical ceramic pellets, each the size of a large pencil eraser. The pellets are stacked inside long fuel rods made of a zirconium alloy, and the rods are submerged in water. During fission, neutrons released from the fuel pellets pass easily through the zirconium and enter other fuel rods, where they sustain a heat-producing chain reaction. The heat turns water to steam, which generates electricity.

Zirconium has long been used to form fuel rods precisely because it is so permeable to neutrons. The thinking was that uranium exploration, mining, processing and enrichment (increasing the proportion of nuclei capable of producing a chain reaction) would be complex and expensive. The science of arranging a reactor core to optimize energy output was young as well. Neutrons seemed too precious to be lost. But as the Fukushima accident demonstrated, on live television, if zirconium overheats, it can react with water (or steam) to produce potentially explosive hydrogen.

Today reactor design and operation are more sophisticated, and uranium has proved plentiful and readily enriched, so plant operators can afford to sacrifice a few neutrons. As a result, scientists and engineers are now perfecting alternative designs that can minimize hydrogen production and withstand more heat.

Spurred on by the Fukushima accident, manufacturers, working with the U.S. Department of Energy, are moving briskly on four so-called accident-tolerant fuels, each with a markedly different approach. Because all of them could be swapped into existing reactors with little or no need to modify reactor hardware, they could be phased into current machines during the 2020s.

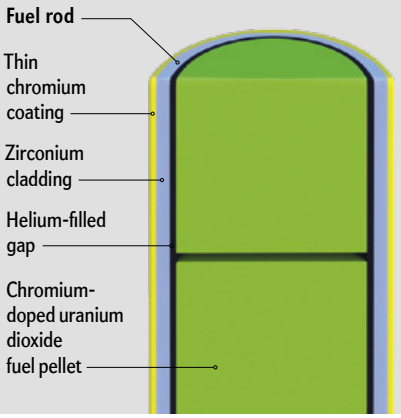
Three competing companies that already produce the bulk of the industry's fuel—Framatome, GE Hitachi Nuclear Energy and Westinghouse Electric Company—have begun to test small quantities in existing reactors. The idea behind these designs is to reduce the likelihood of problematic zirconium reactions by coating the zirconium, replacing it or changing the fuel-pellet ingredients altogether.

PRECEDING PAGES: MARTIN DIVISEK *Getty Images*

Illustration by José Miguel Mayo

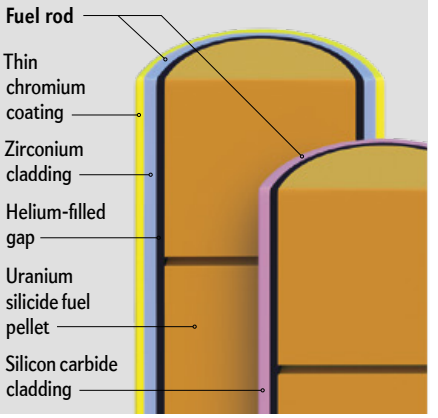
Add Chromium

Coating the zirconium cladding with a thin layer of chromium can prevent the cladding from reacting with water and producing hydrogen—the way a coating of rust-proofing on metal prevents oxidation. The coated cladding can also withstand more heat and last longer. In addition, adding chromium to the uranium oxide pellet helps to prevent the fuel from cracking or deforming under heat, making the entire fuel-rod assembly more resilient under accident conditions and less likely to release radioactive material. (Design: Framatome)



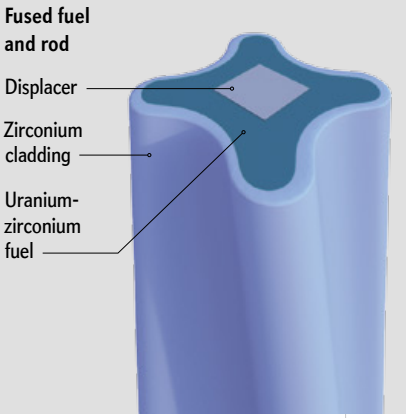
Incorporate Silicon

Changing the pellet material from uranium dioxide to uranium silicide allows it to transfer more heat to the surrounding water. The fuel can thus operate at a lower temperature, which makes hydrogen production and radiation release in an accident less likely. The zirconium cladding can either be coated with chromium (*left*) to reduce potential hydrogen generation or be replaced with silicon carbide, which does not react with water and is less likely to crack or deform, further reducing accident risk (*right*). (Designs: Westinghouse Electric Company)



Twist the Rod

An aggressive redesign eliminates the pellet. The fuel is uranium zirconium, bound to zirconium cladding; the materials have similar expansion rates, so no gap is needed. The fused fuel and cladding is twisted to create a solid rod with more surface area for transferring heat to water. (The displacer helps to distribute heat evenly.) The enhanced transfer allows the fuel to operate at a lower temperature, which makes overheating and potential accident conditions less likely. The uranium has to be enriched to 20 percent rather than 5 percent for the other fuels shown. (Design: Lightbridge)



A fourth concept, from Lightbridge, a new U.S. market entrant, combines uranium and zirconium into a single, less reactive alloy shaped like a licorice stick, a configuration that would transfer heat better. The uranium would have to be enriched to higher levels than are allowed today, so U.S. regulations would have to change.

For decades utility owners have had difficulty gaining regulatory approval for any type of new fuel, but they are trying again, sensing a need to compete with inexpensive natural gas and increasingly abundant solar and wind power. U.S. owners are getting design and manufacturing help from an extensive nuclear research and development infrastructure, notably the National Laboratories. Yet the effort is quickly becoming global. In July 2018 scientists from the U.S. and the European Union held a workshop at Idaho National Laboratory to discuss how to best pool research on both continents. The Organisation for Economic Co-operation and Development is developing a framework for testing new fuels. If accident-tolerant fuels perform well, nuclear power could regain momentum in Japan, where debate continues about how much of the nation's reactor fleet to restart.

Of course, significant hurdles must be cleared. Considerable in-core testing of small fuel quantities and computer modeling of performance, under both normal operating and accident conditions, have to be done before new fuels are ready for commercial use. Industry skeptics will have to be convinced that the new materials will work as promised. More advanced modeling techniques are coming online to aid this effort. Simulation technology at the U.S. Department of Energy's Consortium for Advanced Simulation of Light Water Reactors, based at Oak Ridge National Laboratory in Tennessee, could significantly speed up basic research, engineering development and commercialization.

If data from trials are convincing, the U.S. fuel-supply chain—from the fabrication shop to the reactor-refueling floor—would have to retool, and plant processes and procedures would have to be adjusted. Regulators would have to approve every step.

Rethinking fuel may be just the beginning of greater change. Scientists and engineers are designing high-temperature gas-cooled reactors that would use uranium particles wrapped in exotic coatings; gumball-like pellets themselves would control the nuclear reaction rather than control rods commonly inserted among fuel rods. Also underway are molten salt reactors, in which the fuel and reactor coolant can be combined, allowing simple mechanisms to prevent overheating.

