SCIENTIFIC AMERICAN
Health & Medicine

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April-May 2019

# The Next Chemical Crisis

Fluorochemicals are showing up in rivers, soils, and blood samples.

How worried should we be?

WITH COVERAGE FROM nature

*Plus:*

WANT TO RELAX? TRY BREATHING

AN ECONOMIC CRISIS MAY BE GOOD FOR YOUR HEALTH

A NEW APPROACH IN FIGHTING LYME DISEASE

LIZ TORMES

# A Chemical World

More than 10 years ago a troubling report emerged from the National Toxicology Program laying out concerns about the chemical bisphenol A (BPA) based on a disparate collection of data gathered thus far. BPA, a synthetic chemical used in the linings of food cans and in plastic bottles of all kinds (even baby bottles), had been shown to have ill effects on the brain, especially in developing fetuses and young children. Although the data were not ironclad, the public response was fierce. Consumer groups lobbied hard and pressured manufacturers to swiftly remove the chemical from their products. By 2011 both Canada and the U.K. had banned the compound, and the U.S. followed suit a year later.

Now another group of chemicals is moving into the spotlight. A class of fluorochemicals, abbreviated PFOAs, is found in hundreds of everyday products, from waterproof jackets to food wrappings to cookware. And now the compounds are showing up in human blood samples. Because these chemicals don't easily degrade, scientists are trying to get a handle on how worrisome the latest discoveries are. XiaoZhi Lim investigates in "The Fluorine Detectives."

If you find this news a bit stressful, take a few deep and intentional breaths. As Christophe André writes, ancient breathing techniques and modern science are coming together to help people manage their anxiety and moods (see "Proper Breathing Brings Better Health"). Elsewhere in this issue David Adam reports on a surprising drug that is emerging to treat a rare genetic disease–the medicine got its start as a weed killer (see "A Father's Fight"). For some, this particular chemical might be the cure they've been waiting for.

As always, enjoy!

**Andrea Gawrylewski**
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Health & Medicine

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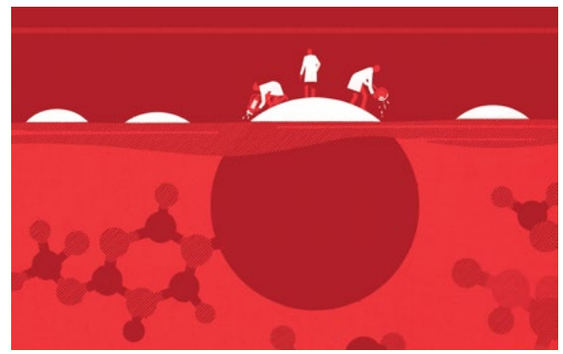

ILLUSTRATION BY CHRIS GASH

***On the Cover***

A type of chemicals called fluorochemicals is showing up in rivers, soils, and blood samples around the world.

How worried should we be?

# WHAT'S INSIDE

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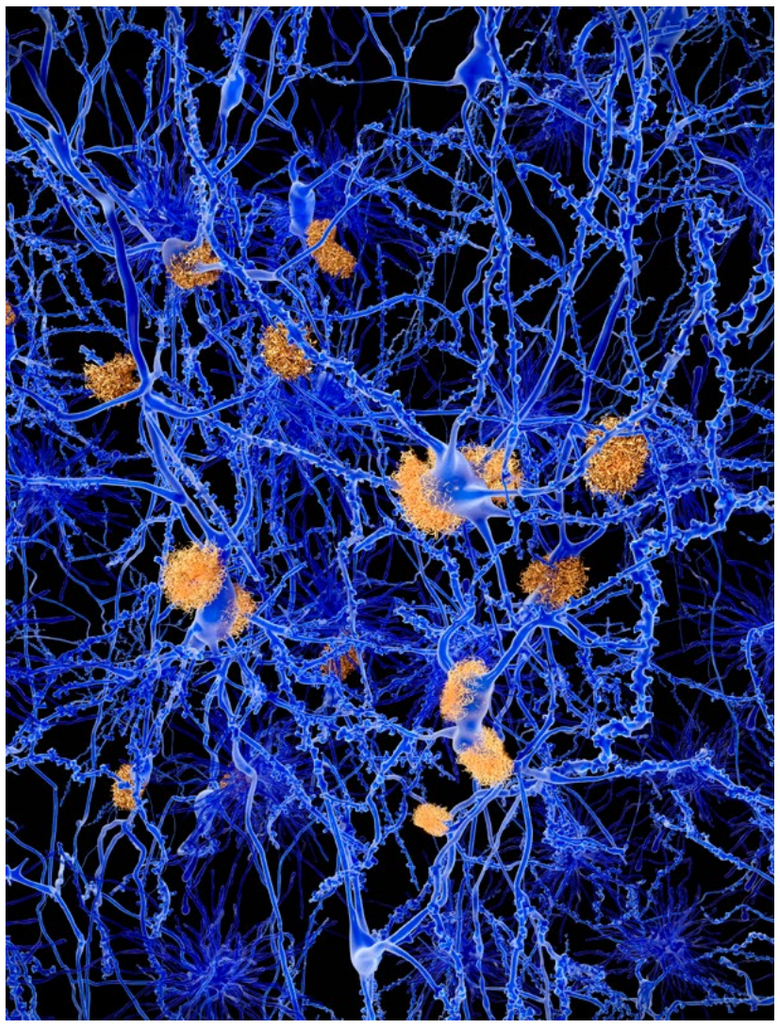
ED RESCHKE *GETTY IMAGES*

## NEWS





JUAN GAERTNER *GETTY IMAGES*



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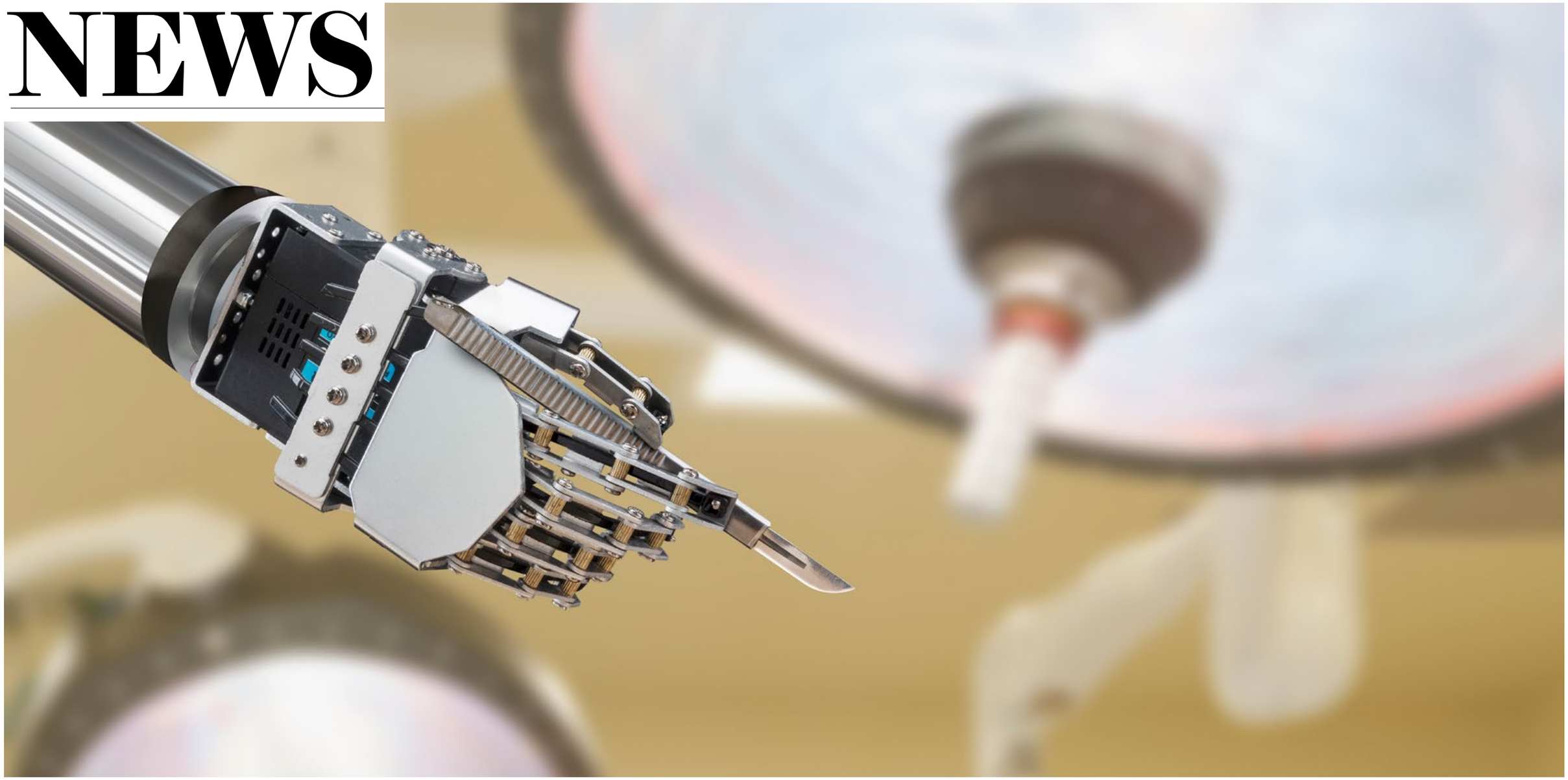
## FEATURES



## OPINION



JOHN LUND *GETTY IMAGES*

## The Surgical Singularity Is Approaching

**AI-powered robots may soon be doing some procedures faster, more accurately and with fewer complications than humans**

THOSE KEEPING ABREAST OF the latest medical developments may be aware of the buzz surrounding applications of artificial intelligence (AI) to medical tasks. To date, these have mainly involved application of computer algorithms to clinical data such as x-rays, images or text-based medical records to diagnose disease. The sensationalism has largely arisen due to the fact that in some instances, these algorithms have met or exceeded capabilities of a specialist physician for particular diagnostic tasks.

With these early accomplishments, a question arises as to how the introduction of clinically viable AI may affect the role of human physicians in the future. Being at a primitive stage and lacking widespread real-world application, the topic remains speculative at present. Much of the debate, however, concerns the effect of AI upon noninterventionalists,* whose primary role is to diagnose and treat diseases noninvasively. An interventionalist (i.e., a surgeon) may therefore wonder how the "AI revolution" may affect him or her; after all, an

algorithm cannot perform a heart bypass or remove a brain tumor.

In 2016, the Smart Tissue Anastomosis Robot (STAR), an autonomous surgical robot, underwent experimental trials in animals. The robot, which utilized "smart sensing" apparatus such as cameras and mechanical sensors, along with AI-control algorithms, outperformed human surgeons at certain tasks, including joining intestine in a living animal *without direct human intervention*.

This was not the first time that AI-controlled robots have experimentally outperformed humans at single surgical tasks such as knot-tying. The closest things to commercially available "autonomous" surgical robots are devices that use external radiation beams to treat cancers (not in direct contact with human tissue) or those offering reduced human input for tasks involving rigid, fixed tissues (i.e., bones) for joint replacements.

A mammal's abdomen is soft, deformable, delicate and contains blood vessels and organs at great risk of damage during surgery. STAR had to perform multiple real-time tasks simultaneously, while minimizing risk of collateral damage: "seeing" the environment which it was working in, "sensing" the features of the tissue upon which it was operating and "reacting" to environmental changes as they occurred, effectively mimicking human surgeons' "judgment" in addition to their physical skill.

In their *Science Translational Medicine* paper, the authors noted: "The intent of this demonstration of feasibility in soft tissue surgery was not to replace surgeons but to expand human capacity and capability through enhanced vision, dexterity, and complementary machine intelligence for improved surgical outcomes, safety and patient access."

Surgical robots have existed for over 30 years and have become widely used by certain specialties because of their technical benefits, which augment human capabilities. These include fatigue resistance, increased range of motion and resistance to shaking. Commercial surgical robot designs utilize a "master-and-slave" arrangement; a human surgeon (master) controls the robot (slave), situated near the patient and a few feet away from the operator, in real time. The technical benefits of using surgical robots have translated into improved outcomes and reduced complications for certain procedures such as prostate surgery.

At present, the costs of purchasing ($1 million to $2.5 million) and maintaining robotic surgical devices are cited as a barrier to their widespread use. Robotic surgical procedures are often more expensive than traditional ones, given the specialized equipment required for the robot. Institutions purchasing these devices must maintain a high volume of cases to recover outlays. Nevertheless, because of the technical advantages of such systems, which include a lower complication rate and better removal of diseased tissue, studies have demonstrated a reduction in overall costs to health care systems for robotic surgery for certain diseases such as prostate cancer.

It is therefore reasonable to predict an evolving symbiosis between the benefits already demonstrated by surgical robots, with the nascent advantages of medical AI. Given further development, we may soon see autonomous surgical robots with capacity to perform complex soft-tissue surgical procedures faster, more accurately and with fewer complications than human surgeons.

If these devices are tested by trial in humans, and the advantages are confirmed, it is also not unreasonable to envision a scenario where continuous technological refinement driven by clinical demand leads to drastic cost reductions for purchasing autonomous surgical devices.

A phenomenon where technological advancement produces real-life cost reductions was described by Gordon Moore of Fairchild Semiconductor and Intel in the 1960s: With advances in semiconductor technology, Moore predicted that the number of transistors held per square inch of circuit board would double every two years. A medically related example of Moore's Law is provided by the Human Genome Project: In 2001, the cost to sequence a single genome was U.S. $100 million.

With improving sequencing technology, costs began to drop in line with Moore's Law until 2008. That year, "next-generation" sequencing technology was introduced, resulting in cost decreases betraying Moore's Law. Sequencing the cost per genome plummeted to U.S. $1,000, or 1/100,000 of its

initial cost by 2017. In 2018, companies such as 23andme offer personalized genome sequencing kits over the internet for under U.S. $100.

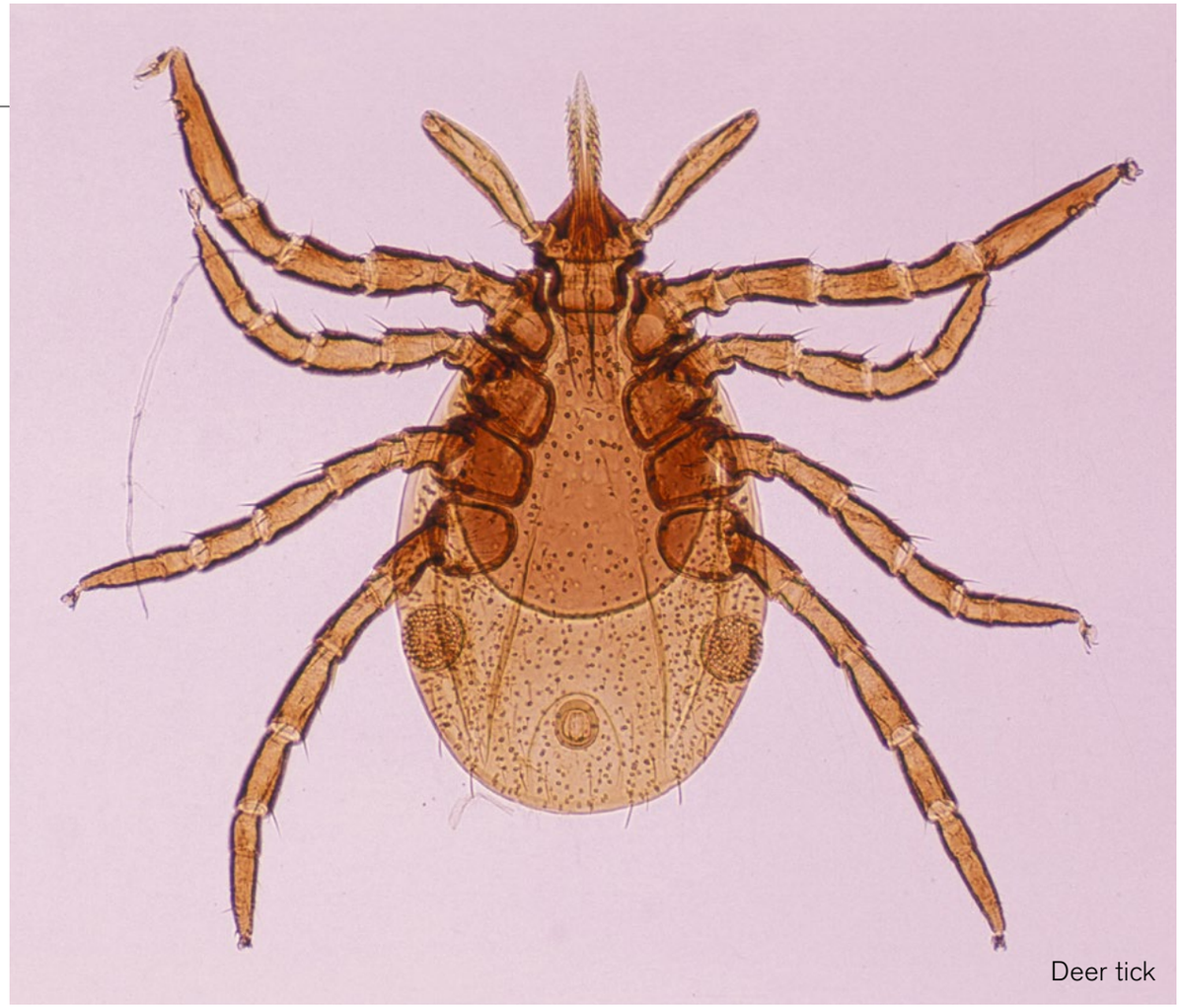
Technological refinement and cost reductions may therefore enable widespread adoption of autonomous surgical robots. A "technological singularity" is a hypothesis that the invention of an artificial superintelligence will result in exponential technological growth, producing unfathomable changes to human civilization. As clinically capable, AI-controlled surgical robots may soon offer technical and economic advantages over human surgeons, a "surgical singularity" may therefore occur when capable, cheap and technically superior autonomous robots are introduced.

It is possible that these devices will transform the technical practice of surgery by enabling optimized removal of diseased tissues, faster operative times and better access to hard-to-reach body areas. These technical benefits will translate into improved survival and fewer complications for patients.

Debate regarding the future role of AI in health care should therefore be extended to include AI-enhanced interventional devices. The issue of how these devices will affect the role of surgeons should be considered and incorporated into any future operating frameworks. An ideal outcome is the augmentation of human surgical capability using AI and robotics, resulting in significantly improved patient care. Aside from encouraging the technical development of these devices, further work should be done regarding the potential impact in terms of workload, regulatory frameworks and the ethical and insurance implications that these devices may have upon surgical practice.

** Physicians can roughly be categorized as noninterventionalists or interventionalists: Noninterventional specialties include diagnostic radiology, pathology, oncology, psychiatry and neurology, among many others concerned with the diagnosis and/or pharmaceutical treatment of medical conditions. Interventionalists are surgeons whose task is the physical removal of pathology, or reconstruction of tissues via cutting and suturing, underpinned by their manual dexterity.*

*–Sandip S. Panesar*



Deer tick

ED RESCHKE *GETTY IMAGES*

## Vaccinating Mice May Finally Slow Lyme Disease

**Killing ticks and inoculating people have failed, so researchers try immunizing mice via vaccine-laced food**

KIRBY STAFFORD, Connecticut's state entomologist, knows only one surefire way to reduce tick populations enough to cut Lyme disease rates: killing deer. Otherwise, he says, "very little by itself really reduces tick numbers enough."

But in some Connecticut neighborhoods Stafford has been testing a new strategy, one he hopes might show real promise after years of stymied efforts to drive new Lyme infections down: a vaccine for mice.

Roughly half of ticks carrying *Borrelia burgdorferi*, the bacterium that causes Lyme disease, pick it up by biting infected white-footed mice.

That makes these fist-size fuzz balls the most important carriers of the bacteria and a prime target for a Lyme vaccine, Stafford says. In theory, vaccinating enough mice should lower the number of ticks that acquire *Borrelia* in the first place. And fewer infected ticks means fewer infected bites on humans.

The U.S. Centers for Disease Control and Prevention learns of roughly 30,000 cases of Lyme disease each year, but not every diagnosis gets reported to the CDC, and the actual number of new infections is likely over 40,000. That makes Lyme the most common disease transmitted by ticks, mosquitoes or fleas in the U.S. If untreated, it can go from rashes, swelling and joint pain to brain damage, weakened muscles and numbness that, in rare cases, can sometimes linger or recur for years.

Researchers began looking into wildlife vaccines for the disease shortly after problems developed with a human Lyme vaccine, says Maria Gomes-Solecki, an immunologist at the University of Tennessee and the creator of the mouse vaccine Stafford is testing in Connecticut. The human version, brand-named LYMErix, came onto the market in 1998 and was effective in adults after three doses. But it quickly became controversial as lawsuits emerged alleging it caused severe joint inflammation, along with other Lyme symptoms it was supposed to prevent.