The natural gas, solar and wind industries have changed considerably in just a few years. The nuclear energy industry may be ready to reinvent itself as well. SA

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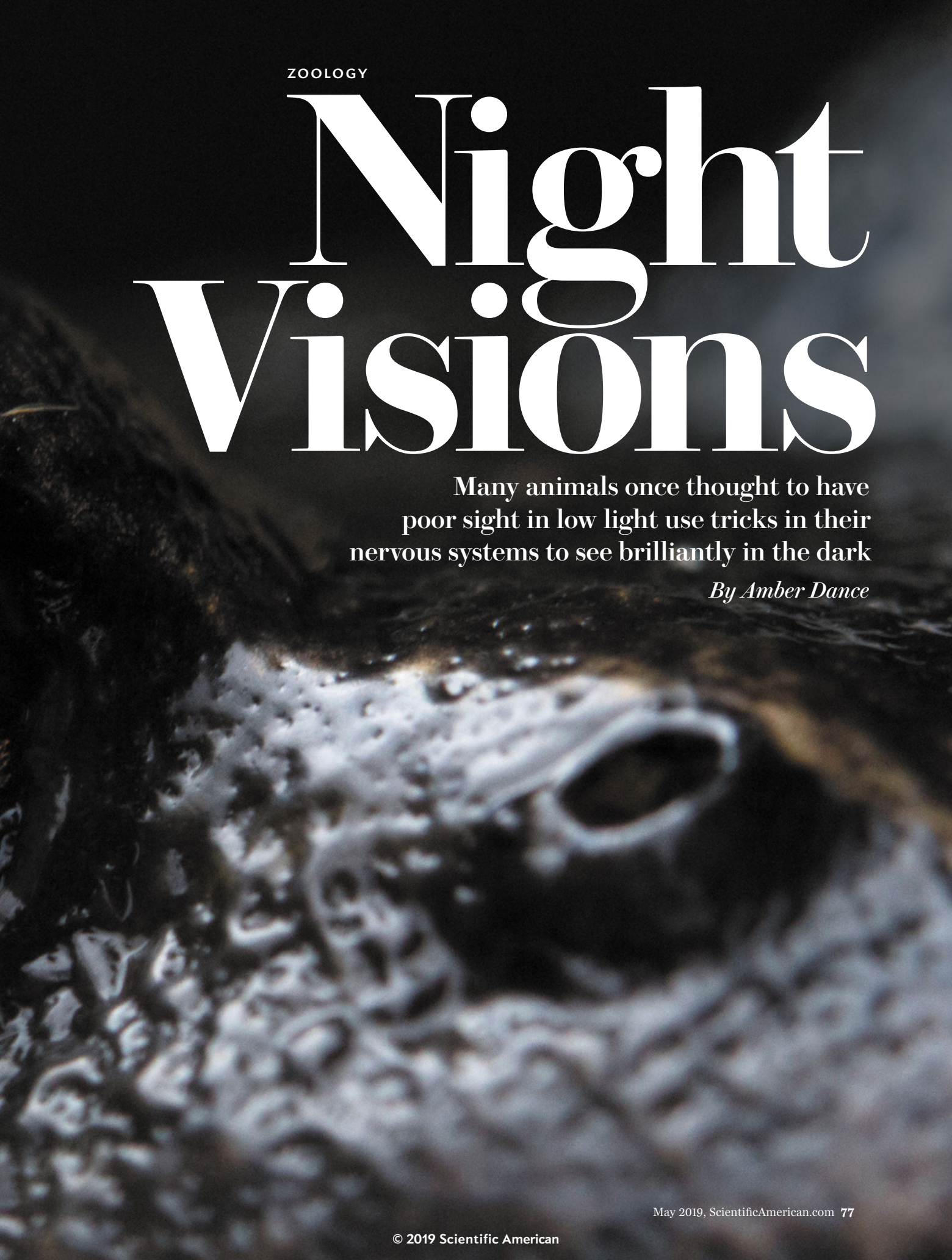
IN THE DARK, the European common frog can distinguish green from blue.

ZOOLOGY

Night Visions

Many animals once thought to have poor sight in low light use tricks in their nervous systems to see brilliantly in the dark

By Amber Dance



Science writer **Amber Dance** lives in the Los Angeles area.

THE SUN'S FINAL RAYS FILTER THROUGH THE LEAVES AS NIGHT FALLS IN THE dense, muggy rain forest. The descending gloam over Panama's Barro Colorado Island obscures the towering, spiky kapok trees, the palms and the shrubs until human eyes can't see much more than the small patches of starlit sky through the canopy above. Crickets commence their chorus as the howler monkeys hush for the night.

In the twilight, a nocturnal sweat bee, with bulging eyes, a metallic green head and a pale brown abdomen, emerges from her nest in a foot-long, hollowed-out stick. She's hungry for nectar and pollen. But before she flits off, she turns to look back at the stick, which has a black-and-white-striped card above it, placed there by scientists. Nearby stick nests also have cards, but these are simply a flat gray.

After the bee flies off, zoologist Eric Warrant and his colleagues at Lund University in Sweden switch things around, moving the striped card to another nest. When the bee returns, she zooms right into the nest with the stripes, assuming it is hers and demonstrating that sweat bees spot and use such visual signals. "Even in the very dimmest intensities, they have no problem seeing this," Warrant says. (He notes that if the humans tracking the insects did not wear night-vision goggles, they would "literally crash into trees" because it is so dark.)

The remarkable night vision of these bees (*Megalopta genalis*) stems only in part from eye adaptations such as larger lenses. Those do improve sweat bees' light sensitivity. Still, the nocturnal insects find their nests at light levels where even those peepers should not be sufficient. Warrant has concluded that in addition to the bees' eyes, the way in which their brain processes the little light available allows them to navigate after sunset.

For decades scientists assumed that most creatures must see the same dim, colorless nightscape that people do. They thought that nocturnal animals relied on other senses, such as smell and hearing. Today a new wave of research is overturning that assumption. "We always thought we knew how well animals saw in the dark, but very few people had actually looked," Warrant explains. Once researchers started peering into this dark world, they discovered that a wide variety of species see a startlingly clear nightscape.

Moths, frogs and geckos, for example, can distinguish colors at night when researchers themselves see nothing but shades of gray. Being more sensitive to color variations gives them an advantage because hue is a much more reliable way to distinguish objects, in bright or dim light, than noncolor indicators such as intensity. It can help them find food, nests or mates in the dark. "It's just amazing that so many animals can be active in dim light and still perform behaviors when we can't," says Almut Kelber, a sensory biologist at Lund.

The secrets to night navigation reside between eye and brain. Nerve cells in the optical systems of these animals add up scarce bits of light to create a brighter picture and carefully prune away other, noisy signals that would muddle the image. The cells perform these summations by grabbing input from neighboring spots in their visual field. They also sum up input from single spots over a long time period, essentially slowing down visual perception to make things much brighter.

IN LIVING COLOR

THE EYES OF PEOPLE, along with those of most other vertebrates and invertebrates, have cells that work as photoreceptors, detecting light coming from outside. The cells are called cones and rods. During the day, we use mainly cones, which send signals back toward the brain when hit by incoming photons of red, green or blue light. They give humans excellent color vision, but they do not respond much in the dark. In dim light, we rely on rods, which are more sensitive because they work together in groups, pooling the information from scant incoming light. They tend to distinguish only shades of gray, however.

Warrant, Kelber and another Lund colleague, Anna Balkenius, were the first to show, in a 2002 study, that an animal had color vision at night. The researchers put insects called hawkmoths in a cage in the laboratory and trained them to associate either a blue or yellow artificial flower with a sugar-water reward. The

IN BRIEF

Several animals possess unexpectedly excellent vision in dim light. Scientists once thought they needed other senses to find food or mates.

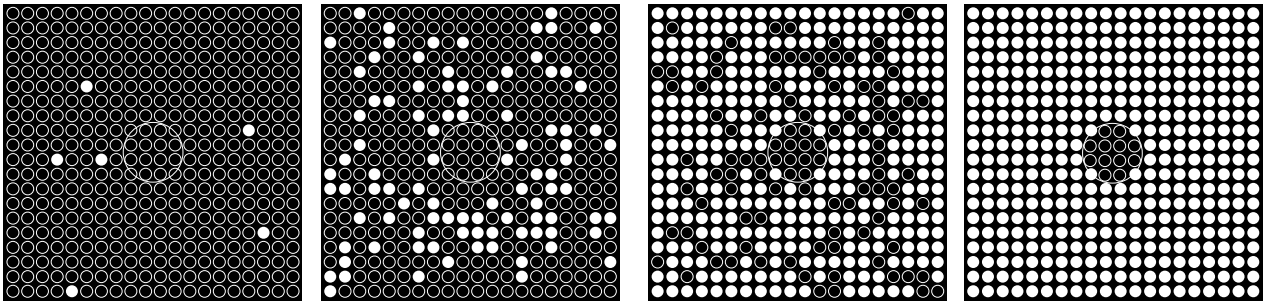
These abilities include seeing colors. Creatures such as moths, frogs and geckos detect color in the dark to navigate the world.

Animals accomplish this feat by using neurons in their optical systems to maximize sparse incoming signals from their eyes.

PRECEDING PAGES: HÅKAN LILJENBERG *Alamy*

Trouble at Night

When it is dark, light-detecting cells in the eye have little chance of catching the few photons (units of light) that might reveal an object. This diagram shows 400 photoreceptor cells trying to discern a circle. With only six photons coming in (*left*), the circle remains identical to its dark surroundings. As photon numbers increase, so does the contrast between the circle and environment. But only after levels are boosted 1,000 times (*right*) does the object become clear.



zoologists started the tests under dusklike illumination, then turned down the light to levels as low as dim starlight. As dark as the surroundings became, the moths could still tell yellow from blue. Since that study, Kelber's team has found nocturnal color vision in carpenter bees and geckos. She hopes to test for color vision in fruit bats and in owls, whose nocturnal hunting prowess has usually been ascribed to keen hearing or big eyes.

Frogs can see color in the dark as well, distinguishing blue from green. Animal physiologist Kristian Donner of the University of Helsinki in Finland and his colleagues tested European common frogs for phototaxis, a behavior by which the frogs typically hop toward light. Donner wondered if they would be choosy about the color of the light. Decades ago lab tests on frogs' rod cells had shown that some specifically reacted to blue light, whereas others responded to green. To find out what the cell differences meant for frog behavior, Donner's group placed 17 amphibians, one at a time, in a bucket with two windows on opposite sides. The scientists shined blue light in one side and green light in the other. Then they measured the frequency and direction of the frog hops at different light levels.

When the bucket was completely dark, the hops were random. But as soon as the researchers let in the least possible amount of light, the frogs showed a clear preference for green. "At the very limit for vision, they can still differentiate between blue and green," Donner says. For human comparison, his students stuck their heads in the bucket and could not see any light, much less tell green from blue.

It's not certain why the amphibians jumped toward green light. Perhaps, Donner speculates, frogs get clues from the stars. Starlight is made up of relatively long wavelengths, and green light wavelengths are longer than blue, so green coming into the bucket might hint at starlit open spaces and a route to escape from the container.

STARLIT PATHS

IF FROGS INDEED FOLLOW THE STARS, they would not be the only animals that do so. Dung beetles travel in a perfectly straight line on moonless nights, when the only light comes from stars. The movement is a good strategy for a beetle with a nice fresh bit of dung, says James Foster, a sensory biologist at Lund. It wants to leave the scrum of other beetles at the dung pat and find a quiet patch of ground to dig in with its prize. Going straight, rather than weaving or turning about, will get the beetle away from the pat as quickly as possible.

How do the beetles do it? Foster's Lund adviser Marie Dacke, Warrant and other researchers had already discovered that the insects use what they can see above them to find their way around. The scientists put cardboard visors on the critters so they could not see the sky. Then they let the insects loose in a circular arena and tracked the way each traveled to the edge. When capped, the beetles took much more circuitous routes, indicating that something in the sky was important to them.

The researchers suspected the beetles might use the pattern of stars for orientation, like six-legged sailors navigating with constellations. To test this idea, Dacke and her colleagues brought the beetles, with their dung balls, to a planetarium where skylight patterns could be easily controlled. Under either a simulation of a full starry sky or just the bright streak of the Milky Way, the beetles sped straight to the circle's edge in under a minute. They took longer if the galaxy was absent. It was the first time any animal was shown to orient itself using this band of stars. (After publication in the journal *Current Biology* in 2013, the work earned a tongue-in-cheek Ig Nobel Prize in Biology and Astronomy.)

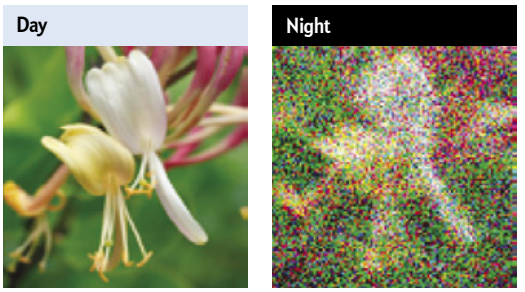
More recently, Foster investigated how dung beetles might use the Milky Way to go in one particular direction. Seen from our planet, the galaxy's thick band of stars is a fairly symmetrical line. From the beetles' perspective, the line would look just the same when they are moving forward or backward. Yet the insects do not get turned around.

Foster suspected that the beetles kept track of subtle differences in light intensity between one end of the Milky Way and the other. When he analyzed photographs of the galaxy taken from the beetles' South African habitat, he found that the intensity of light from the northern and southern ends of the Milky Way indeed differed by at least 13 percent and some-

FROM "THE REMARKABLE VISUAL CAPACITIES OF NOCTURNAL INSECTS: VISION AT THE LIMITS WITH SMALL EYES AND TINY BRAINS," BY ERIC J. WARRANT, IN *PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B*, VOL. 372; APRIL 5, 2017

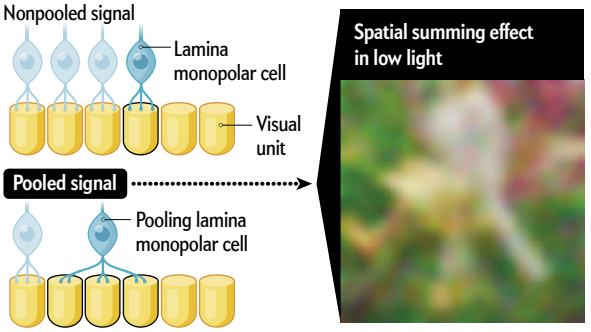
Low-Light Image Improvement

During the day, there is a lot of light for high-acuity vision. But at night, the few available photons rarely stimulate photoreceptor cells and do so only weakly. The result is a grainy, obscure image. Hawkmoths solve this problem by adding up these scarce photons across both space and time.