Gomes-Solecki claims those allegations were never supported by statistical evidence but were "blown out of proportion" and stoked by antivaccine sentiment. "There are many reasons why vaccines are pulled from the market," she says. "I don't think these reasons were scientifically justified [in this case]." Still, the concerns halted sales enough that SmithKline Beecham (now GlaxoSmithKline) pulled the vaccine off the market four years after its introduction.

Gomes-Solecki and other immunologists began searching for new Lyme vaccines for humans, but she says nothing worked as well as the original. LYMErix is based on a protein called outer surface protein A (OspA), found on the surface of *Borrelia* bacteria. The vaccine trains the immune system to recognize that protein and manufacture defenses against anything carrying it. And when a tick slurps up blood from a vaccinated individual, those defenses also destroy any *Borrelia* inside the tick—preventing it from infecting a new host.

Gomes-Solecki—who was a veterinarian before becoming an immunologist—says she found the science around Lyme disease fascinating, and emigrated from Portugal to the U.S. to study it. "With my background being veterinary medicine, I started thinking, 'If we can't use [the vaccine] in humans, maybe we can target the animals that cause the illness,'" she says.

That hunch got its first real test in 2004 when a team of Yale University scientists (of which Gomes-Solecki was not a part) tested an OspA vaccine, designed for mice, on the rodents. It proved effective against *Borrelia* infection and in clearing the bacteria from ticks that bit an immunized mouse—but it was impractical. "Part of the problem with previous methods is they would capture wildlife and do injections," says Joyce Sakamoto, a tick biologist at the Pennsylvania State University who is not involved with Gomes-Solecki's research. "It's incredibly laborious. Animals sometimes die in traps; that doesn't help. Injections are very difficult." In short, no one could ever vaccinate enough mice to make a dent in the Lyme epidemic using needles, Sakamoto says.

So Gomes-Solecki came up with something that could be broadcast into the environment like seeds: kibble that contains an oral vaccine but would be tasty to white-footed mice. "It's our secret sauce, if you will," says Mason Kauffman, a spokesperson with US BIOLOGIC, the company that Gomes-Solecki helped found to manufacture the mouse Lyme vaccine. The company designed the vaccine with layers "like a peanut M&M," Kauffman says. In this case the "peanut" is a gray pet food pellet animal food maker Purina Mills custom manufactured for the vaccine. "The 'chocolate coating' around the peanut is the vaccine, then the 'candy coating' … is a coating that protects the vaccine from stomach acids," Kauffman says. The vaccine enters the bloodstream through the animal's intestines.

The vaccine should erode Lyme disease's pervasiveness steadily each year it is deployed, Gomes-Solecki says. Black-legged ticks only eat twice in their lives. Their first blood meal comes when they are larvae and

feed exclusively on small animals like mice, shrews or birds. They pick up *Borrelia* if they bite an infected host, so the key is to immunize mice before black-legged larvae bite them. The next year, when the larvae have grown into nymphs and are looking for a second meal—either from small animals or larger ones such as humans or deer—fewer of them should carry Lyme.

Gomes-Solecki tested the kibble vaccine from 2007 to 2011 using seven fields, each roughly the size of a football field. In each one she set box traps so she could capture and study the local mice. She put the vaccine inside the traps in four of those fields. After five years the prevalence of infected ticks in some of the fields had dropped by 76 percent, but had risen by 94 percent in the fields without the vaccine. "[The results] were massive. If we could see that in deployment, it would be incredible," she says. "I thought, 'Yes, maybe—maybe this could work.'" It was a moment that paid off in a literal sense, she adds. The study had overextended its funding, leaving insufficient funds for the last year of experiments. "To finish the last plot, I [had] put in $20,000 of my own money," she says.

The results, published in 2014, are "encouraging but also a bit puzzling," says Marm Kilpatrick, a disease ecologist at the University of California, Santa Cruz, who has not worked on the vaccine. "You should see this steady decline from year to year," he says. "The slight challenge of that is the data don't completely support that going on." Data from two fields where Gomes-Solecki's team used the vaccine show a gradual fall in infected ticks, Kilpatrick notes, but data from a different vaccinated field showed no effect from the vaccine until the third year of the experiment. "It falls to 13 or 14 percent [from 55 percent], which is awesome and fantastic," he adds. But those fluctuations give him pause because unvaccinated fields in Gomes-Solecki's experiment also showed significant variations from year to year. Therefore, "you better be very careful when interpreting fluctuations on your treated plots," Kilpatrick says.

On the other hand, Gomes-Solecki says when averaging all fields that had the vaccine together, a sustainable decline in Lyme prevalence was evident. The fields without the vaccine only saw more Lyme appear during the study period.

In any case, Kilpatrick is optimistic about the vaccine's future for two reasons: First, if the kibble is placed in open containers rather than traps, more mice might be willing to eat it. A true deployment of the vaccine would also cover more ground, he says, whereas this study might have been tainted by rogue mice traveling in and out of Gomes-Solecki's small plots. "I think this study design represents the lower estimate of [the vaccine's] efficacy," Kilpatrick adds.

That idea seems to be on the right track, according to study results from Stafford—the Connecticut entomologist—who has been testing the vaccine on a larger scale. When Stafford deployed the kibble across the lawns of 22 homes in Redding, Conn., he says the researchers were able to show over 90 percent of mice were eating it. The final results from that study, to be published later this year, are promising but not magical, he notes. "I think [the vaccine] will be a valuable tool in the tick management box," he says. Using it in areas where Lyme prevalence is extreme—including his home area in suburban Connecticut—could yield a lot of bang for the buck, he says.

There are likely two things standing in the way of the kibble vaccine becoming an ultimate solution for Lyme disease, Kilpatrick says. The first is scientific: The vaccine targets white-footed mice—but shrews, chipmunks and birds also carry Lyme bacteria and can transfer them to ticks as well.

The second reason, Kilpatrick says, is social: "For reasons that are not clear, mosquito control is usually done by county or state health departments, where tick control is not," he notes. "The result of that is it's beholden upon you and I, as the lay public, to do our own control of ticks." He adds there are known ways to manage the arachnids, including the use of fipronil bait (a tick-killing agent commonly known by the brand name Frontline). "The reason why we don't do it is because people are scared or lazy or both—and then it just doesn't get done." Even if the mouse vaccine works spectacularly, Kilpatrick says, it will hardly make a difference unless there is a concerted effort to deploy it.

*—Angus Chen*

# A Novel Way to Fight Drug-Resistant Bacteria

**Host-directed therapy can boost a patient's immune response instead of relying only on antibiotics**

IT WAS THE MORNING of September 3, 1928. After a two-week vacation, Alexander Fleming had just returned to his lab at the St. Mary's Hospital in London. He started to sort through petri dishes containing colonies of bacteria. While doing this, Fleming noticed something unusual in one petri dish, which had mistakenly been left open for the entire time.

He saw a growth of blue-green mold—but the area immediately surrounding the mold was clear of bacteria. Based on this observation, Fleming concluded that the mold secreted a substance, which he later called penicillin, that inhibited or killed the microorganisms. This serendipitous discovery changed the history of modern medicine. Penicillin would go on to save the lives of millions of patients infected with deadly bacteria.

As a bacteriologist, however, Fleming knew that evolution is an unavoidable process, and that bacteria would ultimately become resistant to the antibiotic. His prediction was correct—the first penicillin-resistant pathogen was detected in 1940.

Since then, many other antibacterial drugs (both natural and semisynthetic) have been introduced; however, within a few years of their clinical use, pathogens resistant to those drugs emerged as well.

The recent emergence of a carbapenem-resistant pathogen is the most worrying of all, because this drug is the last known line of defense against microbes that are resistant to multiple antibiotics. This is a growing concern worldwide. In the United States alone, according to the Centers for Disease Control and Prevention, drug-resistant bacterial infections kill more than 23,000 people every year and cost the country annually at least $20 billion in addition to direct health care expenses.

Unfortunately, there is a severe shortage of new antibacterial drugs in the development pipeline, and most of the those that are currently in use


The original petri dish in which Alexander Fleming discovered penicillin in 1928.

GETTY IMAGES

are modifications of existing classes of drugs. This poses great challenges to physicians treating severe infections, and has led to the fear of the arrival of a postantibiotic era.

But recent advancement in the understanding of host-pathogen relationships has given scientists insights into an alternative approach called host-directed therapy (HDT), a suite of treatments whose goal is to enhance the host's own immune response rather than relying exclusively on antibacterial drugs.

Some promising examples of HDT include commonly used drugs for noninfectious diseases: verapamil and metformin, for example, which modulate inflammation and increase host antimicrobial response to pathogens; cytokines, a group of proteins that include interleukins, that induce host pro-inflammatory cell signaling to kill pathogens; and nutritional products such as vitamin D3, which augments the host's cellular defenses.

HDT also aims to balance host reactivity at the site of infection by reducing or preventing an excessive inflammatory response, which can damage internal organs and can even kill. This is achieved through cellular therapy, in which a specific population of bone marrow cells is injected in a host's body, reducing and preventing tissue.

My current research focuses on understanding the role of host factors in the host's defense against bacterial infections. It also involves exploring how host factors contribute to fine-tuning inflammation. To investigate this, I am looking at the effect of host factors on genes that produce cytokines. Also, as iron plays an important role in pathogen growth and inflammation, I am looking at the effect of host factors on genes that regulate iron transport and metabolism.

Fully understanding how these factors contribute to host defense and inflammation control will be extremely useful in personalized medicine, where patients' genetic traits can guide the treatment for infections. I believe that subtle differences, called polymorphisms, in the DNA of host factor genes could explain why some individuals are more susceptible to pathogens than others. By identifying these polymorphisms in humans and linking each one with the patient's level of pathogen susceptibility, my research could lead to a more effective treatment in bacterial infections.

Our understanding of host factors in infection response is still in its infancy. But it represents a possible new avenue in curing or preventing the bacterial infections that claim millions of lives worldwide.

*–Zahidul Alam*

# Clinical Trials Have the Best Medicine but Do Not Enroll the Patients Who Need It

**Most cancer patients never get into lifesaving drug trials because of barriers at community hospitals**

JEAN REIMERS, A 75-YEAR-OLD retired supermarket cashier, enjoys her life in Grand Island, Neb., a small city near the Platte River that boasts attractions such as the Stuhr Museum of the Prairie Pioneer and a sandhill crane nature reserve. Nearly two years ago Reimers found out from her local doctor that she had cancer. The worse news was that it was late-stage metastatic lung cancer, hard to treat and with a dismally low survival rate. The standard approach in such cases is palliative care to keep dying patients comfortable. "It looked like I probably wouldn't be around another year," she says.

Today not only is Reimers still around, but she says she feels great. She has lots of energy and no pain. This past fall CT scans showed all her tumors have shrunk or disappeared entirely. And she was anticipating the birth of her 11th grandchild. "I've got a lot of things I still want to do," she says.

Her high-quality time, Reimers says, comes thanks to experimental drugs she received as part of a clinical trial. The treatment, a combination of two immunotherapies called ipilimumab and nivolumab, is not yet approved for lung cancer by the U.S. Food and Drug Administration. The trial Reimers took part in was one of the tests to see if the regimen works.

This would not be an unusual story if Reimers was a patient at a big-name, big-city academic medical center. The very top cancer hospitals, such as the University of Texas MD Anderson Cancer Center in Houston and New York City's Memorial Sloan Kettering Cancer Center, enroll about 25 percent of their patients in trials. But Reimers, like Grand Island's other 51,000 residents, lives closest to CHI Health St. Francis, a typical small community hospital that is part of a regional network but has no formal ties to any major medical institution. "I didn't think people in small towns had the same

KOTRYNA ZUKAUSKAITE

chances for trials that people in big cities do," Reimers says. Her only option, she thought, was to drive nearly three hours every two weeks to a bigger hospital in Omaha. She would likely have had to stay overnight instead of going straight home to rest, and she probably would not have done it. But the head oncologist at St. Francis's cancer treatment center found out that Reimers met the criteria for the double-drug trial, filled out the forms, followed up and got her in.

The drugs available in clinical trials often represent the latest in research, and many turn out to be significantly more effective than standard treatments. Half of all drugs that make it into the last of three phases of drug trials, when most patients enter those trials, end up being approved by the FDA because of these improved results. The drug Herceptin, for instance, was only available in trials before it became a mainline treatment for breast cancer in 1998 and since then has been prescribed to 420,000 women. More recently, some 90,000 breast cancer patients have been treated with Ibrance, but before 2015 the drug was given only in trials. Another medication, Keytruda, was approved after clinical trials in 2014; now some 70,000 patients with a number of different types of cancer have used it.

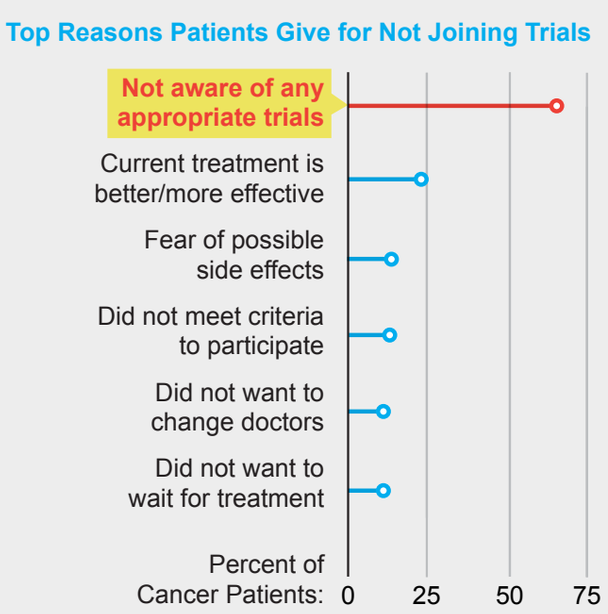
But whereas about one third of cancer patients in the U.S. meet the criteria for a trial with a new drug, only about 4 percent end up in such tests, according to National Cancer Institute estimates, and some experts say the real number is even lower. The main reason for the massive shortfall: in the nonacademic community hospitals where most cancer patients are treated, doctors do not feel they have the time, the incentives or the support to learn about available trials, to qualify and enroll patients, or to provide the extra follow-up care such trials often call for. A National Academies of Sciences, Engineering, and Medicine study concluded that "community practitioners lack the needed infrastructure and support to actively participate in clinical trials." A study in the clinical cancer journal *CA* called trial enrollment "embarrassingly low" and blamed it, in part, on "a lack of knowledge about available studies by community oncologists, a lack of

## Losing Patients

When ill people get into clinical trials, they often do better than patients on standard treatments. Yet only a fraction of trial-eligible patients are offered a chance to participate. Many are not told about trials by their doctors. Trials do have plenty of room for more patients; indeed, many halt without robust results because they do not get enough people.

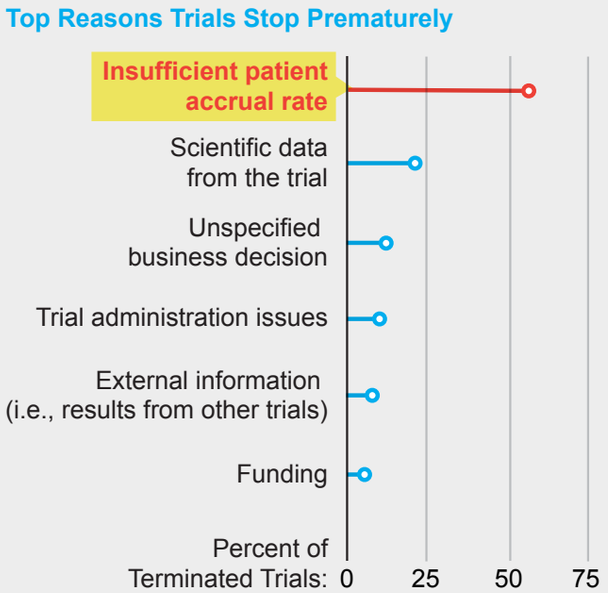
### Cancer Patients in the Dark

Eighty-one percent of cancer patients reported they did not discuss any clinical trial participation with their physicians. That is one finding from a study of 406 cancer patients and 200 oncologists, published in 2009. Patients cited lack of awareness of appropriate trials as the major reason they did not enroll in one.




### Desperately Seeking Participants

An analysis of all U.S. clinical trials that shut down prematurely, published in 2015, found the main cause was that they did not enroll enough patients. Of the 905 trials, 57 percent closed for this reason. In contrast, only 21 percent stopped for scientific causes, such as when the drugs being tested did not perform well.




CREDIT: JEN CHRISTIANSEN; SOURCES: "CLINICAL TRIAL AWARENESS, ATTITUDES, AND PARTICIPATION AMONG PATIENTS WITH CANCER AND ONCOLOGISTS," BY LAURIE FENTON ET AL., IN *COMMUNITY ONCOLOGY*, VOL. 6, NO. 5; MAY 2009 (*PATIENT RESPONSES*); "TERMINATED TRIALS IN THE CLINICALTRIALS.GOV RESULTS DATABASE: EVALUATION OF AVAILABILITY OF PRIMARY OUTCOME DATA AND REASONS FOR TERMINATION," BY REBECCA J. WILLIAMS ET AL., IN *PLOS ONE*, VOL. 10, NO. 5, ARTICLE NO. E0127242; MAY 26, 2015 (*TRIAL TERMINATION*)

time or interest, or a lack of resources to support the cost of performing clinical trials." Because nationally about 85 percent of cancer patients end up at community hospitals, most of the low participation in cancer trials is attributable to the failure of those hospitals to enroll their patients.

Low trial enrollment, which effectively cuts patients off from lifesaving medicine, is a giant national health problem. For example, fewer than 1 percent of patients who have Alzheimer's disease enter a trial. But for cancer, the missed opportunities are especially painful, experts say, because drug development in this area has been particularly strong. "Many of our drug trials involve the most promising agents we've seen," says Tufia Haddad, an oncology researcher at the Mayo Clinic. Thanks to new ways of identifying and targeting mutations in tumors and to immunotherapies that help muster the body's natural defenses against cancers, there are more than 600 experimental cancer drugs that have shown good results in animals and in early small studies in humans. And contrary to common belief, patients in the vast majority of cancer drug trials do not risk getting a placebo—these trials test the best standard treatment against a new medication.

The enrollment problem also handicaps research. Lack of patients forces many trials to stop before getting results, ending the progress of many promising treatments. Most trials are at least delayed by patient enrollment shortages. About one out of six of all trials never manages to recruit a single patient. "The biggest problem in developing new drugs is a lack of patients to treat with them," says John T. Cole, an oncologist at the Ochsner Health System based in New Orleans, who oversees a network of oncology practices. "We can't meet that challenge unless we solve the problem of low enrollment in community hospitals."

Politicians and regulators have done little to help community hospitals and doctors surmount the obstacles, according to R. Alta Charo, a law professor at the University of Wisconsin–Madison, who studies medical research policy. Instead they have passed "right to try" legislation, which prohibits the FDA from denying terminal patients access to experimental drugs that are not available to them in clinical trials. In fact, the FDA almost never denies such access, so the law is unlikely to help more than a handful of patients and does nothing to improve access to clinical trials. "Helping overwhelmed and underresourced doctors at community hospitals would be a much better approach," Charo says.

Finding effective ways to help, however, is not easy. There are partial solutions, such as artificial-intelligence programs that crunch through reams of data to match patients to trials. Other attempted remedies are low tech and involve a range of outreach, education and marketing tools that can change the antitrial culture of community hospitals. To succeed, however, these approaches need to help doctors cope with the time constraints, lack of expertise and financial obstacles that keep them from getting patients into trials. St. Francis, which shares those small hospital disadvantages, manages to place some 35 percent of its cancer patients in trials. That achievement is due almost entirely to the determination and dedication of Mehmet Copur, the head oncologist at the time of Reimers's treatment. But counting on every other community hospital to display the same fervor is a risky gamble.

## ONE DOCTOR'S MISSION

When Reimers became ill, Copur was willing to put in the extra work required to find out about appropriate trials and get her into one—work built into the infrastructure of academic centers but not community hospitals—just as he has been doing for his other patients. To refuse to go that extra mile is to fail to provide seriously ill patients with their best possible prospects, insists Copur, who recently moved to the Morrison Cancer Center in the nearby community of Hastings, where he is building a similar clinical trial program. "The standard of care today is what was in trials 10 years ago," he says. "To put patients in a trial is to give them a chance to get a drug that will be the standard of care 10 years from now."

In 1995 Copur was a young medical scientist from Turkey doing basic research at the National Institutes of Health outside of Washington, D.C., when a change in government policy—an alteration in temporary work permit numbers—suddenly left him in imminent danger

of losing his visa. His only hope for staying in the U.S. was a program that grants permanent visas to doctors who spend three years treating patients in an underserved community. He saw a listing for a job at Grand Island's St. Francis. Copur grabbed the position.