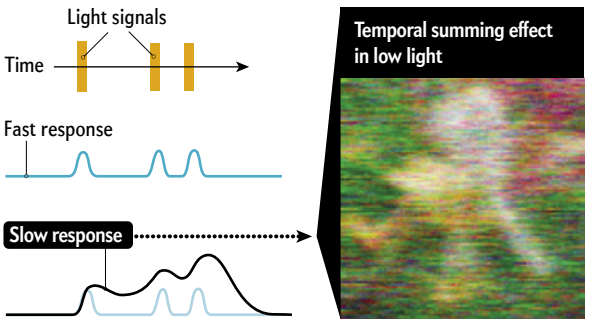
Spatial Summation

In dim light, sparse image signals head from photoreceptors toward visual-processing areas of the brain. But in some insects, in an intermediate region, lamina monopolar cells pool together signals from adjacent spots in the eye. This creates a brighter visual unit, but it loses sharpness because it combines signals from different locations.



Temporal Summation

Photoreceptor cells can slow down the rate at which they pass signals back to the brain at night. Each individual signal, at fast speeds, is too weak to stimulate much of a brain response in visual areas. But by slowing their responses down, the cells let the signals pile on top of one another, creating a stronger stimulus. This also improves brightness, though again with less acuity.



times much more, depending on how he processed the images.

To test this effect on the beetles themselves, Foster built a simplified, artificial Milky Way out of single-file LED lights on an arch over an arena. He could vary the intensity of light on each side. The beetles could go straight if he gave them a 13 percent contrast between one end of the bright line and the other but wavered if the contrast dropped below that. This result indicated the animals should be able to tell the two ends of the real Milky Way apart.

SIGNAL BOOSTERS

IN ADDITION TO BEETLES and bees, a number of other animals are now known to see remarkably well in dark environments: cockroaches, lantern fish, cuttlefish, frogs and nocturnal primates such as owl monkeys. So neuroscientists are turning to the question of how they do it. Bigger eyes collect more light, for example, but do not gather enough photons to explain the highly sensitive night vision that scientists have documented. Other visual processing must take place after the rods have absorbed incoming light. In particular, animals must be able to overcome or filter out visual "noise" created by photoreceptor activity that does not reveal anything useful about the visible world.

Noise in the visual system comes from a few different sources. One, called photon shot noise, happens when only a few photons come into photoreceptors. Because those light packets tend to arrive sporadically, they create a variable, unreliable picture. It's as if you shone three or four flashlights around the ceiling of the Sistine Chapel at night. You would hardly be able to appreciate Michelangelo's complete masterpiece.

A second source of noise arises from the molecular interactions in the photoreceptors themselves. A photoreceptor senses light when an incoming photon hits a molecule called rhodopsin. But every so often—once a minute, at most—a rhodopsin molecule is triggered by accident, or another part of the pathway misfires. This is called dark noise because it can happen even in pitch-black conditions with your eyes closed. A third source, transducer noise, results from variation in the timing and strength of the visual system's response to a single real photon.

Noise isn't a big problem in broad daylight, because the tremendous volume of photons hitting the eyes overwhelms these slight variations. In the dark, however, animals need a strategy to boost the signal to similarly noise-overwhelming levels. They do so by summing up the signals they get from individual photoreceptors across space and time.

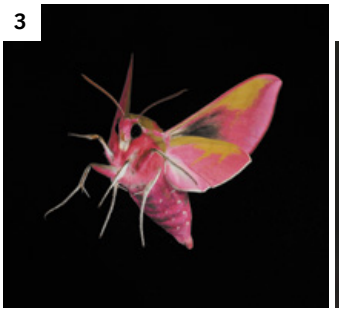
Spatial summation works like this: Imagine you are at a concert where 1,000 fans are waving their illuminated cell phones with excitement. You can't see the light from each individual phone all that well. If every group of 50 concertgoers combined the light of their phones into a single, brighter spotlight, you'd see those 20 spotlights really well. The retina—the sheet of tissue that contains rods and cones—does the same, pooling the input from numerous rods into a single, bigger signal that gets sent to the brain. At the concert, you lose the picture of each individual person waving a phone, and the same thing happens in spatial summation; the resulting image is brighter but also coarser.

Temporal summation also increases brightness. Rods slow

FROM "NEURAL SUMMATION IN THE HAWKMOTH VISUAL SYSTEM EXTENDS THE LIMITS OF VISION IN DIM LIGHT," BY ANNA LISA STÖCKL ET AL., IN *CURRENT BIOLOGY*, VOL. 26, NO. 6; MARCH 21, 2016 (*flower images*)

Graphics by Tami Tolpa

IN DIM LIGHT, sweat bees (*1*) detect detailed patterns, dung beetles (*2*) navigate by starlight, hawkmoths (*3*) blend visual signals to brighten images, and southern pig-tailed macaques (*4*) filter interference from what they see.



their activity down, summing up the input from incoming photons over, say, 100 milliseconds. We experience this effect when we see a shooting star in the night sky. The star is a point at any given moment, but the brain interprets the sight as a line because it is summing those points over a period of time. Again, there's a trade-off. This type of summation makes it easier to detect objects, but it blurs them when they move.

In some insects, spatial and temporal summation happen in parallel, and it occurs in cells farther back toward the brain, according to biologist Anna Stöckl, now at the University of Würzburg in Germany. Stöckl, when she was a graduate student under Warrant, positioned hawkmoths in front of a computer screen showing a pattern of scrolling black-and-white stripes. Then she cut a tiny hole in the back of each moth's head and poked electrodes into its cells. Her goal was to stimulate the photoreceptors with each alternating stripe and compare their activity with that of other nerve cells deeper in the brain, in the optic lobe. This area gets the signal after any processing or summation has occurred, so differences between the unprocessed "input" at the photoreceptor and the "output" in the optic lobe would indicate that the brain altered the visual signal.

Comparing these input and output values, Stöckl calculated that when she transferred moths from light to dark, the size of a "pixel" in their optic lobe quadrupled, showing that they used spatial summation. She also found that moths used temporal summation, slowing their vision in the dark so they added up input over 220 milliseconds. The combination allowed the hawkmoths to see well at light levels 100 times dimmer than when summation was not in use, Stöckl reported in a 2016 paper.

"This hasn't been shown in any other animal apart from hawkmoths, but the principle is so basic that it would be hard to believe it isn't widespread," Warrant says.