"But when I got here I said to myself, 'My God, my career is over,'" he recalls. Copur had intended to continue some clinical research in the job, but he found that St. Francis had no medical library and no Internet access at the time. Clinical trials were almost nonexistent, and when Copur proposed that he at least try to participate in some, neither his fellow oncologists nor the hospital administration seemed open to the idea. "It was a fight from the beginning," he says. "Even in big-city hospitals people don't always see how important clinical trials are, let alone a small-town hospital."

The problem was that to earn his salary Copur had to see a stream of patients, five days a week. But clinical trials require extra work, with each patient taking up on average about three times as much time as a nontrial patient, thanks to extra record keeping and close patient-monitoring requirements. In academic centers, doctors are given that extra time and can draw on a trial-focused support staff. Copur had to do it all on his own, including establishing rigorous data collection, performing extra diagnostic tests, conducting extra patient visits, producing reports, training staff, and more. He also brought in funding from the NCI and joined a research consortium of hospitals that made more trials available.

Many of his patients hesitated to join a trial, saying they did not want to be guinea pigs who might end up with a highly toxic drug or a placebo—widely held misconceptions that are particularly common among rural patients, says James Atkins, an oncologist at the Southeastern Medical Oncology Center in North Carolina. Copur patiently explained to them that cancer trials today are designed with patient benefit in mind and that the worst case was usually getting the drug they would have received anyway. Most of his patients consented. Then other oncologists at St. Francis started to notice that Copur's trial patients sometimes did surprisingly well. Of course, they were doing well, Copur explained: some of them were receiving much better drugs. Soon his colleagues began looking for trials for their own patients.

"Copur has done a great job in a completely rural environment," says Praveen Vikas, an oncologist at the University of Iowa Health Care. "He's that rare kind of community physician who can provide the kind of care that often beats physicians in academic settings in terms of value and patient satisfaction, while staying on top of research."

As of 2018, Copur's team at St. Francis had enrolled patients in 74 different trials. But to do so, Copur worked nonstop from dawn, taking off one hour at 7 P.M. to have dinner at home with his ailing father before returning to spend another three hours at the clinic. "These trials are my whole life," he says. "Sometimes I dream about making that big fundamental research contribution, but then my patients remind me that what I am doing here is a bigger contribution."

One of those patients is a young man (he asked not to be identified) who learned two years ago that his kidney cancer was spreading. Approved chemotherapies did not offer much hope, so he started searching out clinical trials, assuming he would have to go far from his home near Grand Island to get in one. He traveled to Washington, D.C., to meet with a specialist—who told him to get right back to Nebraska and see Copur. "To be honest, I was a little skeptical when I met Dr. Copur, and he told me he'd get me in the right trial," he recalls. "But my phone started pinging with e-mails about trials by the time I was pulling out of the parking lot." Today the patient is thriving and credits the immunotherapy drugs he received through the trial that Copur enrolled him in.

## BREAKING BARRIERS

Copur's experience at St. Francis proves that community hospitals can succeed as clinical trial centers. And if he can deliver on his quest to duplicate that success at the even smaller Morrison Cancer Center, which is part of the Mary Lanning Healthcare community hospital in Hastings, the evidence will be all the more impressive. Community hospitals do not need to hit 35 percent enrollment, as St. Francis has, to make a big dent in the trial gap. If only one fourth of community hospitals boosted their trial enrollment to an average of 10 percent, it

would result in an increase of 50 percent in the number of cancer patients enrolled in trials. In a survey of a wide range of cancer patients, 81 percent reported their doctors did not discuss the possibility of trials with them. In a separate survey of women with cancer, more than half reported that their oncologists either did not mention trials or even actively discouraged patients from participating in one.

The St. Francis work also highlights the obstacles that community hospitals face. But a 10 percent gain in enrollment does not require daunting personal sacrifice, say clinicians who have helped other community hospitals make the jump. Atkins, who directs a large clinical trial consortium across the southeastern U.S., is working with 25 hospitals in five states to help them boost clinical trial enrollment. Many physicians have gotten onboard, Atkins says. It means going beyond the typical physician's 50-or-so-hour week but only by five hours or less. "It's extra work for doctors, but if a doctor doesn't want to do it for patients, that seems a little lazy to me," he says.

Clinical trials can also be redesigned to reduce the burden on community hospital physicians, shifting more of the workload to the research centers that originate the trials. A study led by the University of Pittsburgh Medical Center, along with six other academic medical centers and the National Institutes of Health, looked at 38 steps that clinical trial leaders can take to get more doctors at other hospitals involved in their trials, steps mostly aimed at raising doctors' interest while reducing the workload involved in opening the trial and in enrolling patients. The steps included sending researchers out to hospitals to speak to staff about the trial's relevance, the benefits to patients and the patients' qualifications; providing follow-up teleconference meetings; writing articles for the hospital newsletter and for local and physician publications; establishing 24/7 access for researchers to get questions answered; putting up a Web site dedicated to the trial; and making available patient-recruitment aids such as multilingual brochures and consent forms. The study, published in 2014 in *Clinical Pediatrics*, found there was a 38 percent jump in recruitment after the steps were taken.

Sonika Bhatnagar, lead author and an associate professor of pediatrics at the University of Pittsburgh School of Medicine, notes that some factors stood out during the study. "The biggest physician barrier was time constraints," she says. "Minimizing their workload was critical, and we found making everything as simple as possible made a big difference." Among the aids Bhatnagar and her colleagues provided physicians were prepackaged talking points to use with patients, so the doctors did not have to study a trial's methodology in detail to explain it accurately. The researchers also offered to reach out directly to a patient's family to address their concerns. And physicians worry that putting a patient in a trial will compromise his or her autonomy in making care decisions, Bhatnagar adds, because trials often tightly circumscribe some treatment options. She has found that the best way to counter that concern is for researchers to go to hospitals to meet as many physicians as possible in person to build trust in the trial's protocol and to create enthusiasm about what the trial might do both for individual patients and for the countless patients everywhere who might ultimately be helped by the trial's findings. "Most physicians would take a lot of pride in contributing to research that could ultimately change treatment guidelines for the field," Bhatnagar says.

Another study gave doctors materials designed to streamline the process of patient screening—that is, determining which patients qualify—and to make it easier to follow trial protocols during treatment. The study also involved adding one-on-one meetings between local physicians and trial researchers and on-site discussions about the disease being treated. In that study, enrollment at the targeted facilities more than doubled.

Some trial outreach efforts are being facilitated by the fact that academic medical centers are looking to expand in their states, and sometimes beyond, via acquiring or partnering with community hospitals. Existing big health networks are also pushing outreach. Kaiser Permanente—a nonprofit health care company—has nudged and supported all its 27 northern California hospitals, many of them community hospitals, into enrolling cancer patients into trials. "Instead

of having to drive 50 miles or more to an academic medical center, our patients can be treated in a clinical trial in the same place they delivered their babies and got their flu shots," says Lou Fehrenbacher, a Kaiser Permanente oncologist who oversees the region's cancer trials program. Likewise Yale University's main hospital, based in New Haven, has been bringing in affiliated community oncology clinics around Connecticut into clinical studies. Unfortunately, most of the nation's 4,000 community hospitals are not closely allied with an academic center, so this approach may be limited.

**THE HIGH-TECH FIX**

It may be, though, that technology can help close that particular gap. The Mayo Clinic has been testing a pilot of an ambitious approach, based on IBM's Watson cognitive-computing platform. That system has been looking at all the details in the records of every breast cancer patient at the medical center and matching them against the 16 different clinical trials for breast cancer available there. The Mayo claims that after 11 months the system was able to increase combined enrollment in those trials by 80 percent—though so far only at the clinic itself and not yet at community hospitals. According to the Mayo's Haddad, who is helping to run the pilot, the big jump is owed in part to the fact that the project included increased staffing and focus around patient-trial matching. But she adds that Watson's ability to zip through not only tightly specified data fields in the health records but also clinical notes and other unstructured data has made a big difference in the system's hit rate. "Most electronic health record systems aren't sophisticated enough to be able to answer questions such as which treatments the patient has already had," she says. "More than 90 percent of the data in records is in unstructured form, and cognitive systems can go after it."

A study run by the NCI and Case Western Reserve University, using another experimental cognitive-computing-based system called Trial Prospector, scoured the records of 60 new gastrointestinal cancer patients across several clinics and matched 57 percent of them to at least one of 15 different trials. A group of oncologists brought into the study gave the system a big thumbs-up, deeming all the matches to be accurate. Another system tested at Cincinnati Children's Hospital Medical Center was found to reduce the time needed to match patients to trials by 85 percent.

Exciting results, but they come with serious qualifications. For one thing, such systems generally require that a hospital have a sophisticated electronic health record system in place to feed them data. Most community hospitals currently have systems that are too rudimentary to allow programming in trial-matching capabilities. But given medicine's growing reliance on mining electronic health records for advancing patient care, those systems will inevitably be upgraded to the point where automating trial matching will become feasible—especially as more community hospitals become affiliated with larger hospitals and even academic medical centers.

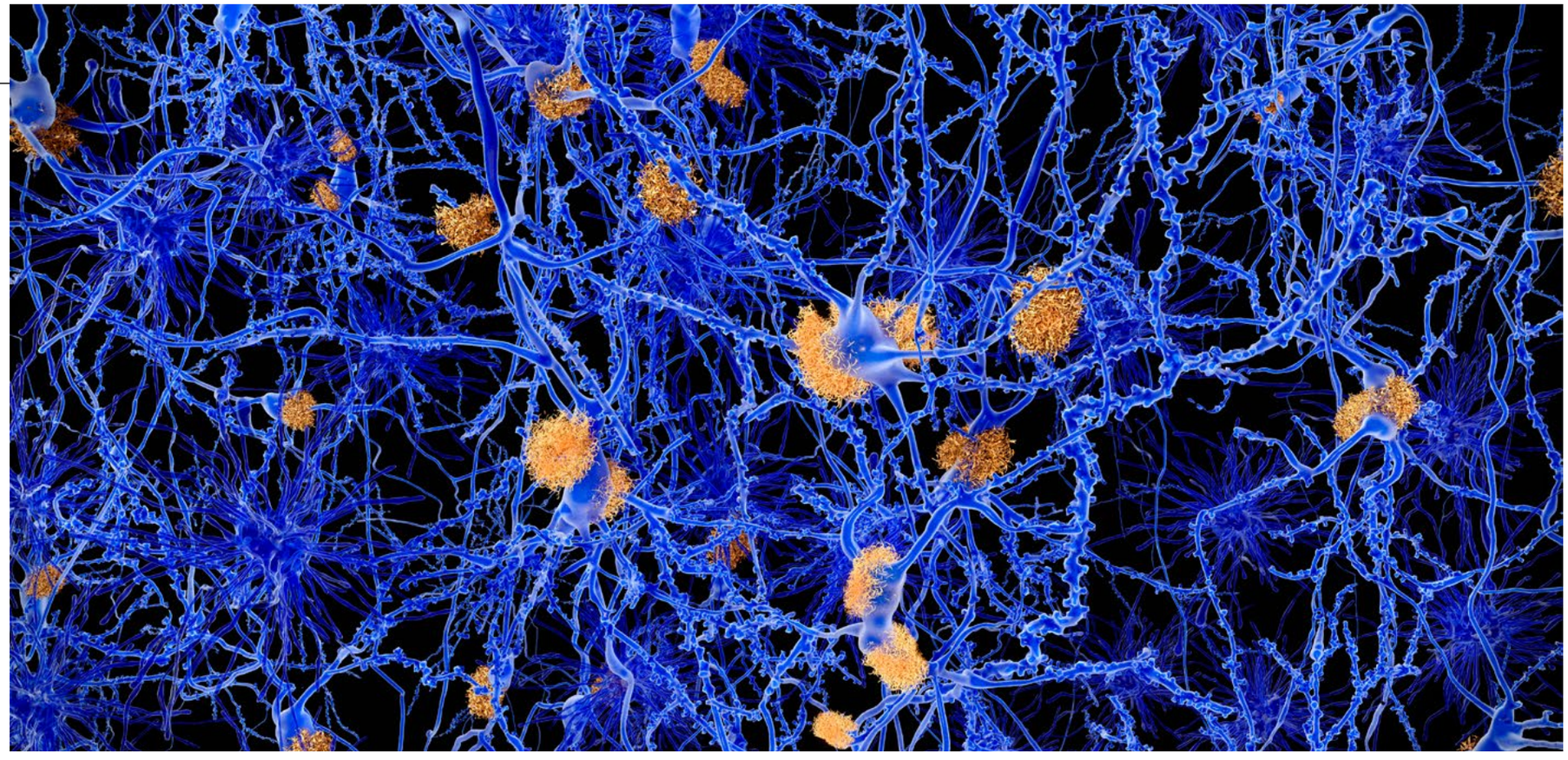
Copur, for his part, maintains that what will ultimately bring clinical trial options to that great majority of cancer patients will be a slowly growing wave of peer pressure as more clinicians in community settings start to see the light. Copur himself keeps publishing—63 papers and articles to date, such as a study in the *Journal of Clinical Oncology* evaluating treatments for metastatic pancreatic cancer—and giving talks about what a community hospital can accomplish. "I tell doctors that if they're not looking for ways to put their patients in clinical trials, they should be referring them to a doctor who will," he says.

What seems poised to effect change, if slowly, is a combination of all those approaches: Trial researchers who get out into communities and market their work to local doctors, trial designs that reduce physician workload, and tools that automate patient-trial matching and related tasks. It will also take strong advocates like Copur and the NCI willing to sound a constant, loud drumbeat that links trials to the duty that all physicians—not just those in academia—have to the profession and to their patients. It will only be then, if those efforts on multiple fronts put more people in trials, that patients win the real right to try.

*—David H. Freedman*

# A New Idea about What Triggers Alzheimer's

**Changes in brain cells' DNA may be responsible—and if so, medicines already developed for other diseases might be used to treat it**



JUAN GAERTNER *GETTY IMAGES*

CERTAIN INHERITED genetic mutations lead to Alzheimer's disease (AD), but they are relatively rare. A recent study from my laboratory, however, shows that gene alterations that are not passed along by one's parents may also play a key role in triggering the disease. This happens as a result of a process that occurs in the cell nucleus, known as gene recombination (GR), which can make changes to the DNA "blueprint" in human neurons.

Neuronal GR acts on a gene called APP (amyloid precursor protein), which plays a central role in Alzheimer's, producing thousands of APP DNA variations. Such variations can occur in the normal brain but are altered further in AD. If our data are confirmed, this would indicate that recombination in these neurons may be involved in the disease process that leads to Alzheimer's. And our findings point as well to a class of existing medicines, approved for other disorders, which can interrupt GR and thus might be used to treat Alzheimer's.

Historically, brain cells—and most cells of our body—have been thought to contain an identical DNA blueprint, or genome. We knew of one exception in cells of the immune system—B and T cells—that were the first and thus far only cell types known to undergo somatic GR, meaning that GR changes are not passed to offspring, unlike germ line changes affecting sex cells.

In the immune system, gene recombination creates specialized receptors recognizing self from non-self (technically, immunoglobulins and T cell receptors formed by GR). The discovery of GR in the immune system by Susumu Tonegawa in the 1970s was preceded by theoretical work and observations on fish nervous systems suggesting that recombination might be relevant for the brain. However, unlike the immune system, there was no molecular candidate for GR in fish let alone humans, and the notion of gene recombination in the brain languished.

But at the start of the 21st century, researchers uncovered a harbinger for GR. We discovered that DNA sequences vary from cell to cell, meaning that our brains are a vast mosaic of distinct genomes, a phenomenon aptly referred to as "genomic mosaicism." These changes are distinct from epigenetic changes that do not directly affect DNA sequences. Scientists have now identified multiple sequence changes that are quite varied and seemingly random, consisting—in order of decreasing size—of entire chromosomes (aneuploidies), smaller copy number variations, even smaller retrotransposon repeat elements and single

nucleotide variations that alter individual nucleotides.

Brain genomic mosaicism thus exists, but what is it good for and how does it work? General observations have lent support to the impact of mosaicism on gene expression and cell survival. However, specifically altered genes have not been identified to date. Of note, a number of candidate genes were examined over the years for GR—genes for olfactory receptors and certain cell adhesion proteins. Other approaches identified DNA strand breaks in neural genes during early mouse brain development that might be involved with gene recombination. However, once again, no proven genes emerged.

Without a bona fide candidate protein or gene, this research is like looking for the proverbial needle in a haystack. Moreover, immune cells—most notably, immune cell tumors—can grow identically as a cell divides through mitosis (or "clonal expansion") to amplify the same genome and thus allow its analysis by conventional means, contrasting with neurons that do not continue to divide. Assessments at the level of single or several cells are therefore essential to understand GR. The problem that must be addressed can be illustrated through an analogy: a brown paint might be homogeneously composed of brown pigment molecules, or instead formed by colorful pigment molecules that also appear brown when mixed.

Taking all this into account led us to conduct studies assessing mosaicism in AD brains. Our findings showed greater mosaicism—in particular, for increased APP copy numbers. Most notably, segments of DNA in the APP gene were found to not only be amplified in some neurons, but certain APP segments increased in number more than others, hinting at GR.

We therefore closely analyzed the APP gene using nine distinct technical approaches applied to single cells or small collections of neurons to account for genomic mosaicism from normal and AD brains. All these analyses yielded the same conclusions, discovering thousands of new APP variations characterized by an array of different sequence changes within the genomic DNA blueprint that resembled what are known as complementary DNAs. These CDNAs, for short, are copies of RNA molecules that provide the code for making proteins.

Involvement of a famous enzyme called reverse transcriptase discovered by David Baltimore and Howard Temin appeared to create cDNAs that inserted themselves back into the genome (gencDNAs), a process that is different from immune system GR, which does not involve reverse transcriptase, and occurs in mitotic cells. In neurons, even a single gene can apparently give rise to many thousands of distinct forms through this process, vastly increasing genomic diversity.

Gene recombination occurs in response to stimuli that can be broadly thought of as a form of recording of a cellular event using gencDNAs. Subsequently, gencDNA "playback" may have the advantage of not requiring as much time and energy as the normal process of transcribing a gene into a protein. For instance, GR may be tied to sensory stimuli like sight, sound, taste, touch and scent, as well as internal neurochemical factors—even drugs—that could effectively record and store produced gencDNAs while later allowing their playback by the same or perhaps different stimuli.

In Alzheimer's, our research implicates an instance of GR gone wild, producing APP gencDNAs with markedly increased numbers and forms, including nucleotide changes identical to those found in inherited AD mutations but occurring somatically and mosaically only in AD neurons. The existence of these myriad APP variations may explain past therapeutic trial failures, which were unable to target the multitude of varying molecular entities. The involvement of reverse transcriptase suggests the possibility of new therapeutics aimed at inhibiting the enzyme.

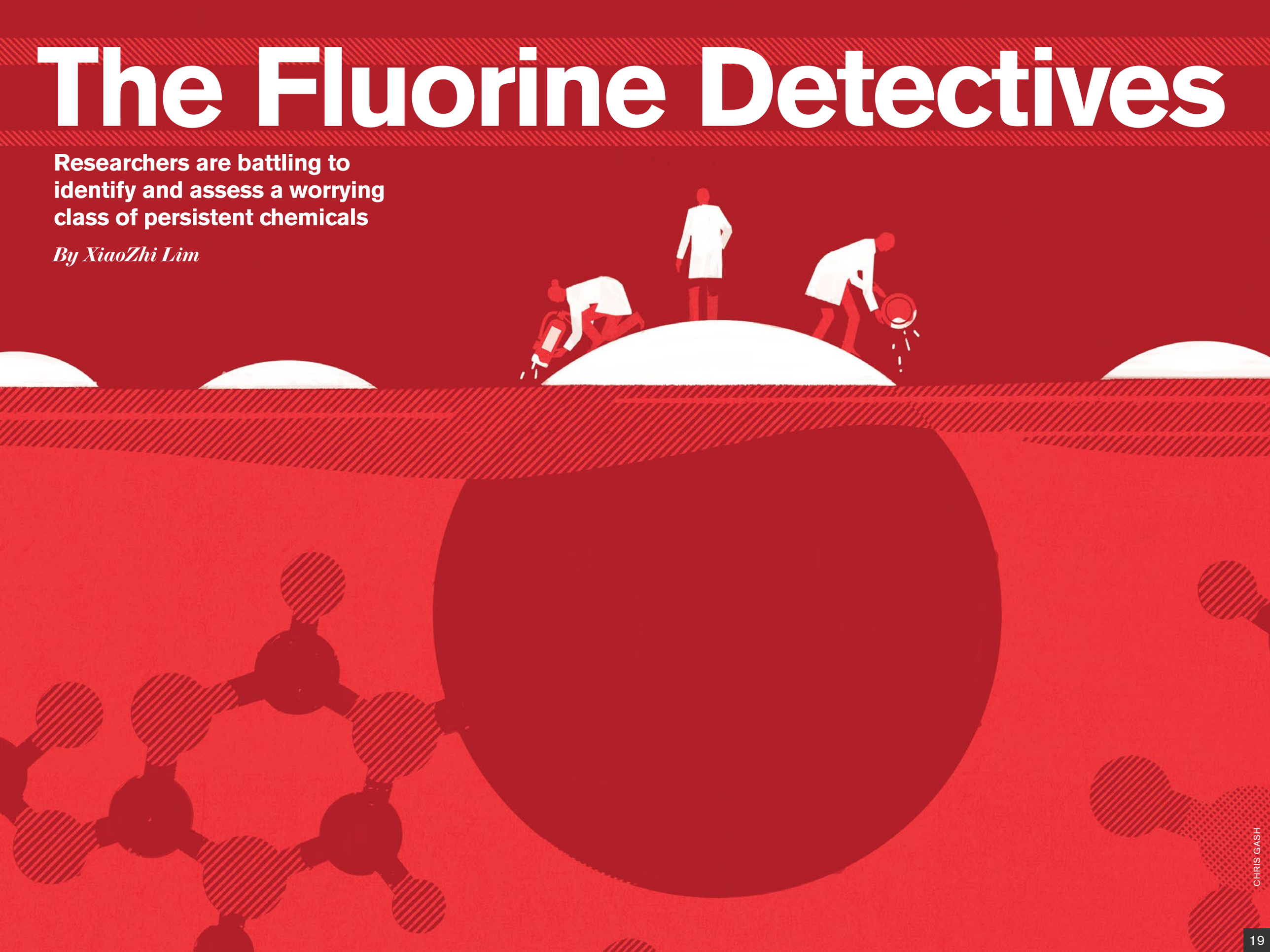
In fact, there is some evidence already that HIV patients who have been taking reverse-transcriptase inhibitors for many years may have a lower incidence of Alzheimer's as they age. In principle, FDA-approved medications such as reverse-transcriptase inhibitors could be used today and may have special benefit for people in high-risk categories for whom no effective treatments currently exist. GR affecting different genes may underlie one or more of hundreds of other brain diseases and might also affect other cell types beyond the brain.

*—Jerold Chun*

# The Fluorine Detectives

**Researchers are battling to identify and assess a worrying class of persistent chemicals**

*By XiaoZhi Lim*



CHRIS GASH

**XiaoZhi Lim** is a freelance science reporter based in Singapore.

Some firefighting foams, such as these poured onto an oil-depot fire in the United Kingdom, spray fluorinated chemicals into the environment.

STEFAN ROUSSEAU *GETTY IMAGES*

A FEW TIMES EVERY YEAR, CHRIStopher Higgins's laboratory in Golden, Colorado, receives a special delivery in the mail. Inside an icebox, Higgins finds several vials, each holding up to 250 milliliters of water collected from boreholes near U.S. military bases. The water looks unremarkable, but it is contaminated with synthetic compounds called fluorochemicals, which have been generating increasing concern around the world. This class of chemical has shown up in worrying concentrations in rivers, soils and people's bloodstreams from Europe to Australia. Some of the oldest compounds have been studied and banned, but new, mystery types are appearing all the time. Higgins's team, at the Colorado School of Mines, is one of several environmental-chemistry labs being funded by the U.S. Department of Defense to work out the chemicals' structures. "I think they are one of the most complex groups of pollutants out there," he says.

The fluorochemicals story used to be simple. In the 1930s, the chemical industry created surfactant compounds with a unique ability to repel both grease and water, because their carbon chains were swaddled in fluorine atoms. Within 30 years, they were everywhere: in nonstick pans, raincoats, food wrappings, firefighting foams and all kinds of stain-proof coatings. Chemists would later call this fluorinated family "per- and poly-fluoroalkyl substances," or PFASs. Their carbon-fluorine bonds are among the strongest known in nature—so the molecules don't degrade.

By the 21st century, internal industry studies had linked growing concentrations of two of the most popular fluorochemicals, PFOA (perfluorooctanoic acid) and PFOS (perfluorooctane sulfonic acid), to a bevy of health issues, including cancers and problems during pregnancies. Companies said they would stop using them, and countries agreed in 2009 to phase out PFOS under the Stockholm Convention, which controls persistent pollutants; this year PFOA is expected to be added to the banned list. But because the molecules don't naturally degrade, hundreds of millions of people in Europe, the United States, Australia and China are still exposed to levels of these compounds that exceed what regulatory agencies deem healthy.

Starting in the 2000s, some industrial firms switched to formulations that they said were safer. But those, too, contain fluorine-carrying carbon chains. And because the chemical industry does not regularly disclose formulations that are trade secrets, scientists are starting from scratch in working out whether PFASs besides PFOA and PFOS might be causing problems. "We're going back to square one," says Philippe Grandjean, an epidemiologist at the Harvard School of Public Health in Boston, Massachusetts, who studies the effects of persistent pollutants.

Now, environmental chemists, epidemiologists and toxicologists are trying to deduce how many PFASs there are, track those that are in the environment and assess potential harm. By last May, researchers had tallied a startling 4,730 PFAS-related structures from patent filings and chemical registries, any of which might be in commercial use (see go.nature.com/2bekua3). That list is still growing, says Zhanyun Wang, an environmental scientist at the Swiss Federal Institute of Technology in Zurich who led the work. (By comparison with other well-known chemical pollutants, there are just 75 known dioxins and 209 polychlorinated biphenyls, or PCBs.) Not all PFASs are cause for concern, says Eeva Leinala, principal administrator in the Environment, Health and Safety Program of the Organization for Economic Co-operation and Development in Paris, which commissioned Wang's study. But for many, there is no toxicity information, she says. That gap is a worry because the compounds hang around so long in the environment. "These are the most persistent chemicals we are facing today," says Wang.

For researchers, tracking PFAS contamination is an urgent and fascinating challenge, says Emma Schymanski, an analytical chemist at the University of Luxembourg in Belvaux. "These chemicals are changing all the time," she says. "It's the worst-case scenario—and the most interesting."

Christopher Higgins and Ph.D. student Anastasia Nickerson, with water samples from sites affected by firefighting foams that contain fluorinated chemicals.

## THE PFAS PUZZLE

Water and soil near military bases worldwide are rich in PFASs because of firefighting foams sprayed there during training exercises. The foams tend to be complex formulations and can contain hundreds of PFASs. They were introduced in the 1960s to extinguish fuel fires, and performed so well that the U.S. military set them as the standard for fire protection at bases and major airports. They represent a small fraction of fluorochemical production, but are a major part of the contamination problem because they get discharged directly into the environment, says Jennifer Field, an environmental chemist at Oregon State University in Corvallis, who collaborates with Higgins.

Field and Higgins's research teams analyze the water using mass spectrometers: machines that separate out and weigh the molecules present in a sample, and then break these compounds into ionized fragments before weighing each smaller piece again. It's easy to spot known PFASs, such as PFOS and PFOA, because their characteristic fingerprints are already known. But for fragments with unfamiliar masses, researchers must deduce the structures, and then surmise what the original compounds might be. "You start using a chemist's brain and a pencil and a piece of paper to sketch things out," says Mark Strynar, an analytical chemist at the U.S. Environmental Protection Agency's National Exposure Research Laboratory in Research Triangle Park, North Carolina.

After proposing structures, chemists then search patent databases and other registries to see whether a firm has ever recorded a molecule that matches their guess. The method, called "nontarget" searching—because scientists start off without knowing what their target looks like—is a slow process, Schymanski says. "You can analyze a sample in 20 minutes—and do nontarget data interpretation for a year."

Using high-resolution spectrometers that have become widely available only over the past decade, Higgins, Field, Strynar and others think they have discovered almost 500 kinds of previously unrecorded PFASs in the environment. "We're not revealing chemistry to the industry that they don't know about," says Field. "We are using taxpayer dollars to reveal compositions of complex mixtures that the industry has known have been there forever."

To be sure that the chemical is what they think it is, researchers would ideally compare their findings with a mass-spectrometer reading of a clean, pure sample—a reference standard. But these are hard to come by because manufacturers don't always have them, and when they do, they often say that precise structures are confidential business information. So researchers instead declare that they have found PFASs to varying degrees of confidence, on a scale that Schymanski introduced in 2014.

Researchers also need reference standards to accurately quantify PFAS concentrations in the blood and investigate health impacts. To meet that need, chemists Alan McAlees and Nicole Riddell at Wellington Laboratories in Guelph,

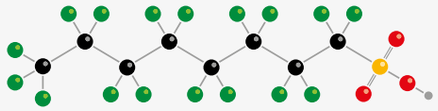
# Fluorinated Family

Chemicals with fluorinated carbon chains (PFASs) are found in clothes, carpets, foams and other products. They don't degrade in the environment; researchers have listed more than 4,500 structures.

### Harmful Legacy

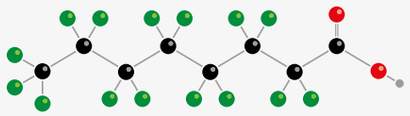
A first generation of PFASs contained chains of eight or more carbons. Some of these are being phased out because of health concerns and their persistence in the environment.

**PFOS** (8-carbon chain)



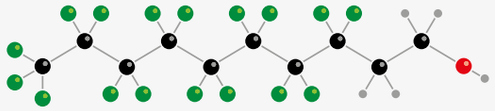
Production now heavily restricted.

**PFOA** (8-carbon chain)



Expected to be similarly restricted this year.

**8:2 FTOH** (10-carbon chain)

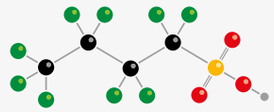


Hundreds of precursor compounds can degrade into PFOS or PFOA in the environment.

### The Next Generation

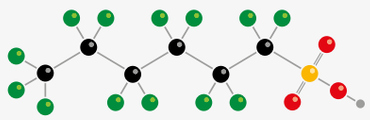
Industry shifted to shorter-chain PFASs and more complex structures; less is known about the safety risks of these molecules.

**PFBS**



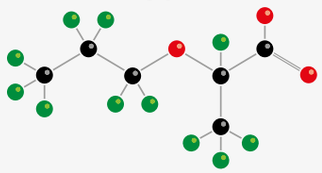
Variations in chain length and branching produce dozens of variant structures.

**PFHxS**



A Stockholm Convention committee is reviewing whether to ban this substance.

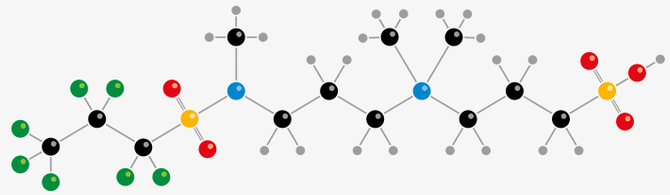
**"GenX"**

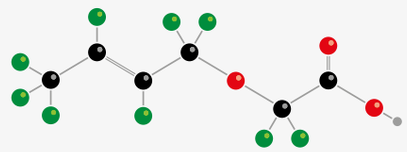


U.S. chemical firm Chemours is being sued over the presence of this chemical in North Carolina water supplies.

### Mystery Compounds

Researchers think they have identified hundreds of new PFASs in the environment–with varying degrees of certainty.





These PFASs are "probable" structures, found in environments affected by firefighting foams. Some molecules found in groundwater have not yet been assigned a structure.

● Carbon ● Fluorine ● Sulfur ● Oxygen ● Hydrogen ● Nitrogen

Canada, have been synthesizing their own PFASs. They have so far made around 100 structures. Three of those were made because they were spotted in Field and Higgins's nontarget analyses—which should help chemists to confirm their suspicions of what's in the environment.

## NEW MOLECULES, SAME HARMS?

The new PFAS molecules have structures that chemical firms say make them less problematic than PFOA or PFOS. PFOA has a chain of eight carbons—it is sometimes called, simply, C8—but firms have shifted to molecules with chains of six or four carbons. They say that these are more soluble and leave the bloodstream more quickly, so are less likely to accumulate in animals and people. Another design inserts an oxygen atom in the fluorinated carbon chain, a structure that is said to break down faster.

But despite industry assurances, molecules with fluorine-carrying carbon chains won't degrade easily, says Rolf Halden, an environmental engineer at Arizona State University in Tempe. Asked to comment on this controversy, the FluoroCouncil, an industry group in Washington, D.C., argues that at least some PFASs are safe: it points to reviews that it funded and published in January indicating that the six-carbon perfluorohexanoic acid (PFHxA), which some more-complex PFAS structures naturally transform into, is noncarcinogenic and nonbioaccumulative, and that human exposure to it is "low and infrequent."

Those claims are technically correct, says Ian Ross, who leads consulting on PFASs at Arcadis, an engineering and consulting company headquartered in Amsterdam. But PFHxA is only one of many PFASs, he says, and complex mixtures can leave all kinds of mystery intermediate compounds in the environment. A study published

last month, for instance, found that one PFAS commonly used in foam could turn into nine different intermediates before ending up as PFHxA. Jamie DeWitt, a toxicologist at East Carolina University in Greenville, adds that the volume of data known about PFHxA is much smaller than that for PFOA and PFOS.

Much of the evidence for the dangers of these compounds came from a science panel that emerged from the first huge PFAS class-action lawsuit, brought against the U.S. conglomerate DuPont in the small town of Parkersburg, West Virginia, in 2001. There, several DuPont employees who worked directly with C8 had become sick. The firm was accused of causing harm to people who drank water containing C8, which it had discharged into the environment. In 2004, the lawsuit was settled: the firm agreed to pay U.S.$70 million to a health and education fund, and to fund research to find out whether C8 was linked to disease. The result was an epidemiological study of almost 70,000 people, which, by 2012, had linked C8 to diseases, including kidney and testicular cancers, pregnancy-induced hypertension, ulcerative colitis and high cholesterol (see go.nature.com/2wzex8e). (Under the settlement's terms, DuPont cannot dispute the study's findings.) After this, some 3,550 people involved in the class-action lawsuit who had these diseases sued DuPont individually; in February 2017, the cases were all settled together for $671 million. Neither settlement established wrongdoing by DuPont.

In other research, Grandjean has studied how some of these substances affect children's development. For 20 years, he has followed 500 children in the Faroe Islands from birth, measuring concentrations of five PFASs in their mothers' blood and the children's blood. (Grandjean picked the Faroese because, owing to their relatively isolated location, only a few PFASs show up in their blood, making the group easier to study than populations elsewhere.) In 2012, he reported that children with higher PFAS levels were less able to develop antibodies in response to vaccines.

**"We are using taxpayer dollars to reveal compositions of complex mixtures that the industry has known have been there forever."**
***—Jennifer Field***

That finding, among others, led the European Food Safety Authority in March 2018 to revise its decade-old safety limits for exposure to PFOS and PFOA: down from 1,050 nanograms per kilogram of body weight per week to 13 $ng/kg^{-1}$ for PFOS, and from 10,500 $ng/kg^{-1}$ to 6 $ng/kg^{-1}$ for PFOA. That, says the agency, means that a "considerable proportion" of the population is exposed to unsafe levels. The agency also says that it will publish a decision by December this year on whether to set safety limits for 25 other PFASs—and on whether those PFASs could be assessed in mixtures, rather than individually. The U.S. Environmental Protection Agency did not set guidelines for PFOS and PFOA exposure until 2016; those recommend that drinking water should not contain concentrations higher than 70 parts per trillion (p.p.t., or 70 $ng/kg^{-1}$) of the two substances combined. Last year, the U.S. Department of Health and Human Services released a draft study suggesting that safe levels should be set much lower, at 7 p.p.t. for PFOS and 11 p.p.t. for PFOA (see go.nature.com/2crcs3c). Some 110 million Americans drink water with PFAS levels that surpass this recommendation, and six million have water with higher levels than the EPA's guidelines.

## MISSING MECHANISM

Despite studying PFOS and PFOA for two decades, toxicologists are still struggling to work out how PFASs cause problems in the body. "I don't think we have achieved a consensus on the understanding of a specific mechanism," says DeWitt. Studies in rodents exposed to PFOA for long periods of time, for instance, show that this can result in activation of a receptor called PPAR-α, a protein that regulates lipid metabolism in the liver and elsewhere, and so can lead to liver tumors. Humans also have this receptor—but do not seem to get liver tumors from PFOA exposure. The finding could be related to the other kinds of toxicity that PFASs have been linked to, but it's not clear yet, DeWitt says.

While toxicologists and regulatory agencies have focused on PFOA and PFOS, new structures have appeared. "It seems as though the number continually grows," says DeWitt. Some PFASs now contain a double bond, or a chlorine or hydrogen atom in place of a fluorine. Others are branched or cyclic. There are entire families that look like PFASs, but have not fallen under the umbrella of that description yet, says Wang. "It's a mess."

Wang hopes to build a more comprehensive PFAS universe than the thousands that he has already described. A potential new source of information will come from Europe. Under chemicals legislation introduced in 2006, manufacturers have since November 2010 had to file information about compounds they put on the market, although compounds produced or imported in small volumes (1–100 metric tons) per year were exempt until last May, and production at even lower levels doesn't need to be registered at all.

"We just keep finding all sorts of weird structures," says Ian Cousins, an environmental chemist at Stockholm University, who works with Wang. "I think we're still a long way from the final number."

Wang's studies could help speed up the nontarget

detective work. He and Schymanski are now collaborating to build a software tool that would automatically compile the structures in the PFAS universe, then fragment them and classify the fragments by mass. One day, researchers could use the tool to identify unknown masses spotted in environmental samples.

### TRACK AND DESTROY

Early last October, a tanker truck tipped over on a ramp joining the I-95 highway in Providence, Rhode Island, and spilled roughly 48,000 liters of gasoline. Firefighting foams containing six-carbon PFASs were sprayed over the spill as a precaution. The accident occurred next to the Providence River, which empties into Narragansett Bay some 10 kilometers away.

Christine Gardiner, a master's student at the University of Rhode Island in Kingstown, quickly e-mailed staff at the Rhode Island Department of Environmental Management, who maintain a network of buoys in Narragansett Bay during the summer to monitor water quality. Gardiner joined the next trip out to the bay, bringing empty bottles to collect water at each buoy, and homemade porous tubes filled with ionic powders that trap PFASs. These "passive samplers" get attached to a rope on each buoy and remain in the water for about two weeks.

Gardiner plans to analyze the samples for about 20 known PFASs to see whether the method can capture them. She also hopes to see how the PFASs traveled through the bay. Together with her supervisor, Rainer Lohmann, and Grandjean, Gardiner is participating in a five-year $8.5-million project funded by the U.S. National Institute of Environmental Health Sciences. A collaborator in the project, Elsie Sunderland at Harvard University in Cambridge, Massachusetts, is tracking some 30 PFASs from their sources to where they end up in the environment. Sunderland hopes that researchers could help people with high PFAS levels in their blood to trace the source of their exposure—perhaps to their fish consumption, drinking water or house dust.

Christine Gardiner, working in Narragansett Bay, adjusts filters that trap fluorinated chemicals so that she can track the molecules' passage through the water.

How to remove the chemicals is another problem. There are at least 30 PFAS remediation projects happening in the United States, Europe and Australia, each one costing a million dollars or more. These efforts typically use filters that can catch long-chained PFASs: those with eight or more carbons. But the shorter-chained substitutes don't stick as well to the filters and break free much faster. And some new PFASs evade the filter completely, says Detlef Knappe, an environmental engineer at North Carolina State University in Raleigh.

One approach was demonstrated in April 2017, when a firefighting foam spill at Australia's Brisbane Airport caused some 22,000 liters to enter nearby Boggy Creek. Authorities dammed the creek and pumped the water out, storing it in hundreds of tanks on tarmac nearby. Researchers from Arcadis used ozone to oxidize much of the organic matter, a process that created lots of minuscule air bubbles to trap the pollutants, says Ross. "They like to stick their perfluoroalkyl chains in air," he says. The bubbly foam, concentrated with PFASs, rose to the top and was skimmed off.

But then there is the question of what to do with the foam, or carbon filters, that have become concentrated with PFASs. Currently, much of that ends up in landfills. But that just moves the problem, says Knappe. PFASs can migrate out of the filters and seep into the ground with rain and other liquids in unlined landfills, threatening groundwater. Indeed, the multinational manufacturing firm 3M was sued in Minnesota for having "deliberately disregarded the high probability of injury to Minnesota's natural resources" by landfilling PFAS-contaminated waste, which then leaked into groundwater. The lawsuit was settled for $850 million in February 2018 and did not attribute any legal responsibility to 3M for contamination or injury.

Even when landfills are lined, fluids that pool at the bottom often end up in wastewater treatment plants that are not equipped to remove PFASs, Knappe says, so the chemicals end up in waterways anyway. In August last year, the EPA put up $6 million for research proposals tackling PFAS-contaminated fluids in landfills.

Ideally, chemists would find a way to remove fluorine atoms from the carbon chains to form stable, safe fluoride ions. But that is easier said than done. High-temperature incineration could break the strong carbon–fluorine bond, and the Boggy Creek foam was ultimately incinerated at more than 1,100 degrees Celsius, says Ross. But very little is known about what the PFASs turn into when incinerated, and whether the incineration products are safe. "I still consider that as a research need," says Knappe.