Another approach that animals use is to filter out noise, say scientists who have investigated visual noise-canceling methods used by mice and monkeys. While not on a par with hawkmoths, these mammals do reasonably well at night. Researchers have found there are at least two threshold points on a path between their photoreceptors and the brain that allow only strong signals through and reject those likely to be noise. Midway along this path are gatekeepers called rod bipolar cells. These cells, it turns out, are tuned to send the "photon detected" signal onward only if they receive significant input from rods. Several incoming photons at once are strong enough. But single photons, and much of the noise in the system, might not be. A second cellular gate lies deeper in the optic system on this same path. This gate blocks errant signals that are missed by the first one or that arise after that point. The result is nearly noiseless vision, says Petri Ala-Laurila of the University of Helsinki, one of the scientists who identified the process.

FORWARD-LOOKING

DESPITE ALL THIS RESEARCH, Warrant says, scientists are just beginning to understand animals' ability to see in the dark and how they manage to do so. Studies of the genes and light-sensitive molecules that nocturnal animals possess can offer new clues. For example, some night-active lemurs have genes and pigments that indicate their eyes might be sensitive to blue or green, which could help them distinguish blue seeds and green leaves in twilight. And some bats—which, contrary to popular wisdom, are not blind—also possess genes tied to color vision.

Still, having the genes and molecules to detect color does not prove an animal's brain uses that information after twilight. For example, some light-sensitive molecules are involved in maintaining bodily rhythms that have nothing to do with vision. Therefore, scientists still need to perform behavioral experiments, such as those carried out on the hawkmoths and frogs, to show those molecules play a role in night sight. That work may indicate that the molecules are not used in the dark—or it could reveal sight-enhancing tricks researchers have not yet envisioned. SA

MORE TO EXPLORE

Nocturnal Colour Vision—Not as Rare as We Might Think. Almut Kelber and Lina S. V. Roth in *Journal of Experimental Biology*, Vol. 209, No. 5, pages 781–788; March 1, 2006.

Vision in Dim Light. Eric Warrant in *Visual Ecology*. Thomas W. Cronin, Sönke Johnsen, N. Justin Marshall and Eric J. Warrant. Princeton University Press, 2014.

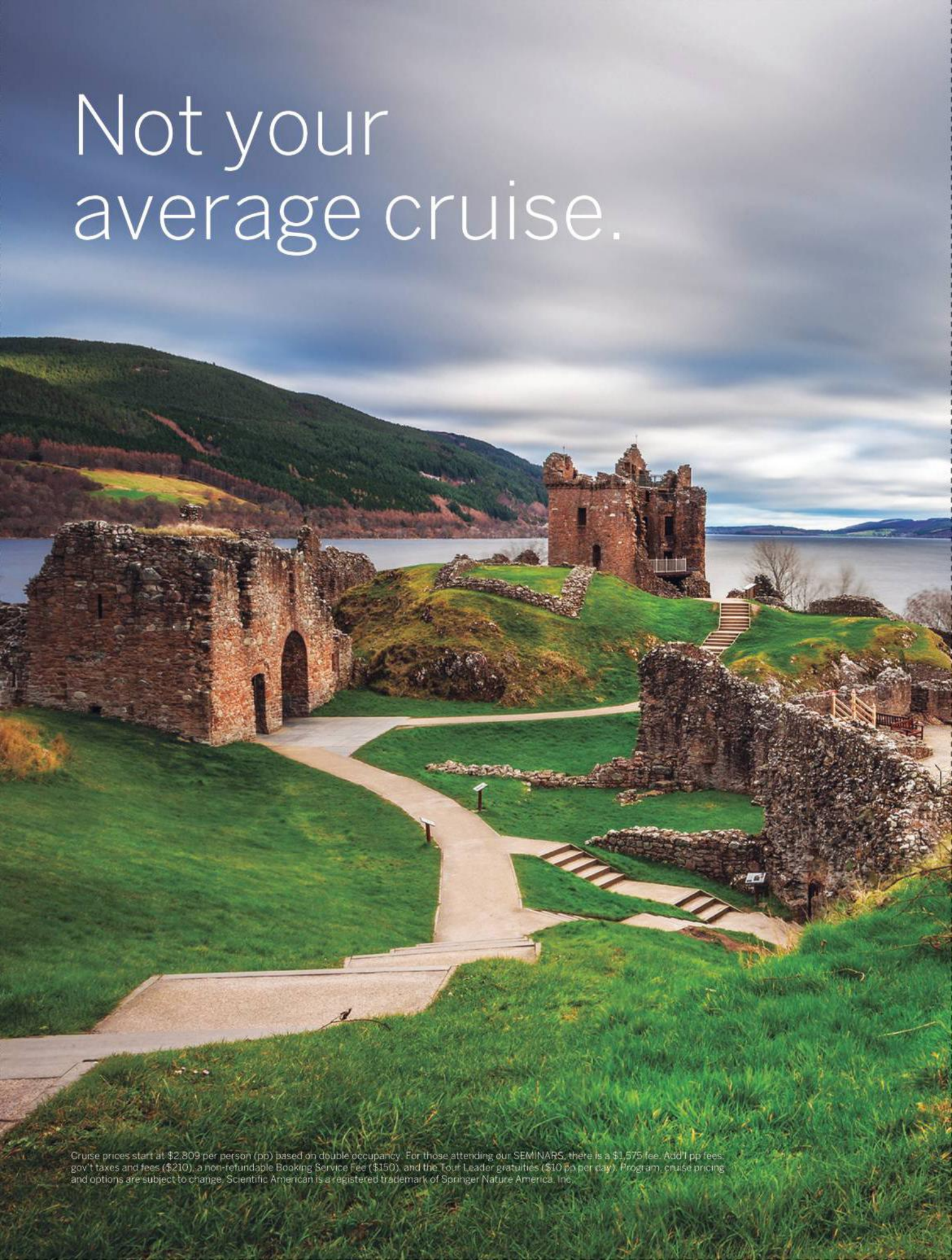
Vision in Dim Light. Compiled and edited by David O'Carroll and Eric Warrant. Theme issue of *Philosophical Transactions of the Royal Society B*, Vol. 372; April 5, 2017.

FROM OUR ARCHIVES

Household Pest Sees the Light. Rachel Nuwer; Advances, March 2015.

scientificamerican.com/magazine/sa

Not your average cruise.