Arcadis researchers are working to improve and scale up an idea to use ultrasound pulses to defluorinate PFASs, says Ross. These create tiny bubbles that expand, contract

XIAOZHI LIM

A remediation system uses ozone to clean up fluorinated chemicals from a huge spill of firefighting foam at Brisbane Airport in 2017.

and ultimately explode; the temperatures on the bubbles' surfaces are high enough to split fluorine from carbon.

### WHAT'S ESSENTIAL?

For now, the biggest priority should be to prevent PFAS contamination, says Knappe. That means pursuing responsible manufacturing and disposal processes, he says. But some suggest going further and phasing out the use of PFASs where they're not needed.

The Stockholm Convention process is used to list problematic PFASs individually; after PFOA is banned, the Stockholm committee has agreed to evaluate perfluorohexane sulfonate, or PFHxS. But Cousins, Wang and Lohmann think that the default position should be to restrict the use of all PFASs in products unless they provide essential functions. They are writing a regulatory framework laying out this idea, which they plan to publish later this year.

The FluoroCouncil disagrees with this idea. "It is not appropriate to make broad conclusions or impose a one-size-fits-all regulatory approach for this wide range of substances," a spokesperson says.

Still, views have already shifted on the need for PFASs in firefighting foams. So long as a foam produces a "stable bubble blanket" that prevents oxygen reaching a fire, says Ross, it can be effective without PFASs. Many airports worldwide, including Sydney, London Heathrow and Changi in Singapore, have already gone fluorine-free, he says. And last September, the Federal Aviation Administration exempted U.S. commercial airports from military standards, allowing them to begin switching to fluorine-free foams.

Cousins is now going over the myriad other applications for PFASs. Among the surprising ones are some cosmetics, which seem to contain PFASs for no apparent reason, he says. And elite skiers use fluorinated ski waxes to give them an edge over their competitors—but no country would disadvantage their athletes by banning fluorinated waxes unilaterally, he says.

Fluorinated polymers present perhaps the trickiest case: they are useful and are widely regarded as safe. They coat almost all electronic components and solar panels. They are in medical devices and even the tubing in high-resolution mass spectrometers. (Researchers take precautions to avoid sample contamination.) And very few PFAS molecules are shed from the polymers while they are in use. Yet lots of PFAS by-products are associated with their manufacture, Cousins says.

Sometimes, there are no viable alternatives. One of seven exemptions in a recommendation on banning PFOA in the Stockholm Convention involves protective clothing for medical personnel and workers in the oil and gas industry. These people need protection from both watery and oily fluids, and only PFASs confer that property in materials.

"The irony is that the polyfluorinated chemistry is kind of magic," says Halden. "If they weren't that useful, it'd be easy to say goodbye."

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IAN ROSS *ARCADIS/EVOCRA*

Breathing is like solar energy for powering relaxation: it's a way to regulate emotions that is free, always accessible, inexhaustible and easy to use.

**Stress reduction, insomnia prevention, emotion control, improved attention—certain breathing techniques can make life better. But where do you start?**

*By Christophe André*

# Proper Breathing Brings Better Health

RUSLAN IVANOV GETTY IMAGES

**Christophe André** is a psychiatrist at the Sainte-Anne Hospital Center in Paris and a pioneer in the therapeutic use of meditation in France. He has contributed significantly to the practice's dissemination, especially through his writings, which include the international best seller *Mindfulness: 25 Ways to Live in the Moment through Art* (Rider, 2014).

**As newborns, we enter the world by** inhaling. In leaving, we exhale. (In fact, in many languages the word "exhale" is synonymous with "dying.") Breathing is so central to life that it is no wonder humankind long ago noted its value not only to survival but to the functioning of the body and mind and began controlling it to improve well-being.

As early as the first millennium B.C., both the Tao religion of China and Hinduism placed importance on a "vital principle" that flows through the body, a kind of energy or internal breath, and viewed respiration as one of its manifestations. The Chinese call this energy *qi*, and Hindus call it *prana* (one of the key concepts of yoga).

A little later, in the West, the Greek term *pneuma* and the Hebrew term *rûah* referred both to the breath and to the divine presence. In Latin languages, *spiritus* is at the root of both "spirit" and "respiration."

Recommendations for how to modulate breathing and influence health and mind appeared centuries ago as well. *Pranayama* ("breath retention") yoga was the first doctrine to build a theory around respiratory control, holding that controlled breathing was a way to increase longevity.

In more modern times, German psychiatrist Johannes Heinrich Schultz developed "autogenic training" in the 1920s as a method of relaxation. The approach is based partly on slow and deep breathing and is probably still the best-known breathing technique for relaxation in the West today. The contemporary forms of mindfulness meditation also emphasize breathing-based exercises.

In fact, every relaxation, calming or meditation technique relies on breathing, which may be the lowest common denominator in all the approaches to calming the body and mind. Research into basic physiology and into the effects of applying breath-control methods lends credence to the value of monitoring and regulating our inhalations and exhalations.

## MIND UNDER THE INFLUENCE

Even a rudimentary understanding of physiology helps to explain why controlled breathing can induce relaxation. Everyone knows that emotions affect the body. When you are happy, for instance, the corners of your mouth turn up automatically, and the edges of your eyes crinkle in a characteristic expression. Similarly, when you are feeling calm and safe, at rest, or engaged in a pleasant social exchange, your breathing slows and deepens. You are under the influence of the parasympathetic nervous system, which produces a relaxing effect. Conversely, when you are feeling frightened, in pain, or tense and uncomfortable, your breathing speeds up and becomes shallower. The sympathetic nervous system, which is responsible for the body's various reactions to stress, is now activated. Less well known is that the effects also occur in the opposite direction: the state of the body affects emotions. Studies show that when your face smiles, your brain reacts in kind—you experience more pleasant emotions. Breathing, in particular, has a special power over the mind.

This power is evident in patients who have breathing difficulties. When these difficulties are sporadic and acute, they can trigger panic attacks; when they are chronic, they often induce a more muted anxiety. It is estimated that more than 60 percent of people with chronic obstructive pulmonary disease (COPD) have anxiety or depressive disorders. These disorders probably stem in part from concerns about the consequences of the disease (what could be more distressing than struggling to breathe?), but purely mechanical factors may contribute as well: the difficulty these patients experience often leads to faster breathing, which does not necessarily improve the quality of their oxygen supply but can aggravate their physical discomfort and anxiety.

Rapid breathing can contribute to and exacerbates panic attacks through a vicious circle: fear triggers faster breathing, which increases fear. In 2005 Georg Alpers, now at the University of Mannheim in Germany, and his colleagues observed significant and unconscious hyperventilation when people who had a driving phobia took their vehicles on the highway (where they might not be able to pull over if they become agitated).

Whether anxiety derives from breathing problems or other causes, it can be eased by a number of breathing techniques derived from traditional Eastern approaches (see "Six Techniques for Relieving Stress"). For example, "follow your breath," an exercise that focuses attention

on breathing, is one of the first steps in mindfulness meditation, whereas alternate nostril breathing comes from yoga. Combining reassuring thoughts with breathing is an approach incorporated into sophrology, a technique that emphasizes harmony of body and mind and that borrows exercises from many approaches, including yoga and mindfulness.

Overall, research shows that these techniques reduce anxiety, although the anxiety does not disappear completely. Breathing better is a tool, not a panacea. Some methods have been validated by clinical studies; others have not. But all of those I describe in this article apply principles that have been proved effective. They aim to slow, deepen or facilitate breathing, and they use breathing as a focal point or a metronome to distract attention from negative thoughts.

## SPOTLIGHT ON CARDIAC COHERENCE

A close look at one popular technique—cardiac coherence—offers more detail about the ways that breathing exercises promote relaxation. With the help of biofeedback, the approach attempts to coordinate breathing with heart rate, slowing and steadying breathing to slow and stabilize the heartbeat.

The method was developed based on the understanding that slow, deep breathing increases the activity of the vagus nerve, a part of the parasympathetic nervous system; the vagus nerve controls and also measures the activity of many internal organs. When the vagus nerve is stimulated, calmness pervades the body: the heart rate slows and becomes regular; blood pressure decreases; muscles relax. When the vagus nerve informs the brain of these changes, it, too, relaxes, increasing feelings of peacefulness. Thus, the technique works through both neurobiological and psychological mechanisms.

Cardiac coherence's stabilization of the heartbeat can dampen anxiety powerfully. Conversely, patients with overactive heartbeats are sometimes misdiagnosed as victims of panic attacks because their racing heartbeat affects their mind.

**A typical cardiac coherence exercise involves inhaling for five seconds, then exhaling for the same amount of time (for a 10-second respiratory cycle).**

A typical cardiac coherence exercise involves inhaling for five seconds, then exhaling for the same amount of time (for a 10-second respiratory cycle). Biofeedback devices make it possible to observe on a screen how this deep, regular breathing slows and stabilizes the beats. (The space between two heartbeats on the display is never exactly the same, but it becomes increasingly more consistent with this technique.) Several studies have confirmed the anxiety-diminishing effect of these devices, although the equipment probably has more influence on the motivation to do the exercises ("It makes it seem serious, real") than on the physiological mechanisms themselves. Simply applying slow breathing with the same conviction and rigor could well give the same result.

Some versions of cardiac coherence recommend spending more time on exhaling than on inhaling (for example, six and four seconds). Indeed, your heart rate increases slightly when you inhale and decreases when you exhale: drawing out the second phase probably exerts a quieting effect on the heart and, by extension, on the brain. This possibility remains to be confirmed by clinical studies, however.

Other work suggests that the emotional impact of the breathing done in cardiac coherence and various other kinds of exercises stems not only from effects on the periphery—on the parasympathetic nervous system—but also from effects on the central nervous system. Breathing may well act directly on the brain itself.

In 2017, for instance, Mark Krasnow of Stanford University and his colleagues showed in mice that a group of neurons that regulates respiratory rhythms (the pre-Bötzinger complex in the brain stem) controls some of the activity of the locus coeruleus, a region involved in attention, wakefulness and anxiety. Breathing techniques may influence this seat of emotions by modulating the activity of the pre-Bötzinger complex.

Beyond any direct effects produced by slowed breathing, the attention given to inhaling and exhaling may play a role in the brain's response. In 2016 Anselm Doll and his colleagues, all then at the Technical University of Munich, showed that this attentional focus eases stress and negative emotions, in particular by activating the dorsomedial prefrontal cortex, a regulatory area of the brain, and by reducing activity in the amygdala, which is involved in these emotions.

In addition, paying attention to breathing causes most people to slow it down and to deepen it, which as I have mentioned, is soothing. Cognitive resources are limited, and so when individuals concentrate on breathing, they are not thinking about their worries. Those who practice

mindfulness learn to notice when their attention drifts away from breathing and goes back to their concerns, and they train themselves to return periodically to their breathing. This refocusing has a relaxing effect on anyone and helps to combat ruminative thinking in people who have anxiety or depression, especially those who are particularly prone to negative thoughts that run in a loop.

**Rapid breathing can contribute to and exacerbates panic attacks through a vicious circle: fear triggers faster breathing, which increases fear.**

### WHEN TO USE BREATHING TECHNIQUES

What is the best time to apply slow-breathing techniques? One is during occasional episodes of stress—for example, before taking an exam, competing in a sporting event or even attending a routine meeting at work. In 2017 Ashwin Kamath of Manipal University in India and his colleagues studied stage fright before a public speaking engagement. The participants, all medical students, spent 15 minutes doing alternate nostril breathing—that is, slowly inhaling through one nostril and exhaling through the other by applying finger pressure to the side of the nose not being used. Compared with members of the control group, participants experienced somewhat less stress when speaking publicly.

These exercises may also help when insomnia strikes. In 2012 Suzanne M. Bertisch of Harvard Medical School and her colleagues reported, based on survey data, that more than 20 percent of American insomniacs do these breathing exercises to sleep better. They may be on to something. In 2015 Cheryl Yang and her team at National Yang-Ming University in Taiwan showed that 20 minutes of slow breathing exercises (six respiration cycles per minute) before going to bed significantly improves sleep. Insomniac participants went to sleep faster, woke up less frequently in the night and went back to sleep faster when they did wake up. On average, it took them only 10 minutes to fall asleep, almost three times faster than normal. The investigators attributed the results both to the calming mediated by the parasympathetic system and to the relaxing effect of focused breathing.

But respiratory techniques do not work only for acute stresses or sleep problems; they can also relieve chronic anxiety. They are particularly effective in people with psychiatric disorders such as phobias, depression and post-traumatic stress disorder. In 2015 Stefania Doria and her colleagues at Fatebenefratelli e Oftalmico Hospital in Milan, Italy, offered 10 training sessions of two hours each, spread out over two weeks, to 69 patients with anxiety or depressive disorders. The training included a varied set of breathing techniques (such as abdominal breathing, acceleration and deceleration of rhythm, and alternate nostril breathing), combined with some yoga stretches. The researchers observed a significant decrease in symptoms at the end of the protocol. Even better, improvement was maintained two and six months later, with follow-up sessions just once a week and some home practice during this period.

Breathing exercises also help to counter the accumulation of minor physical tension associated with stress. Therapists recommend doing them regularly during the day, during breaks or at moments of transition between two activities: you simply stop to adjust your posture and allow yourself a few minutes of quiet breathing. Therapists often suggest the "365 method": at least three times a day, breathe at a rhythm of six cycles per minute (five seconds inhaling, five seconds exhaling) for five minutes. And do it every day, 365 days a year. Some studies even suggest that, in addition to providing immediate relief, regular breathing exercises can make people less vulnerable to stress, by permanently modifying brain circuits. In a practice that may seem counterintuitive, however, counselors may encourage some anxious patients to breathe rapidly instead of slowly, as part of an effort to train them to cope with their anxieties (see "Inhale for Panic!").

But why confine breathing techniques to negative emotions? It is also worth applying them during pleasurable moments, to take the time to appreciate and remember them. In short, one can pause and breathe for enjoyment as well as to calm down.

### OPEN QUESTIONS

Tradition and experience encourage the use of respiratory-control techniques, and scientific studies increasingly suggest that it is a good idea. Nevertheless, further research is still needed, particularly given that some studies lack control groups. One exception stands out: focusing on breathing often is not a good idea for people having a panic attack that stems from anxiety over their physical state (also known as interoceptive anxiety). In this case, focusing on physiology, such as muscle tension or breathing, may actually amplify panic ("Now

that I'm paying attention to it, my breathing doesn't seem regular. Am I choking? What will happen if I suddenly stop breathing?") For these people, breathing techniques should be tested and practiced under the supervision of a therapist.

Otherwise, considering how often everyone experiences emotional discomfort in their everyday life and its negative consequences on health, we would all do well to regularly pay attention to the way we breathe. Start with brief periods of conscious, quiet breathing several times a day. Breathing is like solar energy for powering relaxation: it's a way to regulate emotions that is free, always accessible, inexhaustible and easy to use.

In fact, I am mystified that controlled breathing is not recommended and practiced more widely. Perhaps it is perceived as too simple, commonplace and obvious to be a remedy. Faced with the complexity of negotiating the ups and downs of human life, many people may assume that simple solutions cannot be effective.

Or maybe we are intimidated by the sacred aspect of breathing, by its connection to life and, especially, to death. In the 1869 novel *The Man Who Laughs*, Victor Hugo wrote: "Generations are puffs of breath, that pass away. Man respires, aspires, and expires." Ultimately, we don't like to think that we are nothing more than "puffs of breath."

## SIX TECHNIQUES FOR RELIEVING STRESS

Here are some commonly used breathing techniques. Five to 10 minutes of exercise can relieve sporadic stress and even fend off panic attacks. More regular practice can lower the daily levels of anxiety.

### STAND UP STRAIGHT

Posture is important for breathing: hold yourself straight, without stiffness, shoulders back, sitting or standing. This body posture facilitates the free play of the respiratory muscles (of the diaphragm and between the ribs). Good posture enables your body to breathe properly on its own.

### FOLLOW YOUR BREATH*

Simply observe your respiratory movements: be aware of each inhalation and exhalation. Focus on the sensations you feel as air passes through your nose and throat or on the movements of your chest and belly. When you feel your thoughts drift (which is natural), redirect your attention to your breath.

### ABDOMINAL BREATHING

Breathe "through your stomach" as much as possible: start by inflating your belly by inhaling, as if to fill it with air, then swell your chest; as you exhale, first "empty" your stomach, then your chest. This type of breathing is easier to observe and test while lying down, with one hand on your stomach.

### RHYTHMIC BREATHING

Near the end of each inhalation, pause briefly while mentally counting "1, 2, 3" and holding the air before exhaling. This counting while not breathing can also be done after exhaling or between each inhalation or exhalation. It is often recommended for anxious patients to calm anxiety attacks because it induces a beneficial slowing of the breathing rate.

### ALTERNATE NOSTRILS*

Breathe in and out slowly through one nostril, holding the other one closed using your finger; then reverse and continue by alternating regularly. There are many variations of this exercise—for example, inhaling through one nostril and exhaling through the other. Research suggests that what is most important, aside from slowing the breathing rhythm, is breathing through the nose, which is somewhat more soothing than breathing through your mouth.

### THINK REASSURING THOUGHTS WHILE BREATHING

With each breath, think soothing thoughts ("I am inhaling calm"). With each exhalation, imagine that you are expelling your fears and worries ("I am exhaling stress").

### INHALE FOR PANIC!

Whereas slow breathing soothes, overly rapid breathing can induce feelings of stress and anxiety. This phenomenon is used in behavioral therapy sessions to train anxious patients to confront their emotions directly. By deliberately hyperventilating, patients artificially trigger an unpleasant anxiety, which they get accustomed to feeling and learn to put in perspective. This technique also enables them to see that poor breathing habits amplify their fear.

**Technique validated by clinical studies.*

# A Father's Fight

## Nick Sireau's quest to give his sons weed killer could help thousands struggling with rare genetic conditions

*By David Adam*

Nick Sireau quit his job to help find an effective treatment for alkaptonuria.

BRIAN DAVID STEVENS

**David Adam** works for *Nature* magazine.

RED CABBAGE? NICK SIREAU COULDN'T UNDERSTAND WHY THE doctor was asking about red cabbage. It was late one night in October 2000, and Nick and his wife Sonya had just made an alarming discovery. Urine from their two-week-old baby son Julien had suddenly turned dark red, almost black. The physician who came to their cramped London flat assured them that it wasn't blood. Perhaps, he suggested, the pigment from some red cabbage that Sonya had eaten for lunch had made it into her breast milk and was coloring the boy's urine. He told them it was nothing to worry about.

Nick hadn't studied biology since school, but something about the doctor's explanation didn't feel right. So he and his wife sought a second opinion and were referred to a specialist at a London hospital.

The color wasn't from the cabbage. Tests revealed that Julien had a rare genetic disease called alkaptonuria (AKU). The staining came from a rogue chemical metabolite, a by-product of not being able to fully process certain proteins. The boy's body was dumping massive amounts of the substance into his urine, which turned red when exposed to air.

Worse, the chemical was circulating in his blood and accumulating in his joints and soft tissue—in his eyes, his tendons and even his heart. By adulthood, the specialists said, Julien's body would show the wear and tear of a much older person. AKU is not usually fatal, but people with it often have to get elbows, knees and hips replaced by the time they turn 40. Nick and Sonya could limit the amount of protein in Julien's diet to slow these effects, but aside from that there was nothing to be done. No treatment was available.

"It was a real shock," Nick says. "We had never heard of it and had no idea what to do. The doctors told us not to look it up on the Internet, but of course that's the first thing we did. It was horrible."

Nick plunged himself into trying to find some relief for his son. As it turned out, researchers had identified a possible treatment. But the drug was being given to help infants survive a different condition—it wasn't approved for AKU. And the path to approval was blocked by a considerable obstacle: the need for a full-scale randomized clinical trial. That's expensive and difficult enough for medicines used to treat common diseases. It's much harder for a condition that is almost unheard of.

Now, in no small part due to Nick's efforts, this treatment could be widely available for people with AKU in Europe within the next few years. It would be the first effective way to stop the disease, which researchers identified more than a century ago. But the web of challenges that Nick faced serves as a cautionary tale for patients and researchers battling other rare disorders. The number of such conditions will no doubt increase as genetic advances identify the need for treatments targeted to smaller and smaller populations.

"We do need rigorous and robust scientific processes," says Alastair Kent, former director of Genetic Alliance U.K., an umbrella body for more than 200 rare-disease patient groups. "But we also need new ways of proving the quality, safety and efficacy of new drugs." Nick is trying to ensure that the journey will be smoother for others than it has been for him and his family.

## HISTORIC FOE

Archibald Garrod first described AKU in 1902, drawn to it by the color-changing urine, which is caused by the buildup of homogentisic acid(HGA). He noticed that it followed Mendelian inheritance patterns, and it became the first disease ascribed to an inherited cause—although the part of the genome responsible would not be discovered for another 90 years or so.

It occurs when a person has mutations in both copies of the gene for an enzyme known as HGD. The enzyme is found in the liver and kidneys, and helps cells to break down the amino acid tyrosine. AKU became a staple of genetics textbooks, but Garrod's early description of the

disease was as a harmless curiosity, and that has unfortunately stuck.

Like many rare conditions, AKU was not seen as big or lucrative enough to warrant much attention from drug developers. Physicians didn't see it as serious, and people with the disease were too few and scattered to lobby for change. So when Nick started to search the Internet for help with his son's newly diagnosed condition, he found little to go on—just some information posted by a patient in Liverpool, U.K. Nick caught a train north to pay him a visit.

Bob Gregory was a straight-talking former trade-union and city-council official who had been diagnosed with AKU later in life. Like Nick and Sonya, he had been told there was no treatment. But Gregory told Nick that he was trying to change that. He had met with a consultant at Liverpool's university hospital and unleashed his frustration. Why had medicine abandoned people with this condition? The disease had solidified his joints, he said, and made it feel like he lived his life wearing a suit of chain mail. Why were scientists not trying to find a cure?

The physician—Lakshminarayan Ranganath, widely known as Ranga—said he would do whatever he could do to help. Or at least, that's how Gregory remembered it—and he promptly registered Ranga (without initially telling him) as the medical director for a charity he wanted to set up. Nick came on board too, promising to raise money to support Ranga's research.

Ranga agreed to take part. But he didn't actually plan on doing much research. He was busy with his work on diabetes and obesity, and he knew that U.S. physicians were planning a clinical trial for a promising drug. "I really did think it was going to take up very little of my time," Ranga says. "I thought the main challenge was going to be how to make the drug available once the trial finished."

That trial was of a drug called nitisinone, which was originally developed as a weed killer in the 1980s but was found to have toxic effects in fish and rats. Its development as a weed killer was halted, but the company that owned it, Zeneca Agrochemicals, asked some specialists in the United Kingdom to investigate how it worked. The researchers discovered that it kills plants in an unexpected way: it chokes off their supply of chlorophyll by disabling an enzyme called HPPD. According to the scientific literature, the world's leading expert on HPPD was Sven Lindstedt, a clinician at a hospital in Gothenburg, Sweden, so in 1991, the researchers gave him a call. His response astonished them: he wanted to give nitisinone to children.

Lindstedt was searching for a way to inhibit the enzyme in order to save the lives of babies and children with a condition called type-1 hereditary tyrosinemia (HT1), which results from a disruption to the same metabolic pathway affected in AKU. Although the weed killer was toxic, the effects of HT1 were so devastating and deadly that it was considered worth a shot. Lindstedt described the results in a 1992 paper in the *Lancet*: the treatment worked better than anyone had hoped.

Under laws that popped up around the world in the 1980s, companies could reap financial incentives—such as extended patent protection—to commercialize treatments for rare diseases such as HT1. These "orphan drugs" could command a hefty price. So, the Stockholm-based company Swedish Orphan Biovitrum acquired the license for nitisinone and marketed it as Orfadin.

Now, a compound so cheap that it was intended to be thrown on the ground is generating millions of dollars in sales—U.S.$96 million in 2017. And all without a randomized controlled trial. HT1 was considered so serious that the drug was first given under a compassionate-use exemption, and later under an agreement that the company would gather the necessary data on safety and efficacy afterwards.

## INFLEXIBLE END POINTS

Physicians realized that what worked in HT1 should, in theory, also work in AKU. Disabling HPPD halts the breakdown of the amino acid tyrosine. Slowing down the metabolism of tyrosine in people with AKU should also stop them producing so much HGA.

Patients knew this, too, and many were desperate to get their hands on the drug. Some succeeded, and reported improvements, but most attempts by physicians to prescribe the drug "off-label" were turned down by medical insurers and other gatekeepers because it was too expensive. "I couldn't get nitisinone for Bob. It cost £4,000 [U.S.$5,000] a year," says Ranga. In the United States, the price tag was closer to $30,000. To get it covered required approval, and that meant a trial.

The U.S. government stepped in. From 2005 to 2008, researchers at the National Institutes of Health tested nitisinone on people with AKU. This was the trial that Ranga had hoped would report positive results. With hindsight, however, the study was doomed from the start: just 40 patients were recruited, half of whom were not given the drug. And success of the treatment—the clinical end point—was defined in a very narrow way. Doctors measured participants' hip flexibility. When the treatment group didn't show a significant difference over the control group in this measure, the trial was deemed a failure.

"It was very difficult news," says Wendy Introne, the NIH scientist who led the study. "I knew the scientific community was waiting and we all expected nice clinical results to come out of it."

Part of the problem was that the hip movement in the control group didn't deteriorate as much as expected. Introne speculates that this was because all trial participants received regular physical therapy as part of the study. The failure of the trial was especially frustrating, she says, because nitisinone worked exactly as expected from a biochemical perspective: HGA levels plummeted

in the participants receiving treatment.

Still, without meeting its endpoint goals, nitisinone was not going to win approval in the United States. And insurers and other health officials refusing to pay for off-label use elsewhere now had another reason: the evidence suggested that it didn't work. Suddenly, the Liverpool charity was the disease's next great hope. "We knew it could work," Ranga says. "And we knew we could show that."

## A LARGE TRIAL

For a clinical trial to succeed, and to convince regulators, the Liverpool team would have to find a more-reliable end point. That meant tracking how the disease progressed, both in animals and in people. This would require more research, and that meant money.

Nick's first fundraising effort was probably not what he initially had in mind. In 2005, he ran a sponsored half marathon to raise the money needed to transport the dead body of a 74-year-old with AKU from Nottingham to Liverpool. ("It cost £450," Ranga says. "I've still got the receipt.")

The results of the postmortem were intriguing: although the woman's soft tissues were completely rigid and black with HGA buildup, the patterning in tissue such as bone was patchy. This suggested a complicated mechanism by which the damaging deposits build up. "That was the starting point," Ranga says. "Our ideas for researching AKU began from the findings of the postmortem."

Nick—who gave up his job and started working on AKU fundraising full time in 2010—secured £500,000 (U.S.$633,000) from Britain's Big Lottery Fund. This went to James Gallagher, a musculoskeletal researcher at the University of Liverpool, to develop a mouse model of the condition. With the right gene knocked out, mice showed the expected buildup of HGA—and the expected decline in that chemical when they were given nitisinone.

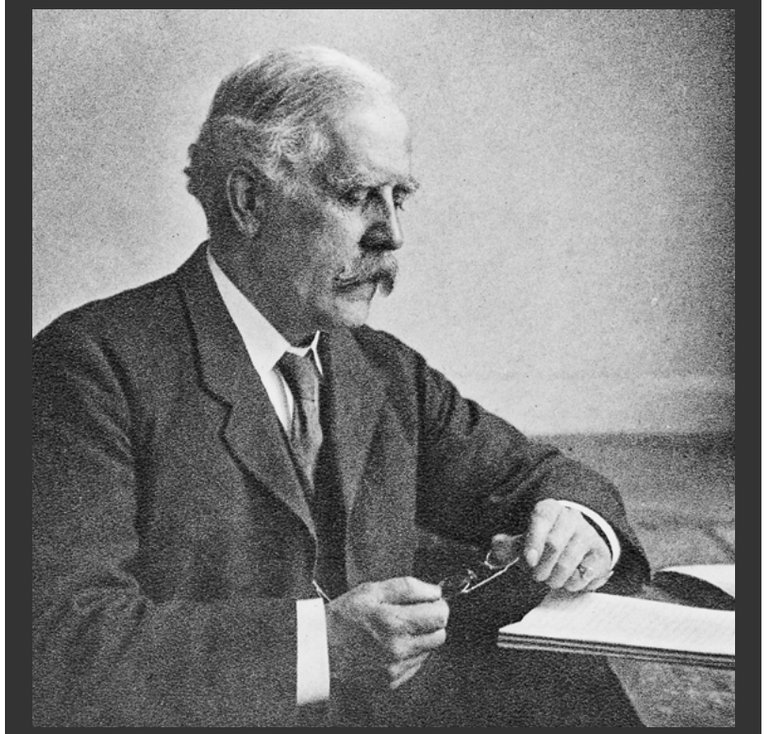
By writing to Britain's 60,000 general practitioners, the Liverpool group then managed to identify and analyze the symptoms of 81 people with AKU in the United Kingdom. (An astonishingly high number given that only 70 to 280 such people exist in the region.) The researchers used these observations to generate a severity index and assess the combined impact of symptoms.

Next was the big one: a full-scale clinical trial. "We knew more about AKU than the NIH by then," says Ranga. "We thought we could do it right." In 2012, the European Commission agreed and said it would hand over £5 million to fund a full-scale trial.

A complication emerged, however. Thanks in part to Nick's lobbying, the U.K. National Health Service agreed to make nitisinone freely available to all patients over the age of 16 in England and Scotland, as long as they traveled to a center in Liverpool (that is now named after Gregory, who died in 2014).

In a sense, Nick had achieved his original goal: his son Julien, and younger son, Daniel, who is also affected, would get access to nitisinone. But now, patients in the United Kingdom couldn't join the trial—too many had access to the drug through the NHS. So the team looked abroad and identified another 400 people with the disease across countries in Europe and beyond. The new crop of recruits includes a group of 19 patients from Jordan, where AKU is unusually prevalent in some rural villages. Mohammed Alsbou, who is coordinating efforts there, says that he has uncovered large pockets of the disease. "Many of them are relatives from my village in the south of the country," he says.

The European nitisinone trial began in 2015 with 138 patients, and the researchers were able to stretch some of the usual confines of randomized trials. Unusually, there is no placebo—the drug stops urine from turning black, so it's obvious to patients whether they are on it. Instead, the control group is left untreated, and are very much aware



### HISTORY OF AN ORPHAN

Alkaptonuria (AKU) has been known about for more than a century and has been a prominent disease in the course of modern medical genetics.

**1500 B.C.:** Signs of the disease are seen in the Egyptian mummy Harwa.
**1902:** Archibald Garrod (*pictured*) proposes that AKU follows Mendelian inheritance patterns, making it the first genetic disease ever identified.
**1958:** Bert La Du and colleagues demonstrate biochemically that a single missing enzyme is responsible for the condition.
**1993:** Martin Pollak and colleagues pinpoint chromosome 3 as the location of the gene encoding that enzyme.
**2003:** Bob Gregory starts the AKU society with physician Lakshminarayan Ranganath.
**2005–08:** A U.S. clinical trial exploring the use of nitisinone finds some clinical benefit for AKU, but does not meet its primary end points.
**2012:** The National Alkaptonuria Center launches in Liverpool, U.K. Nitisinone is made available to residents as part of an observational study.
**2015:** A large-scale, randomized controlled trial begins to test nitisinone in Europe. It includes surrogate end points and no placebo, but should satisfy European regulators.
**2019:** European trial is expected to end.

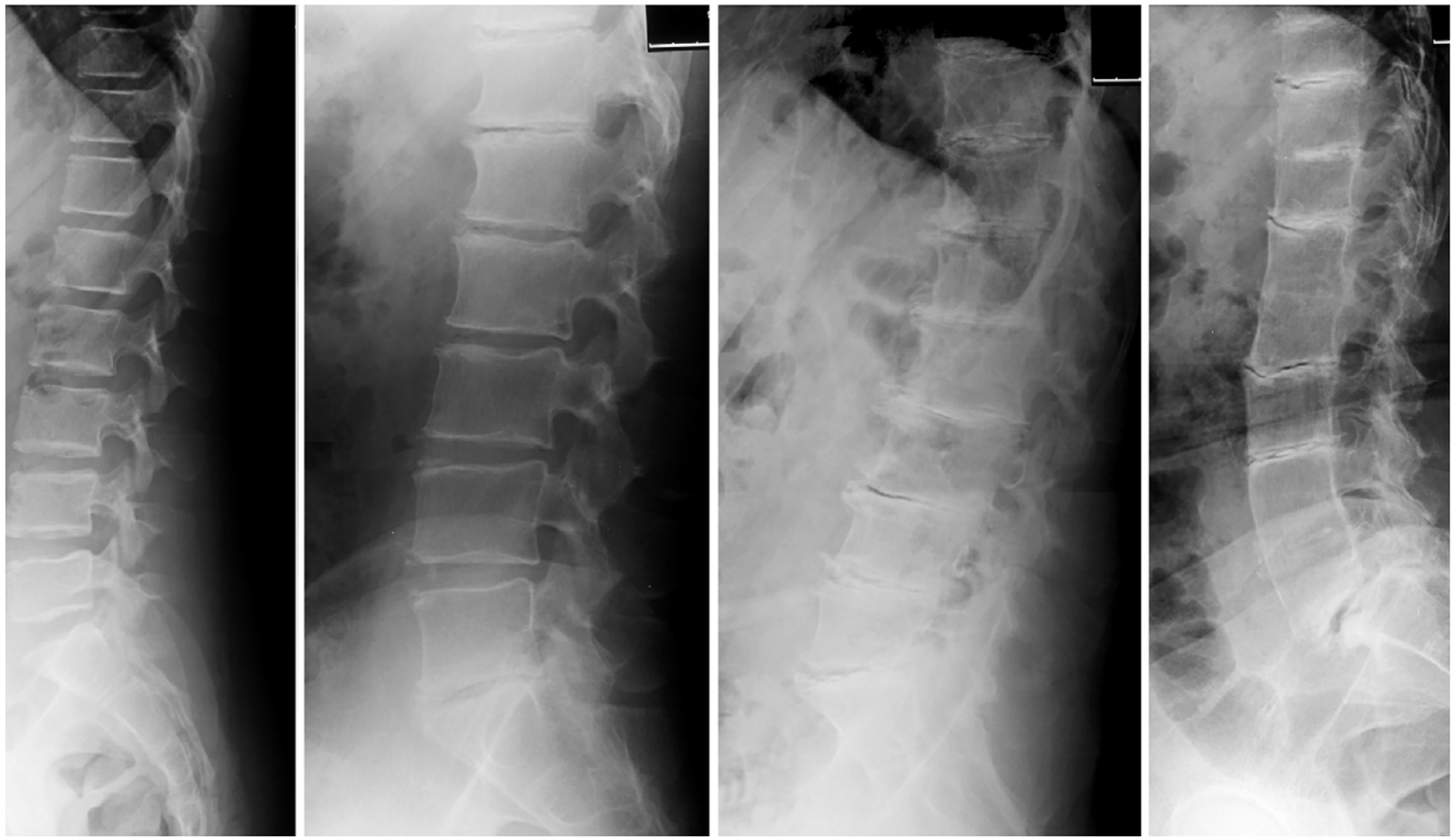
of that. That was a "heartbreaking" decision, says Nick. Still, only a dozen or so of those patients dropped out—which Ranga says demonstrates their dedication to finding a treatment. "These are motivated patients since they were previously completely isolated," he says.

The European trial is bigger than the NIH effort, but there is another, more important difference. Instead of having to demonstrate a significant clinical benefit (in hip rotation or any other anatomical measure) regulators suggested that the trial be judged mainly on a surrogate end point—reduced levels of HGA—accompanied by a vague "positive trend" in alleviation of symptoms. If these can be met, nitisinone will be approved for AKU in Europe.

That's a good example of trial flexibility, says Kent. He suggests that regulators also consider variations such as *N*-of-1 trials, in which a treatment is introduced one patient at a time to build up a trend. He also argues for efforts that move more quickly toward conditional approval, which requires more data to be gathered after patients get access. Such steps will become more important for common diseases, too, he says, as genetic analyses split patient populations into smaller distinct subgroups. "At that point, the traditional approach starts to fall apart," he says.

Around the world, regulators are under pressure to speed up the approval of therapies without sacrificing safety and efficacy assessments. Some of these efforts are controversial—a scheme in Japan to approve stem-cell treatments before they are known to work, for example, and "right to try" laws in the United States that allow people who are terminally ill to take unlicensed medicines. Nick co-founded another charity in 2012 to help people with rare diseases and their carers advocate for orphan-drug development.

In the AKU trial, everybody involved expects people receiving the treatment to show the necessary improvements—not least because of some positive results reported earlier this year by the NHS, which officially labeled its access program as an "observational study." The results showed not only the anticipated drop in circulating HGA, but also a reduction in the speed of disease progression, as measured by the symptom-severity index developed by the Liverpool team. The paper concludes simply: "Nitisinone is a beneficial therapy for alkaptonuria."



Homogentisic acid can obliterate cartilage in the spine as alkaptonuria progresses (*from left to right*).

Ranga says: "I can tell you the difference is immense. I think we've made a real difference, and it's lovely to be able to do that."

In large part thanks to his father, Julien Sireau—now 18—received his first dose of nitisinone in August last year. His brother, Daniel, should get it soon, too. If all goes well in the European study, approval of the drug will put what is now a temporary U.K. supply on a more secure footing, and patients across Europe will gain access.

But that's not the case elsewhere. Nitisinone will still need to be approved by the U.S. Food and Drug Administration to reach patients there. And unlike the Europeans, U.S. officials have signaled that a surrogate end point won't be acceptable. "I haven't given up. I'm still optimistic about the drug," says Introne. Yet for many more couples who find red-black staining in their infant's urine, the long journey through—and against—the system is just beginning.

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LAKSHMINARAYAN RANGANATH

# HOW THE NEXT RECESSION COULD SAVE LIVES

**Death rates have dropped during past economic downturns, even as many health trends have worsened. Researchers are scrambling to decipher lessons before the next big recession**

*By Lynne Peeples*

Soup kitchens sprang up around the United States at the onset of the Great Depression in the 1930s, including this one in Chicago, Illinois, run by notorious gangster Al Capone.

GETTY IMAGES

**Lynne Peeples** is a science journalist based in Seattle.

IN 1922, A PAIR OF SOCIOLOGISTS at New York's Columbia University were poring over 50 years of U.S. economic and mortality data, when they noticed a surprising result. Lean times in the country's history didn't correspond with more deaths, as they expected. In fact, the opposite was true. More people—babies included—died when the economy prospered.

William Ogburn and Dorothy Thomas were skeptical enough to delve further. Would accounting for a possible lag in time between the downturn and the rise in deaths change the outcome? Or perhaps deaths had simply been recorded more rigorously during boom times? No, and no. Their peculiar finding seemed to hold.

About a decade later, data from the Great Depression, which hobbled the U.S. economy for much of the 1930s, pointed to a similar conclusion. "After several years of severe economic stress, the gross death rate has attained the lowest level on record," wrote Edgar Sydenstricker, a social epidemiologist with the U.S. Public Health Service, in 1933.

Even numbers from the global financial crisis of the late 2000s follow suit. José Tapia Granados, a health economist at Drexel University in Philadelphia, Pennsylvania, has calculated that death rates in Europe dropped faster during this downturn, known as the Great Recession, than before the crisis hit. The trend held even in his birth country of Spain, where unemployment topped 20 percent.

"Everyone was expecting a strong increase in mortality. Again, it was the opposite," he says. Now he calls the link between recessions and lowered death rates, "almost as strong as the evidence that cigarette smoking is bad for health."

And yet, no one is quite ready to toast economic crises as a boon to public health. "If that were really true, then why don't we just recommend recessions?" says Ralph Catalano, a public-health researcher at the University of California, Berkeley. He and other scholars point to data showing clear negative consequences for individuals facing financial hardships, from stress-induced chronic diseases to mental-health problems.

Small salubrious effects spread among the majority of people could be masking a significant decline in health among the few—and a deepening of health inequities, warn some social scientists. Suicide rates, for example, usually seem to rise when the economy falls. And the opioid epidemic in the United States has caused particular harm in the populations most affected by the financial crisis. As leading causes of death have shifted there and elsewhere in the world—with greater contributions now from drug overdoses and cancer—signs are also emerging that the historical pattern between mortality and economic cycles has weakened in the past two to three decades.

A decade since the start of the Great Recession, and nearly 90 years after the onset of the Great Depression, researchers continue to debate how the economy affects public health. Meanwhile, lessons are emerging that could help to steer policymakers as they brace for the next crash, one that leading economists now predict could strike by the end of this year.

"Is a booming economy really good for people or bad for people? The answer, of course, is yes," says Harold Pollack, a social-policy and public-health specialist at the University of Chicago in Illinois. "What we have to do is understand the ways it is protective or harmful. And then determine how we can maximize the protective dimension and minimize the harmful."

## SILVER LININGS

Christopher Ruhm has spent the past two decades investigating the links between downturns and health. When he started his research, he wasn't aware of the early 20th-century literature. That work had been generally forgotten, he says, because it "didn't fit the obvious narrative."

He began by plugging data from more than a century of U.S. history into a complex statistical model. Then, like his pre-Depression counterparts, he thought he had made an error. "So, I started looking at the raw data," says Ruhm, an economist at the University of Virginia in Charlottesville. "But it wasn't some programming mistake; it was real." In fact, he and others replicated the finding—in different situations, in different time periods, in different countries. In every case, Ruhm notes, the health of a majority of people improved, while the health of a minority declined.

There are many potential contributors. One of the more predictable perks of a poor economy is fewer job-related accidents. The most-experienced workers are the ones most likely to keep their jobs during a recession, and slower production can allow for more attention to safety.