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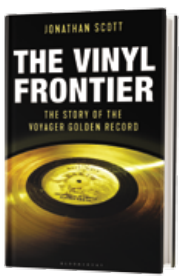
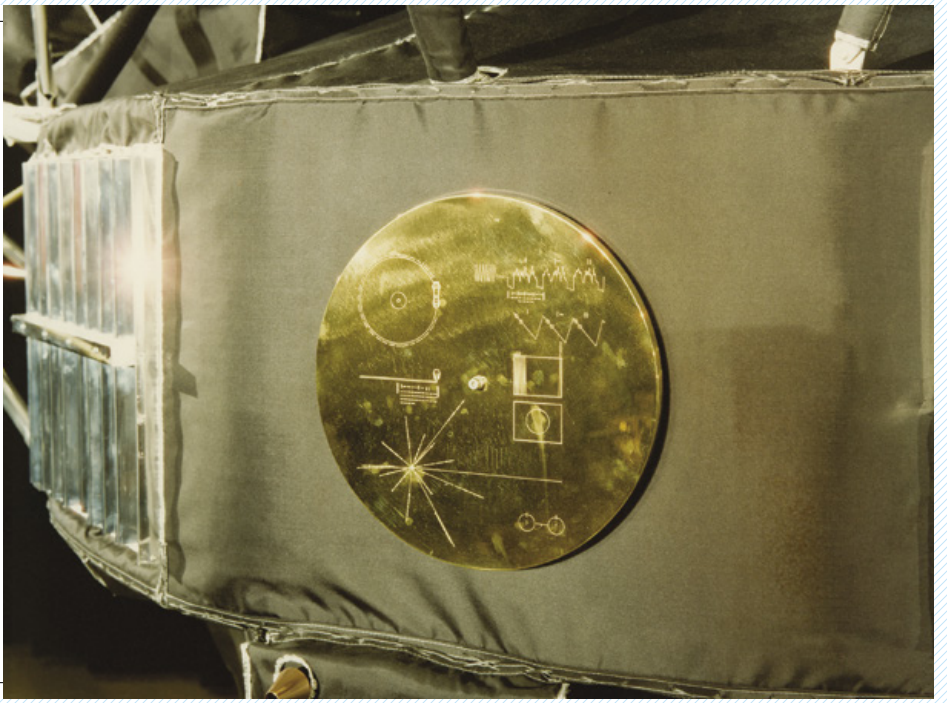
RECOMMENDED

By Andrea Gawrylewski

The Vinyl Frontier: The Story of the Voyager Golden Record

by Jonathan Scott. Bloomsbury Sigma, 2019 ($28)





When the twin Voyager spacecraft blasted off in 1977, each carried a phonograph record containing sounds and images intended to represent life on Earth to any alien civilization that might find them (*pictured above*). In an approachable narrative, music writer Scott tells the story of the astronomers, writers, artists and musicologists who, led by Carl Sagan, compiled the interstellar playlist, which in the end included "Johnny B. Goode," the Brandenburg Concerto No. 2 and whale songs, among many others. With nostalgia, Scott compares the undertaking to his own attempts at recording the perfect mixtape as a teenager. Ultimately the mission was an endeavor for incurable romantics: the music of humanity sent to the cosmos in the hope that somewhere someone might be listening. *—Jim Daley*

Black Death at the Golden Gate: The Race to Save America from the Bubonic Plague

by David K. Randall. W. W. Norton, 2019 ($26.95)

At the start of the 20th century Wong Chut King was living in squalor in a San Francisco flophouse, working at a lumberyard and sending every spare cent he could to his family in China. In February 1900 he developed a painful lump in his groin, followed by a high fever; by March he was dead. He was the first documented case of an outbreak of bubonic plague in the city. Journalist Randall recounts the ensuing drama, as doctors raced to prevent a national epidemic. It is a story steeped in racial tensions and scientific ignorance but also one of discovery: federal health officer Rupert Blue, trying to get a handle on the deadly disease, made invaluable breakthroughs about the pathogen and how to contain it.

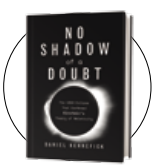
Power Trip: The Story of Energy

by Michael E. Webber. Basic Books, 2019 ($30)

"Energy is magical," writes energy researcher and professor Webber. We cannot see, create or destroy it. But when harnessed, it can help produce all the ingredients for a prosperous society: clean water, abundant food, sufficient light and heat, transportation, medicine and security. In *Power Trip,* energy becomes the central character in the human saga, from waterwheels and wood fires to oil wars and climate change. It is an accomplice in the rise and fall of civilizations and both an oppressor and an ally in issues of social and environmental justice. Expanding access to energy without devastating the planet, Webber writes, will require long-term thinking that addresses its multifaceted links to society. Even in the face of this century's "grand challenge," Webber remains faithful to the transformative power of human ingenuity. *—Frankie Schembri*

No Shadow of a Doubt: The 1919 Eclipse That Confirmed Einstein's Theory of Relativity

by Daniel Kennefick. Princeton University Press, 2019 ($29.95)



In 1915 Albert Einstein put forth his general theory of relativity, a new view of physics that described gravity as the curving of space and time rather than an attraction of two bodies. If proved correct, his ideas would overthrow Newtonian physics, which had reigned for centuries. Physicist Kennefick narrates the buildup to, and fallout from, the experiment that confirmed Einstein's radical idea and made him an international star: to glimpse the light of stars during a total solar eclipse and determine if it is shifted by the sun's mass and gravitation. The day of the eclipse was overcast, but scientists obtained several photographic plates of starlight, which would quickly usher in a new paradigm in physics.

GETTY IMAGES

Zeynep Tufekci is an associate professor at the University of North Carolina School of Information and Library Science and a regular contributor to the *New York Times*. Her book, *Twitter and Tear Gas: The Power and Fragility of Networked Protest*, was published by Yale University Press in 2017.

Quantified Self

People who track their behavior aren't always better off

By Zeynep Tufekci

I was among the many people excited by fitness trackers and purchased one soon after they came out. It was fun. Look, 20,000 steps in one day (trip to a new city)! Two nights this week of uninterrupted sleep and 21 miles walked!

There's something captivating about numbers, which can explain the existence of the quantified-self phenomenon—that is, people who measure many things about themselves. Nowadays a smartwatch or even just your phone can keep track of a wide variety of markers, including heart rate, sleep patterns, steps in a day and even arrhythmias. People who run, swim or bike can measure their pace, distance covered, calories burned or total exercise time. A clip on your lapel can monitor your exposure to the sun. And perhaps warming the heart of every parent who got tired of reminding their children to "stand up straight," you can even wear a device that buzzes you if you slump for more than, say, 15 seconds!

You can even spice it all up with "gamification," setting up daily or weekly goals, and the program will award you badges and play celebratory tunes when you hit them. You can also upload your data to share with others—perhaps in friendly competition. Meanwhile workplace wellness programs that offer incentives or discounts on health insurance to employees who use such tracking devices and meet certain goals are spreading.

Unfortunately, despite some early encouraging studies that suggested that wearers of such devices were healthier than those who were not, the first large-scale experimental study, where people were randomly assigned to wear a fitness tracker, showed no difference in outcomes. Findings are similarly discouraging for workplace wellness programs: early research hopefully suggested that they were effective for lowering health care expenditures. But once again, better-designed studies showed practically no difference in outcomes over time.

What's going on? In fact, probably something very common. Early studies for new treatments or devices tend to be observational: they compare individuals who have chosen to take a specific action (eat a healthy diet; exercise regularly) with those who do not. Yet that engenders confounding biases because of the way people self-select into the groups, a problem that can be resolved only with true randomized experiments.

Should you sport one anyway? One concern is that these tracking devices are … tracking devices. Many also track location, and they've already been invoked in court cases. In one, the unfortunate victim's heart rate spiked significantly and then stopped while the suspect was with her despite his claims he had left before she died. Solving a murder is good, but it's easy to imagine health insurers or employers requiring a certain number of steps a day or using such health data for making decisions.