People also tend to drive less, which translates to fewer traffic accidents. And fewer vehicles on the road might also help to explain why air quality is better. "When employment pops up, so do things related to pollution—commerce, industry, trucks on the road," says Mary Davis, an environmental-policy specialist at Tufts University in

Medford, Massachusetts. The air-quality connection might also help explain why studies have also linked recessions to reduced cardiovascular and respiratory problems, as well as infant mortality.

Researchers have suggested other explanations. In addition to dirty air, cardiovascular issues are known to be exacerbated by stress, a poor diet, lack of exercise, drinking alcohol and smoking tobacco. Working less and having less money to spend could translate into more sleep, exercise and home-cooked meals, as well as less job-related stress and less money for pints of beer and cigarettes. There is some evidence that this logic plays out. Based on data from 1987 through to 2000, Ruhm found that smoking and excess weight declined during economic downturns, whereas leisure-time physical activity increased. When Iceland's economy crashed in 2008, and the price of imported goods such as tobacco and alcohol rose, citizens consumed fewer of those products. And U.S. data from 1977 to 2008 showed that a husband's unemployment reduced how much alcohol his wife drank, on average, irrespective of her own employment status. Even people who fear job loss, but remain fully employed, Catalano's research suggests, might still cut back on alcohol to seem a more indispensable employee.

Yet studies have shown that people cope with economic insecurity in unhealthy ways, too. Although overall alcohol consumption decreased during U.S. recessions in the 1980s and 1990s, binge drinking increased. And researchers have found that opioid prescription rates during the Great Recession were highest in the south, Appalachia and rural western United States, some of the areas hardest hit.

"If people are depressed and stressed out, they might drink more, use tobacco more, or eat more comfort foods," says Sarah Burgard, a sociologist at the University of Michigan in Ann Arbor.

**"If people are depressed and stressed out, they might drink more, use tobacco more, or eat more comfort foods."**

***—Sarah Burgard***

### DOWNTURNS' DOWNSIDES

Burgard and Ruhm met in Ann Arbor, in October 2004. They were two of a couple of dozen economists, epidemiologists, sociologists and psychologists tapped to co-author a book on the health effects of social and economic—or "nonhealth"—policies. The meeting had brought them together to share initial outlines for their chapters. But a divide soon appeared. As fellow participants proposed disparate takes on how a failing economy helps or harms health, some people grew "red and heated," Burgard recalls.

"Economists were really pushing hard on positive effects. But the occupational psychologists and sociologists in the audience were not having it," she says.

She knew that many negative effects could stem from unemployment, income shock and vanished investments. A study published last March linked the Great Recession with high blood pressure and high blood glucose levels in Americans. Losing a job when a business closed increased the odds of developing a stress-related condition such as hypertension, arthritis, diabetes or psychiatric disorders, according to a study published in 2009. And the effects might linger.

A person in the United States who lost their job—and, thereby, their employer's health insurance—might seek fewer prescription refills or preventive screenings, and that could lead to greater complications from diabetes or a higher risk of late-stage cancers years later. Or the chronic stress of unemployment and a thin wallet might take its toll on the body—increasing inflammation, reducing immunity and altering levels of hormones that are crucial to keep the body functioning normally.

The Great Recession has also been tied to outbreaks of infectious disease. The abandonment of home swimming pools during the foreclosures that followed the crisis helped to trigger a nearly threefold rise in cases of mosquito-borne West Nile virus in Kern County, California. And part of Greece's response to the economic downturn—cutting back on mosquito spraying and needle-exchange programs—resulted in a return of malaria and a doubling of HIV infections.

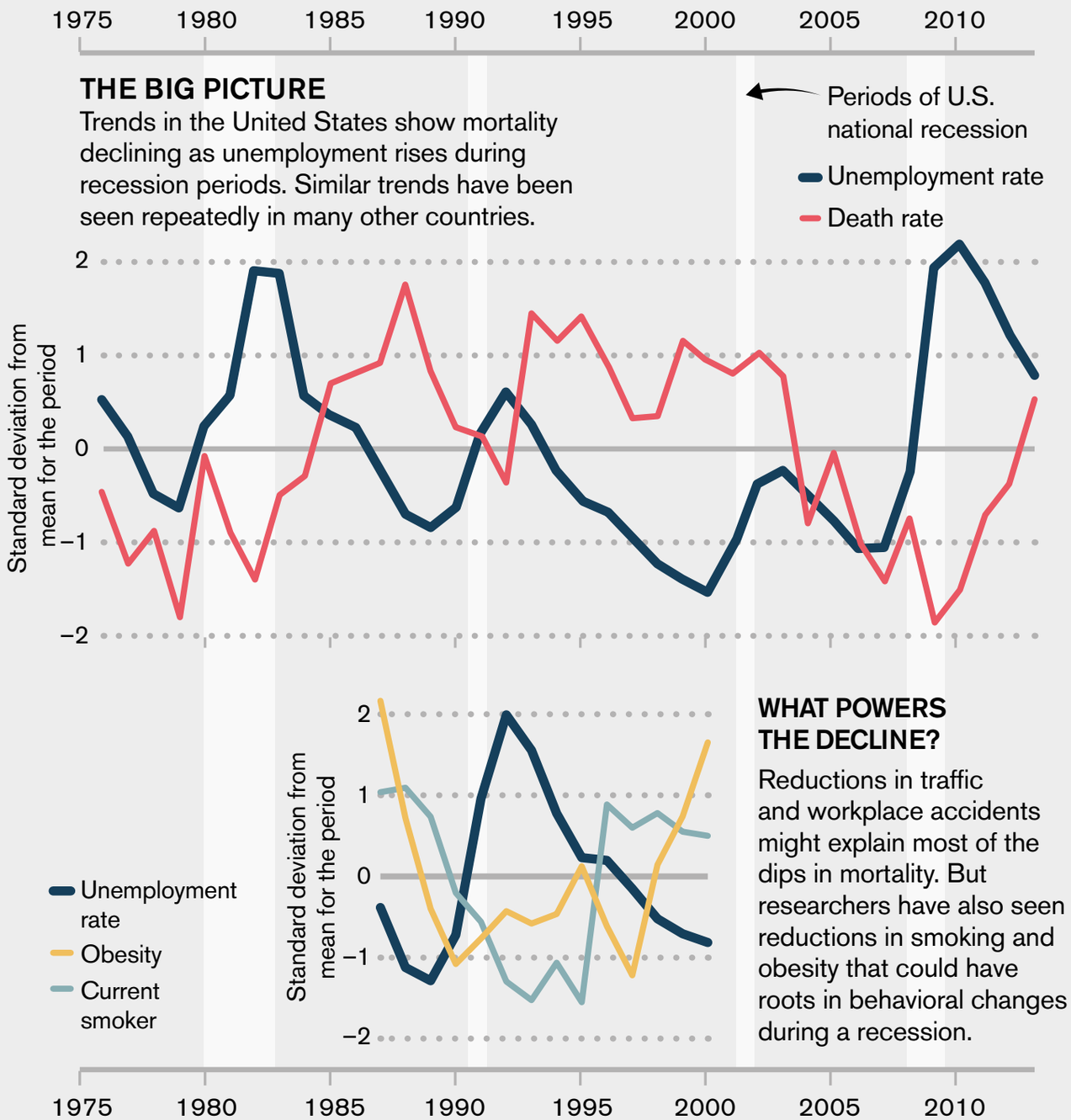
These health consequences have not been evenly distributed across populations. In a study of European countries during the Great Recession, Kjetil van der Wel, a social scientist at Oslo Metropolitan University, found that health inequality increased by as much as 15 percent in countries that experienced a severe drop in gross domestic product along with cuts to government-funded social programs and other austerity measures.

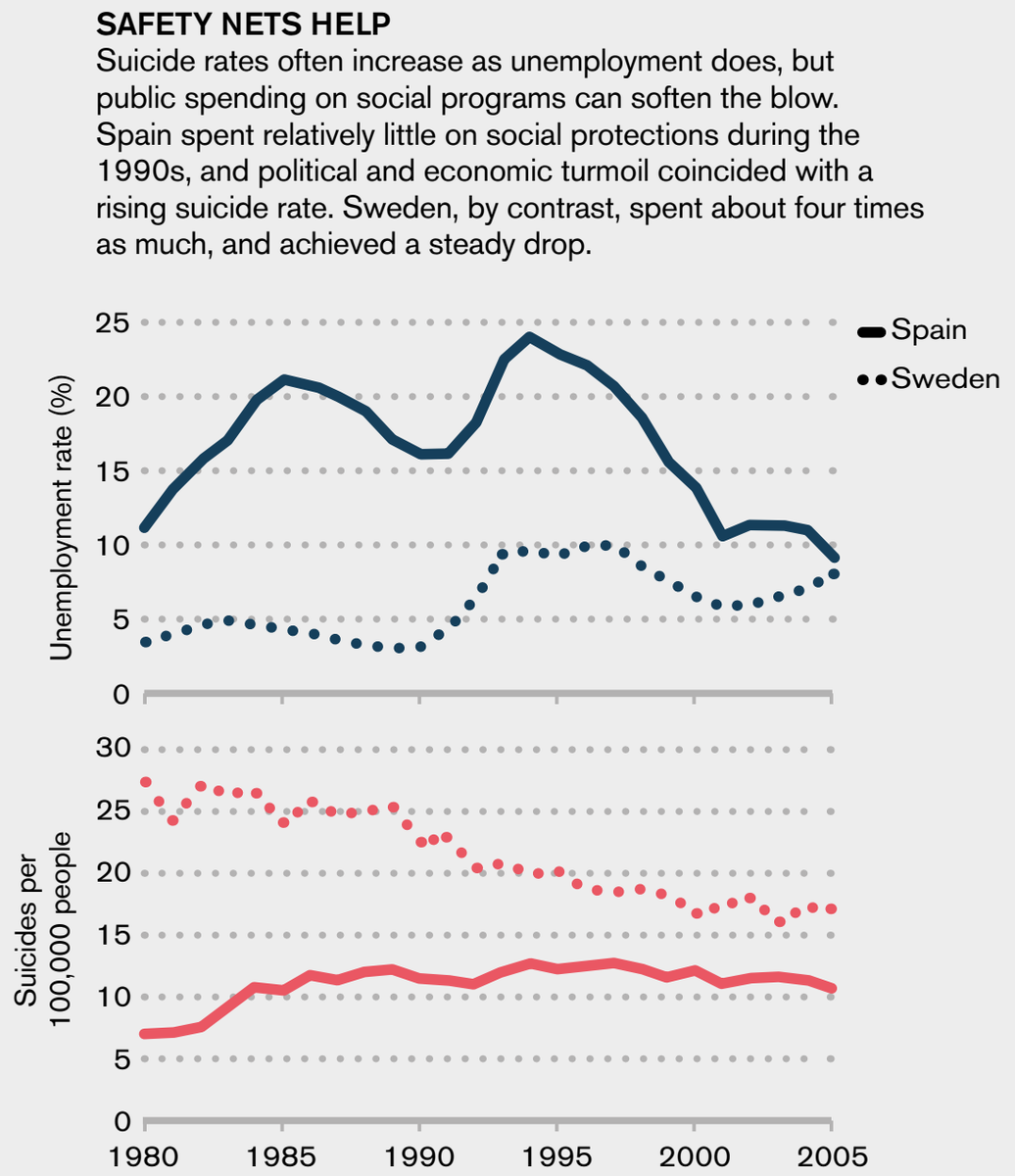
And most of the data available, whether showing positive or negative effects, come from the developed world. Much less is known about the impacts of recessions in poor and developing countries.

Social scientists and epidemiologists are beginning to

# The Tenuous Benefits of Economic Crises

Researchers have long noted a counterintuitive relationship between human health and the economy in developed nations. When recessions hit, the mortality rate drops faster than during boom years. But hiding in the data are many detrimental effects to mental health and the health of people low on the socioeconomic ladder.




SOURCES: C. J. RUHM, *HTTPS://GO.NATURE.COM/2ATMYXW*; C. J. RUHM, *HTTPS://GO.NATURE.COM/2TIDGOP*; D. STUCKLER ET AL. *LANCET* 374, 315–323 (2009)

find more common ground, especially in the possibility that losing a job might be bad for an individual's health, whereas a declining economy could still be good, on average, for a population's physical health—although not necessarily mental health. Burgard left the Ann Arbor meeting intrigued enough to read the studies by Ruhm and other economists, as well as the papers dating back to the 1920s and 1930s.

"That was a big revelation," she says. "The conclusions we were drawing from different research perspectives can actually coexist."

## DRIVING DESPAIR

In President Franklin D. Roosevelt's inaugural address in 1933, he told the U.S. people that the nation's "common difficulties" at the time concerned "only material things."

He wasn't entirely correct. Everyone seems to agree that a poor economy is bad for mental health. And that can be linked to more than just money and material things, suggests Burgard. Someone who becomes unemployed can also face the loss of a major social role that once provided a sense of purpose and identity. And losing a home can undermine people's sense of self-worth. "It's not just a hit to your credit rating," she says. Burgard has linked perceived job insecurity to depression and anxiety even in those who avoided unemployment in the Great Recession.

Across the decades, suicide rates have generally risen during recessions. Sydenstricker noted this in the 1930s, and it has continued. David Stuckler, a political economist and sociologist at Bocconi University in Milan, Italy, estimates that the United States saw 4,750 more suicides between 2007 and 2010 than would have been expected given prerecession trends. Although some evidence suggests that economic fluctuations might not be the strongest contributing factor.

Suicide and overdose rates continued to rise in the United States even as the economy rebounded from the recession, for example. Stuckler suspects that this boom-time bump has been driven by a long-term upwards trend linked to factors such as the availability of guns and opioids.

A homeless man gets dressed in a tent city for the homeless October 6, 2008 in downtown Reno, Nevada. The city of Reno set up the tent city when existing shelters became overcrowded as Nevada struggled with one of the highest unemployment rates in the country.

MAX WHITTAKER *GETTY IMAGES*

The U.S. Centers for Disease Control and Prevention announced last November that 2017 was the third straight year of decline in U.S. life expectancy—despite its continued ascent in other high-income countries and despite the United States' oversized spending on health care.

One explanation could be that the United States also spends the least on social safety nets, relative to those healthier countries. "If you underspend in social services and overspend in medical services, that's associated over decades with worse health outcomes," says Elizabeth Bradley, a global-health scholar and president of Vassar College in Poughkeepsie, New York.

When they faced major recessions, Sweden and Fin-

land invested heavily in worker retraining and other programs to improve people's chances of getting jobs. As a result, these countries escaped rises in suicides, says Stuckler. "These programs help people stay plugged in," he says. "They give people a reason to get out of bed in the morning."

## HEALTH MAKES WEALTH

Health-promoting investments, such as those made by Sweden and Finland during recessions, might also help an economy to bounce back by boosting productivity and reducing the burden on welfare. An analysis of Denmark's active labor market programs calculated savings equal to about U.S.$47,000 per worker between 1995 and 2005.

A similar connection emerged during the New Deal, the social and economic programs championed by Roosevelt between 1933 and 1938, and widely credited with pulling the United States out of the Great Depression. The initiatives included housing, nutrition and healthcare support. Stuckler estimates that for every $100 in New Deal spending per capita, there was a decline in pneumonia deaths of 18 per 100,00 people, a reduction in infant mortality of 18 per 1,000 live births and a drop in suicides of 4 per 100,000 people. More generally, according to Stuckler's calculations, investing $1 in public-health programs can yield as much as $3 in economic growth.

International creditors might have been using different calculations when they implored countries to implement harsh austerity measures during the 1997 Asian financial crisis. The result was widespread hunger and infectious-disease outbreaks in Thailand and Indonesia; Malaysia, which resisted the creditors' call, survived the crisis with its public health relatively unscathed. Greece, too, implemented an austerity plan in 2010 in an attempt to resolve its enormous debt. The more spending the country cut, the more its economy shrank. And health plummeted, with the greatest impacts in those most reliant on safety-net programs: young and elderly people.

Health problems that arise during recessions, Stuckler suggests, might have less to do with the recession itself and more to do with the policy response. "Cutting public health is a false economy," he says. "Unfortunately, it is a soft, easy target for politicians."

Economists now predict another impending recession, which could widen the gap between wealthy and poor, and healthy and sick. Yet researchers hope that the next crash will lend more data and help to understand the nuanced links between economic cycles and health. Is the growing contribution of cancer to modern mortality—and the increasingly unaffordable price of effective treatments—dampening the historically downwards trend in deaths during downturns? What social safety nets and other policies—such as those that affect access to alcohol, drugs or guns—are most protective for public health? And how might leaders leverage the potential of communities working together during a crisis?

Such insights might also hint at ways to improve health in economic boom times, by reducing dangers associated with overconsumption, traffic accidents or pollution. The ultimate goal, notes Stuckler, is to identify and prevent avoidable suffering.

"There has been a lot of intellectual infighting in the debate over whether economic crashes are good or bad for health," he says. "Now, the key question is how can we protect people who are put in harm's way by these crises. What choices do we have?"

*This article is reproduced with permission and was first published in* Nature *on January 26, 2019.*

**David Plans** is founder and CEO of BioBeats.



OBSERVATIONS

# We've Lost Touch with Our Bodies

**But we can get it back through a process known as "interoception"**

GETTY IMAGES

The widespread availability of medicines has made it possible for us to avoid suffering in a way that no previous generation from any era could. But in many cases, drugs just mask the symptoms of our illnesses, discomforts and disorders without addressing the underlying disorders that cause them. This is not to denigrate pharmacological psychiatry and its many successes and advances, or clinical psychology, or molecular medicine. The alleviation of suffering is a natural and worthy aim, and often the only thing we can do.

But drugs can cause their own problems: getting rid of heartburn with omeprazole and other proton-pump inhibitors, for example, can hide serious gastrointestinal issues, and might allow us to continue eating foods that are ultimately harmful. Benzodiazepines such as Valium dull anxiety but also create profound dependence, and they also can sidetrack investigation and treatment of underlying causes. Antidepressants, though often necessary and lifesaving, have side effects, including weight gain, constipation, drowsiness, nausea, blurred vision and sexual dysfunction; more worryingly, many appear to double the risk of suicidal ideation. And so on.

Our use of drugs to mask symptoms has contributed to a lack of awareness about our own

bodies. So has the emergence of technologies such as computers, smartphones, remotes and game controllers, which only involve our bodies—usually just our fingers—as control inputs.

This lack of connection to our bodies can be looked at through a concept called interoception, which describes our awareness of internal bodily signals, including the detection of sensations such as hunger, thirst and heartbeat. Interoception is a process by which our brains/minds make sense of these signals, which serve as a running commentary or mental map of the body's internal world across conscious and unconscious levels of perception.

Our culture, technology and medicine have progressively made us into poor interoceptors.

Disrupted interoception is now understood to play an important role in mental health conditions, including anxiety and mood disorders, eating disorders and addiction, and it is thought to be a feature of most psychiatric disorders. *Scientific American* has previously explored the role of interoception in eating disorders ("A Broken Sense of Self Underlies Eating Disorders"), emotional awareness ("Emotional Ignorance Harms Health"), and the location and function of such awareness in the brain ("Where Mind and Body Meet"). And results from relatively recent neuroanatomical and neuroimaging studies have shown how dysfunctional interoception can cause or exacerbate anxiety and depression.

However, a number of logistic and theoretical challenges have so far made it difficult for interoception to be measured accurately, so it has seen little application in mental health research and therapeutics. Recent studies have shown, however, that some progress has been made in not only measuring interoception but also in training it in order to potentially improve resilience to mental illness. In addition to direct effects on symptoms, an increased ability to represent one's internal state is linked to increased ability to understand the emotions and thoughts of others, as found in a recent study linking interoception, emotion and theory of mind. This increased ability to read, understand and respond to other individuals is likely to lead to increased levels of social support, which is of proven efficacy in increasing resilience and well-being.

**Our use of drugs to mask symptoms has contributed to a lack of awareness about our own bodies. So has the emergence of technologies such as computers, smartphones, remotes and game controllers, which only involve our bodies—usually just our fingers—as control inputs.**

Interoception training could thus be used to help us form a better, healthier sense of our own bodies by focusing on our internal sensations both at the visceral level (interoception) and that of our body's movement (proprioception). This is in fact what ancient health systems like yoga try to do, by combining calisthenics with interoceptive and mindful awareness. And in one of technology's redeeming qualities, whereby it can offer data on our bodies never before available to us, new forms of biofeedback could help enhance our interoception by illuminating internal body signals, to help us be more aware of and in concert with them.

The history of interoception science goes back to Charles Darwin, who discussed the role of visceral sensations in emotion in *The Expression of the Emotions in Man and Animals*, and then William James and Carl Lange, who explored the relationship between interoception and emotional experience and developed the James-Lange theory of emotion. Not much later, in 1906, Charles Sherrington published *The Integrative Action of the Nervous System*, a collection of lectures where he spoke of "interoceptors" as part of his explanation of the visceral system. The scientific community wasn't going to use the word in scientific journals until the 1940s, and by the 1960s there was an increased focus on interoception as a result of interest in biofeedback interventions.