When I first got my tracker, I tried to hit 10,000 steps a day. It felt gratifying when it catalogued 10-plus-day streaks of meeting my goals. This is called the Hawthorne effect, after experiments in a relay factory outside Chicago, Hawthorne Works, showed productivity increased when the lights were turned up—but also when the lights were turned down. A change, any change, and a feeling of being observed seem to put us on alert and better behavior—but only for a time. The novelty does wear off, and then we return to our baseline behavior.

Still, could it hurt to know the number? Maybe. Employees who were offered financial rewards along with a tracker fared worse after the trial ended and the cash dried up as compared with those who had never been offered incentives. External rewards seem to "crowd out" internal motivations—and once they go away, we don't always get the internal motivation back.

When my wrist tracker broke down after about a year, I just didn't feel like shelling out for another one. Anyway, even by the end of the third month, I could pretty reliably guess my steps or hours of sleep for the day without checking the app. Instead I took inspiration from people who argue that exercise is also about the right ecology—individuals in walkable cities get a lot more than those in suburbia, for example. So I now have a treadmill desk at work, and I set things up at home so that almost all my TV viewing is done on an elliptical. And honestly, I get cranky if I don't get some movement in during the day. That seems to be the best motivation to keep turning those pedals. SA

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Illustration by Thomas Fuchs

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 36 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Et Tu, Fido?

Even man's most loyal companion can't be trusted around guns

By Steve Mirsky

In this space back in February 2012, I addressed the issue of hunters being shot by their dogs. These rare cases of canine culpability inevitably result from a stray paw, or a stray's paw, happening onto the trigger of an unsecured firearm. The dogs may be wearing one, but the police don't get a collar, because the incidents are accidents. Well, they're probably accidents—some dogs can be cagey. (Okay, I admit that writing those shameless sentences really hit the Spot.)

Anyway, recent events inspired me to revisit this dog-shoots-man topic, which of course is a fascinating variation on the man-bites-dog story.

In February the online British newspaper the *Independent* ran a story with a headline that started out goofy—"Man Shot by His Pet Dog …"—but then turned sensibly serious—"… Is Ruled Unfit to Own Guns." The tale begins in 2016, when a German man got a shot in the arm—and not in a good way—when his supposed best friend, according to the article, "managed to release the trigger on a loaded rifle left in his car." Oddly enough, dogs and firearms both have muzzles, which in this case, was at least one too many.

The victim, described as a "passionate hunter," then had his rifle license and hunting permit revoked. He appealed that decision, which a court has just recently decided not to roll over. The news article quotes the ruling's reasoning, which is as follows: "it must be assumed that he will handle firearms and ammunition carelessly in the future as well." Bull's-eye.

By the way, in a subversive act of dogmatic commentary, the *New York Daily News* illustrated its coverage of this story with a photograph of a happy, healthy deer: buck unshot. Which, after posing for the camera, presumably wandered away into the woods, stag.

(The *Daily News* also reported that the initial revocation of the man's credentials was made by the municipality of Pfaffenhofen. Which is a fun word to say but is also intriguing because, according to Google Translate, *Affen Hof* means "monkey court" in English. And depending on the firearm's visual-aid accoutrement, we could have had a Scopes trial.)

Back in the U.S.A., in November 2018 a man in New Mexico joined his brother from another fatherland. Again, the *Independent* was on the case. "Man Shot by Pet Dog …," the headline began before turning even more surreal, "… Insists 'He [the dog] Didn't Mean to Do It.'" And I believe that. Because the dog was a 120-pound Rottweiler mix and therefore didn't need any help to inflict damage. Although a gun still makes it easier.

The seriously injured man was in his pickup truck with the shooter and the gun that he left "positioned in the truck with the barrel facing up, towards [the man]," according to a sheriff's spokesperson quoted in the piece.

I'm sincerely happy to say that the man, who reportedly suffered "three broken ribs, a punctured lung and a broken scapula," survived. And I'm sincerely sad to say that as this piece went to the printer, the Associated Press reported that the dog had died—shot by a rancher after it escaped from its owner's property. As has been said many times, we don't deserve dogs.

The actual good news on shooting accidents, whatever species pulls the trigger, is that deaths caused by them in the U.S. are down. The *Los Angeles Times* reports that in 2015, the most recent year with available data, "there were 489 people killed in unintentional shootings..., down from 824 deaths in 1999," according to the Centers for Disease Control and Prevention. "Experts attribute the decline to a mix of gun safety education programs, state laws regulating gun storage in homes and a drop in the number of households that have guns," the article says.

So to anyone who thinks such measures won't make us all safer: that dog won't hunt. SA

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Illustration by Matt Collins

50, 100 & 150 YEARS AGO

INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Daniel C. Schlenoff

MAY

1969 Lead Poisoning Epidemic

"Though lead pigments were eliminated from interior paints in the U.S. some 20 years ago, multiple layers of lead-based paint still cover the walls and woodwork in many old houses and apartments. Therefore lead poisoning, once an occupational hazard for painters, is now primarily a disease of small children: toddlers between one and five who live in slum housing and nibble steadily at the paint that flakes off dilapidated walls and can be gnawed off peeling windowsills. At a conference at Rockefeller University in March, participants estimated that lead poisoning in children is much more prevalent than is generally assumed, but they pointed out that the 'silent epidemic' could be eliminated by aggressive medical, social and legal action."

Wartime Silver

"More than 2,100 tons of silver worth $124 million have been removed from the electromagnetic separation plant at Oak Ridge, Tenn., and returned to the Department of the Treasury. The silver was part of nearly 15,000 tons lent to the Manhattan project in 1942 to be converted into windings for the huge magnets that were part of the 'calutrons' used to separate fissionable uranium 235 from nonfissionable uranium 238. The process was beset by many technical difficulties but helped to produce the highly purified U-235 in the atomic bomb that destroyed Hiroshima. The silver, then worth more than $400 million, was used as a substitute for copper, then in short supply."

1919 Sex and Intersex

"The elaborate investigations of sex phenomena in various plants and animals made by Dr. Arthur Mangun Banta, under the auspices of the Carnegie Institution, lead that biologist to some interesting ideas. 'We are coming,' he says, 'to the time when it would seem imperative to revise our ideas of the fixity of sex, with the relativity of sex so emphatically shown in hybrid pigeons, in hybrid moths, and in different species of Cladocera [water flea].' He cites the phenomena of the 'crowing hen' and the 'sitting cock,' the masculine woman and the effeminate man, as merely conspicuous examples of sex intergrades, which refute the common conception of maleness and femaleness as complete, opposed and mutually exclusive phenomena."

Worst Airplane Ever

"With the death of Aviator Jolly a few weeks ago, the Christmas 'Bullet,' or 'strutless biplane,' has two victims as its record to date. The day following the accident which resulted in the death of Jolly, the writer of these notes happened to be at one of the flying fields on Long Island, where the unfortunate airman was well known and liked. Feeling was running rather high among the airmen and mechanics, who criticized the design of the William W. Christmas cantilever plane. They pointed to the previous collapse of the 'Bullet.' Jolly, so it seems, met with the same kind of fate; in midair one of the wings broke off and he was hurled to earth. They were agreed, that this is a rather late day to experiment with uncertain designs."

1969

1919

1869

1869 Infant Walking Gear

"The device herewith represented is intended to aid infants learning to walk, to prevent them from getting into danger and receiving hurts, and to relieve the mother, nurse, or attendant, from constant care and anxiety. Around the infant's body is secured a cushioned ring made to open on a hinge and properly fastened. The base is supported on easily-working casters that allow the contrivance to turn or move in any direction over the floor. Patented through the Scientific American Patent Agency, June 12, 1866, by P. Pallissard, who may be addressed at Kankakee City, Ill." *Such walkers have since been proved to increase the probability of injury and may delay a child's ability to walk.*

1869: Baby walkers have always seemed like such a great idea. But they're not.

Buffalo vs. Telegraph Pole

"The buffaloes found in the telegraph poles of the overland line a new source of delight on the treeless prairie—the novelty of having something to scratch against. But it was expensive scratching for the telegraph company, for the bison shook down miles of wire daily. A bright idea struck somebody to send to St. Louis and Chicago for all the brad-awls that could be purchased, and these were driven into the poles, with a view to wound the animals and check their rubbing propensity. Never was a greater mistake. The buffaloes were delighted. For the first time they came to the scratch sure of a sensation in their thick hides that thrilled them from horn to tail, until the brad-awl broke or pole came down."

SCIENTIFIC AMERICAN, VOL. XX, NO. 19; MAY 8, 1869

Text by Mark Fischetti | Graphic by Pitch Interactive

Silencing Science

A tracker reveals more than 300 government attempts to suppress knowledge

Journalists and whistle-blowers have exposed some alarming moves by federal and state governments to restrict science research, education or communication. But the Silencing Science Tracker, updated continuously online, shows just how pervasive the attempts have been since the 2016 U.S. national elections. Tactics run the gamut from censorship and funding cuts to destroying data, twisting studies and removing scientists from advisory boards (*main graphic*).

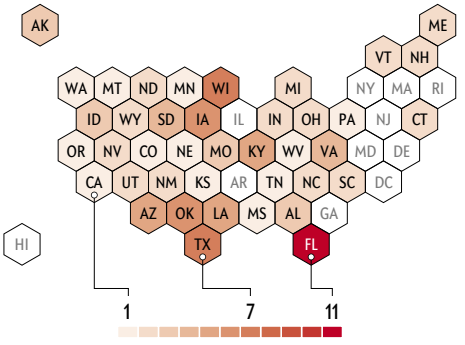
Some deeds have been "really outrageous," says Romany Webb, a senior fellow at Columbia Law School, who runs the site. Actions by states have been rising recently (*map*), especially to manipulate education. "It's concerning to imagine a generation of schoolkids not learning basic principles such as climate change and evolution," Webb says. But she thinks committee leaders now in the House of Representatives are ready to push back on federal abuses, which she finds "very encouraging."

Attempts to malign science fall into several categories. Certain actions involve more than one category (*multicolored dots*); for example, the U.S. Department of Agriculture prevented government scientists from presenting work at a key conference (censorship), which also limited collaboration at the meeting (research hindrance). Entries are culled from media reports, as of February 20, 2019. The tracker* notes when a case is later rectified—a rarity.

Gray indicates climate cases

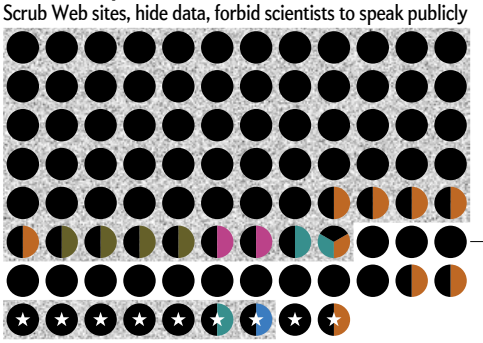
★ Star indicates state or local action

State and Local Incidents (112)



Government Actions

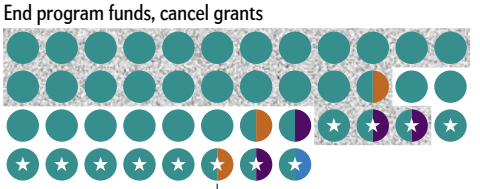
Censorship
Scrub Web sites, hide data, forbid scientists to speak publicly



Impede study on formaldehyde health hazards

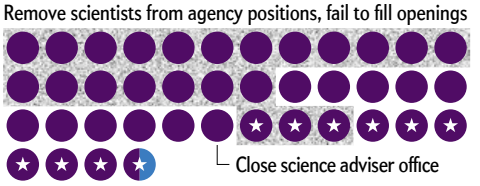
Bias and Misrepresentation
Discount studies in policy making, mischaracterize papers

Budget Cuts
End program funds, cancel grants



Deactivate water-level gauges

Personnel Changes
Remove scientists from agency positions, fail to fill openings



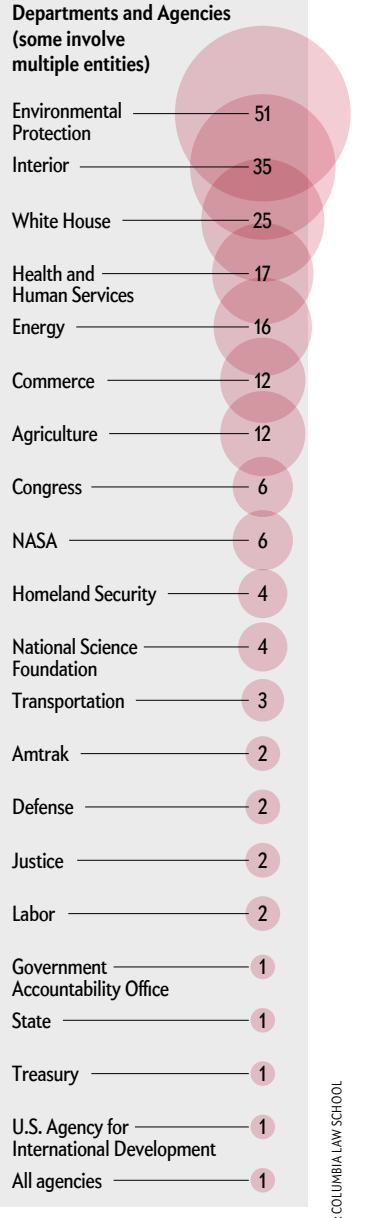
Close science adviser office

Interference with Education
Limit teaching of theories, prevent use of materials

Research Hindrance
Destroy data, prevent publication, pressure researchers to alter findings

Self-Censorship
Voluntarily suppress or distort information

Incidents (195) at Federal Departments and Agencies (some involve multiple entities)



*http://columbiaclimatelaw.com/resources/silencing-science-tracker

SOURCE: COLUMBIA LAW SCHOOL

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