We can, however, look much further back than modern psychology: contemplative traditions have all explored the idea of the "subtle body," grounded in traditions and medical practices that proposed holistic rather than dualistic under-

standings of body and mind. Indian, Tibetan and Chinese medicine have all explored body sensations and their modulation, creating anatomical maps of energy points (*chakra*s in Sanskrit, *dan t'ian* in Chinese) and channels in the subtle body for the movement of energy known variously as *ch'i*, *prāṇa* or *lung*. In those practices, all mental states were understood to travel the energy currents described in their maps.

Although it isn't currently clear whether or how such conceptualizations map onto current scientific understandings of interoception, these ideas suggest that attention to somatic, embodied experience has been important in self-understanding and well-being for millennia. They potentially support the hypothesis that overreliance on abstract and disembodied concepts, as opposed to information grounded in bodily awareness, could significantly limit our ability to relate to ourselves and others.

The clear benefits of training interoceptive awareness should therefore be explored in new forms of digital therapeutics. We might begin simply by adapting typical mindfulness practice concepts: developing an awareness of bodily sensation in time was outlined as a primary goal in early texts of both Indian and Chinese contemplative practice. To tell apart this kind of awareness from pure thought, contemporary forms of biofeedback could incorporate recent neuroscientific understanding of the networks involved in our sense of bodily experience versus our understanding of the experience itself, helping better use our corporeal intelligence (the gut, the heart) rather than relying largely on our cerebral intelligence.

In this age of disembodiment, learning to attend to signals from within could thus reconnect long-lost networks of perception that used to root us to the world, to inform our experience of love, affection, belonging and coherence with our environment. We perhaps need that now more than ever. As Thomas Joiner has lucidly written in *Mindlessness*, we've been sold an idea that "mindfulness" is a miracle drug, a quick remedy to our attention-starved, frantic perception of the world as ever-increasingly fast-moving and out of reach.

Our culture—in Joiner's words, a culture of "superficiality, mediocrity and selfishness"—has adopted mindfulness as a way to "empty the mind," a way to stop caring and to observe the world in a detached, disembodied way. Instead of fully investing in our awareness of the world, we have hawked thousands of years of understanding in how our bodies and minds interact for a quick fix of undifferentiated, narcissistic self-preoccupation, a contemplative extension to the selfie.

True mindfulness is currently being usurped by a loud, strutting imposter who lacks social empathy (and if this sounds familiar and political, it is so because the nature of the problem is the same). There could be no stronger sign that we are looking inward in the wrong way. To build better well-being, individually and societally, we must look within, as the signals that give us insight into the emotional world come from there. But to build a better world, to exist usefully within it and improve it, we must look without and learn again to pay sustained, compassionate attention.

**Marc Ringel** is a family doctor, teacher, writer and consultant. His most recent book, which examines using information technology in healthcare in a way that enhances humanity as well as efficacy, is *Digital Healing: People, Information and Healthcare*.



OBSERVATIONS

# Ob-Gyns Do Too Much Fetal Monitoring

**It's important in high-risk pregnancies, but most pregnancies aren't risky**

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For nearly three decades, I reminded every woman I saw in my family practice, from adolescence onward, to do a monthly self-breast examination (SBE). It made great sense in theory: the earlier you find a malignancy, the earlier you can treat it, and the better the outcome.

But when researchers looked at actual outcomes, they found that women who discover lumps when doing a routine self-exam live no longer or better than women whose tumor is found with an exam by a health care provider; a mammogram; or accidentally, by the woman herself or a lover. The one difference between the two groups was that the women who found lumps with a self-exam had more procedures, expenses and worry.

Based on solid evidence, the American Cancer Society recommended in 2003 that self-breast examination be optional for women over the age of 20. By 2015, ACS guidelines for women at normal risk (e.g., with no family history of breast cancer) didn't even mention the SBE, nor even clinician exams. Mammograms, starting from the age 40 or 45, became the sole focus for screening low-risk populations. Of course, any woman who does find a breast lump (or man, for that matter) should see a provider right away.

Continuous fetal monitoring (CFM) is another of those widespread measures that makes much better logical than clinical sense. In the 1880s, midwives learned to assess the well-being of a fetus by counting the baby's heartbeats, audible

through a stethoscope applied to the mother's abdominal wall. The modern cesarean section was added to the surgical armamentarium at about that time, providing a powerful option for managing fetal distress. Doctors could literally snatch compromised babies right out of their mothers' wombs.

By the 1960s, monitoring technology had progressed to an ultrasonic gizmo, held against the mom's belly with an elastic band, that could pick up the fetal pulse continuously and record it as a squiggle on a long strip of paper. Paired with a tocometer, which measures uterine contractions (and is also held against the mother's abdomen and outputted to that same strip of paper), this gave health care workers a powerful way to track fetal well-being from moment to moment. Continuous fetal monitoring quickly became de rigueur. I spent a good deal of my medical school obstetrics rotation adjusting ultrasound and tocometer heads that had lost the signal.

Trouble is, when you compare the labors of women with low-risk pregnancies who have been monitored continuously to labors of women who have not, the babies come out about the same. But the continuously monitored mothers are subjected to significantly more interventions—oxytocin stimulation, forceps deliveries, episiotomies, C-sections, etc.—with their attendant expenses and complications. The critical phrase here is "low-risk pregnancies," which is what most pregnancies are. For uncomplicated patients, fetal well-being can be assessed more than adequately by intermittently measuring babies' heart rate with a handheld ultrasound device. There are still plenty of good reasons to monitor some labors continuously—just not most.

**In the 1880s, midwives learned to assess the well-being of a fetus by counting the baby's heartbeats, audible through a stethoscope applied to the mother's abdominal wall.**

Moreover, despite reams of studies and guidelines about CFM, diagnosis of fetal distress based on monitor data is still dismayingly imprecise. Two doctors can look at the same strip and draw opposite conclusions. So far, artificial intelligence hasn't helped much to distinguish reassuring from nonreassuring monitor tracings.

If there is any doubt about a baby's well-being, professionals reflexively want to do something. Anything but a reassuring tracing heightens vigilance, steering the birth process down a path that may well lead to more intervention.

Mammals, including humans, move about a good deal in labor. Women naturally change position. They may thrash or pace. Making them stay still so that finicky electronic monitors can remain in position is unnatural. It inhibits a laboring mother's instinctual movements that help her fetus find an optimal lie for its journey down the tight birth canal. Restricting her freedom of movement may cause a mother to experience more anxiety and pain, making it likely that she will require more labor-slowing pain medications.

Many labor and delivery units have now changed their protocols for low-risk pregnant women. Instead of automatically resorting to CFM, on admission staff obtain a "baseline strip" of about a half hour, just to reassure themselves that the baby is starting out okay. Once again, studies have shown that such strips too often nudge normal women with normal pregnancies who will deliver normal babies in the direction of instrumented or operative deliveries, with no better outcomes for their babies and more complications for themselves.

Many a doctor has acceded to routine CFM for her patients because she has asked herself, "What am I going to say in court, with the plaintiff sitting there before the jury, her pitiful 'damaged' child in her arms, when her attorney asks me, 'So, in the absence of monitoring her continuously during labor, how did you know, *Doctor*, this poor baby was okay?'" Never mind that the vast majority of newborn problems have nothing to do with what happens during labor and delivery, nor that a fetal monitor strip is equally likely to hurt as to help a malpractice defense.

The best protection against being sued, study after study has shown, is a good relationship between provider and patient. Placing an electronic device between mother and professional doesn't help. When I taught obstetrics to family medicine residents, I'd often have to remind these young doctors-in-training to stop and ask their laboring patient how she is doing before they walked over

to the monitor to see what the strip appears to say about how she and her baby are doing. Practicing doctors too often forget the maxim that everybody learns in medical school, "When all else fails, listen to the patient," let alone that it's supposed to be sarcastic.

Women were glad to learn they didn't need to be checking their breasts every month. It was one less thing to do or to feel guilty about not doing. And I was relieved to have one less thing to nag them about.

Diminishing routine use of continuous fetal monitoring has been much harder to accomplish. As of 2013, 89 percent of labors in the United States were monitored, 80 percent of those continuously. "Nonreassuring fetal heart rate tones" remains the second most common reason given for a first cesarean (after "failure to progress," which means that it doesn't look like the baby will come out on its own).

Unlike the self-breast exam, which is patient-initiated, the decision to do continuous fetal monitoring is essentially up to health professionals, who are likely too scared not to do something if it appears that something could be done. Trouble is, there's a big difference between what could be done and what should be done. How we employ continuous fetal monitoring is but one example of the pervasive challenge of shifting medical practice from coulds to shoulds. Practice change depends much more heavily on adjusting attitudes, incentives and culture than it does on gathering and analyzing ever more data.

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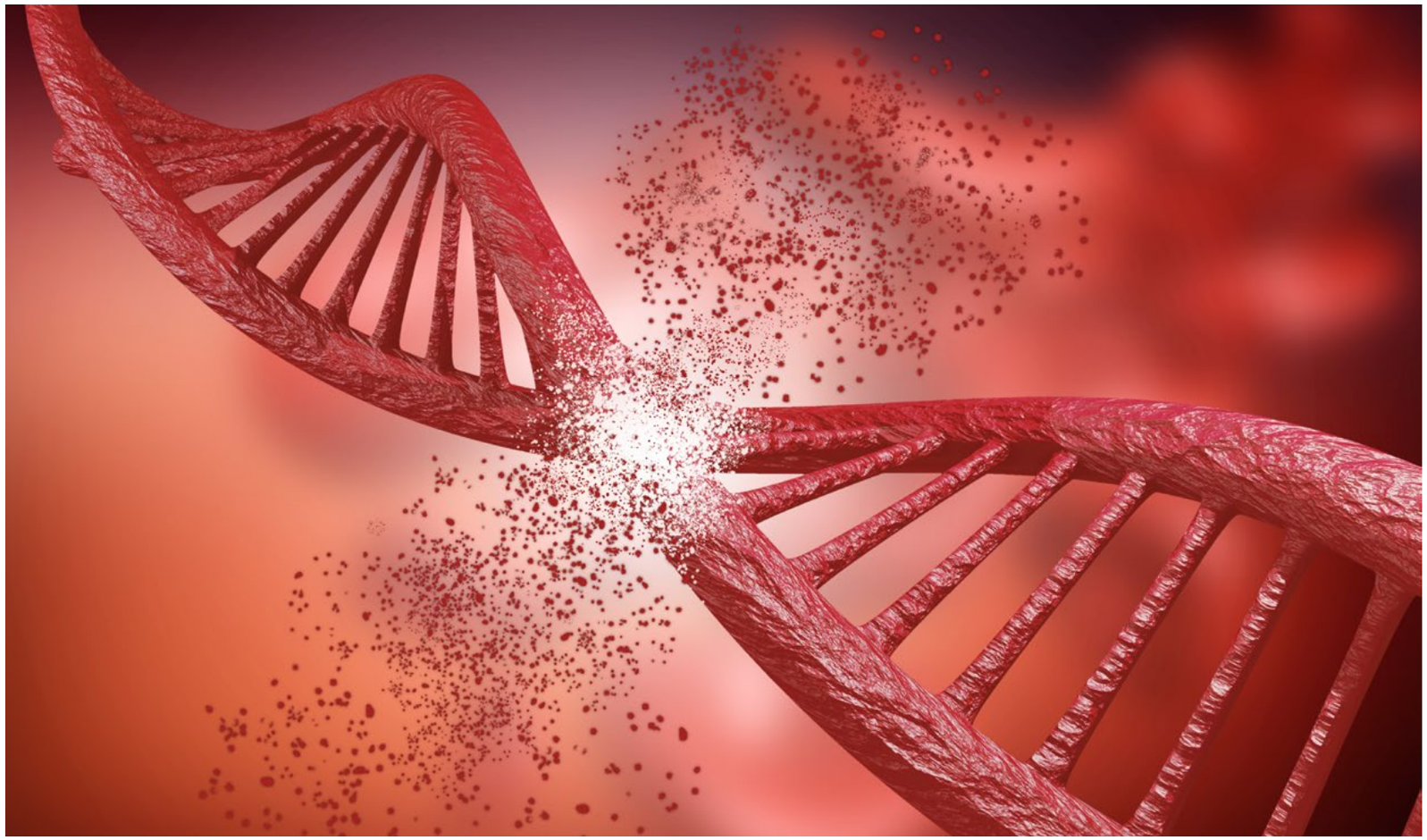
OBSERVATIONS

# Human Gene Editing: Great Power, Great Responsibility

**Modifying the human germ line has profound implications and must be approached with extraordinary care**



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We are at the point where our technology will soon surpass our humanity. It used to be that what we had in our jeans was just what we had in our genes. But we no longer are reliant on choosing our parents wisely. It was always going to happen. The new gene-editing techniques were always going to be used to alter the genome in nonmedically indicated cases. But it wasn't anticipated we'd so soon have nontherapeutic application in human embryos.

On November 28, 2018, He Jiankui, from the Southern University of Science and Technology in Guangdong China, revealed that he had performed ex vivo gene editing on two human embryos. This was presented at the International Summit on Human Genome Editing in Hong Kong. It was not a therapeutic, medically indicated procedure, but, regardless, it was unethical and illegal in most countries.

As an actual practicing scientist and as a human, I strongly advocate for advancement of science and leveraging our advances to enhance our species. Despite that, and somewhat ironically, when I began writing my most recent book, *Chasing Captain America: How Advances in Science, Engineering, and Biotechnology Will Produce a Superhuman*—a book explicitly focused on examining the science of altering human biology—I was skeptical about enhancing humanity. I challenged my perspective while writing and came to think we have an obligation to modify human form and function so we have the best chance to flourish on Earth and in space. Given the recently revealed experiments in which human embryos underwent nontherapeutic gene edits and

were brought to term, we need to consider deeply the implications of this and ensure that what we do and how we proceed are grounded in ethical principles agreed upon by all of us.

The idea of genetic engineering contained in gene editing is really no different in outcome than the pioneering work of Gregor Mendel in the mid-19th century and his detailed experiments with plants, particularly beans and peas. Mendel's detailed observations of more than 10,000 plants taken over just about 10 years were published in 1866 and revealed the targeted changes in a living organism that could be obtained by breeding for desired characteristics.

Instead of producing desired characteristics, most of the biomedical work on gene therapy in our modern age focuses on therapeutic, medically indicated applications in inherited diseases and cancers. Many of these medical conditions arise because of dysfunctions in cellular metabolism, growth and viability. Of course, it is probably natural that along with the therapeutic application, there's been interest in applications not aimed at "curing" disease but rather altering human performance in the otherwise "healthy."

Gene-editing techniques generally involve proteins that cut DNA, such as those employed in CRISPR-Cas9, transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases. The most commonly used Cas enzyme, Cas9, comes from *Streptococcus pyogenes*—the one that gives you strep throat and was proven viable in mouse and human cells in 2013. The basic process is that the CRISPR molecule is programmed to search for a specific nucleotide sequence among the three billion in the human genome. Once the correct sequence is identified, CRISPR unwinds the coils of DNA coils and "snips" the sequence out of the strand. DNA strands are then repaired in the case of a gene deletion, or, for an insertion, a new sequence can be included to alter the genome.

**Performed in an embryonic germ line cell, an egg or a sperm cell, gene "edits" will be part of the genetic code that goes to the next generation.**

Performed in an embryonic germ line cell, an egg or a sperm cell, gene "edits" will be part of the genetic code that goes to the next generation. But there can be errors—in other words, editing more than intended—with targeting associated with the guide RNA used to target the deletions. It is the presence of these "off-target repeats" that indicates extreme caution and a need for better regulation before techniques like CRISPR can have safe clinical application.

As such, we as scientists and society must also balance the potential good associated with new techniques and the prospect of doing something just because we could. Gene editing places great power over altering the fundamental principles of biology, and our whole society needs to be part of the discussion on what is okay to do and what is not. And we need to move quickly but not in a hurry.

It's critical to think about the path ahead—which one to take and to where—before we arrive. Scientists and engineers right now are working to enable the realization of our common futures. But guiding the implementation of that future is the right and responsibility of us all and cannot be entrusted exclusively to those in the field and laboratories, nor to those who attempt to regulate their work, our lawmakers and bureaucrats.

The future we invent can be bright—but there are strings attached. The most important string is that we need input from as many sectors in our society as possible. The decisions that are made will literally affect the future of our species and cannot be made in isolation from our society as a whole.

Science works as a machine of chance effects with experimental outcomes; tested against a backdrop of random occurrences and biological evolution is the emergence of chance survival characteristics expanding over millions of years. There is a pace and timing to adaptations. Yet any modifying of the human germ line—editing sperm or egg cells—has direct implications for the next generation and must be done carefully in light of regulations specifically addressing this kind of experimentation. In many countries there is a de facto moratorium on human germ line and embryo editing because such work is illegal. It is also completely unethical, not least of all because of lack of consent.

Eike-Henner Kluge from the University of Victoria has written that "germ line alteration would be performed without the consent of those who are most affected: namely, future generations."

And C. S. Lewis, when he wasn't enthralling us with *The Chronicles of Narnia*, wrote in his1965 *The Abolition of Man* that if a society gains power to make descendants "what it pleases, all men who live after it are patients of that power… the rule of a few hundreds of men over billions upon billions of men."

All of us citizens, scientists, engineers and future users of human-enhancement methodologies must proceed with conviction but also caution, with purpose but also extreme care. It's critical to appreciate the implications of the power of science as articulated by Richard Dawkins that "science is the most powerful way to do whatever it is you want to do. If you want to do good, it's the most powerful way of doing good. If you want to do evil, it's the most powerful way to do evil." Never before have we—or any other species on this planet—had such influence and so much power over the fundamental nature of our own biology.

The nontherapeutic use of gene editing on human embryos was and remains unethical and illegal on every level. Yet now we need to leverage attention on gene editing and human enhancement into a real conversation about the future our species. As the late Stan Lee wrote back in 1962 in *Amazing Fantasy*, the first comic book featuring Spider-Man, "with great power there must also come—great responsibility!"

Both must be exercised judiciously here and now in real life.

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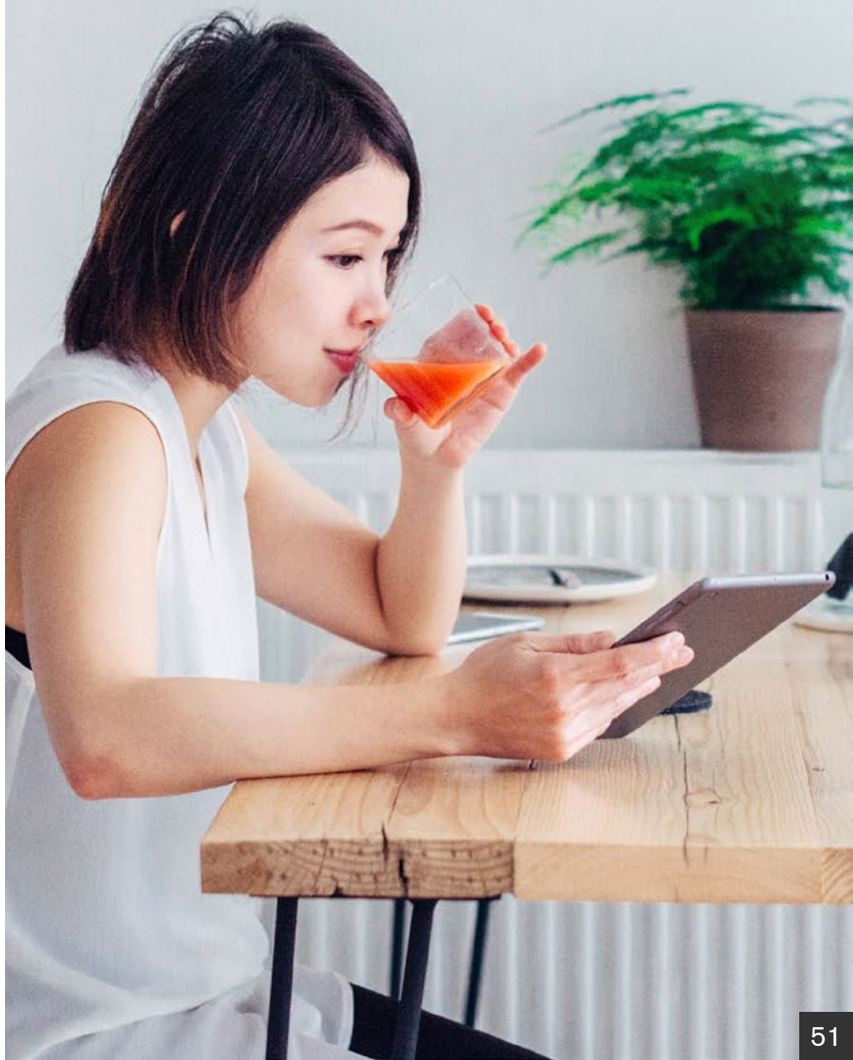

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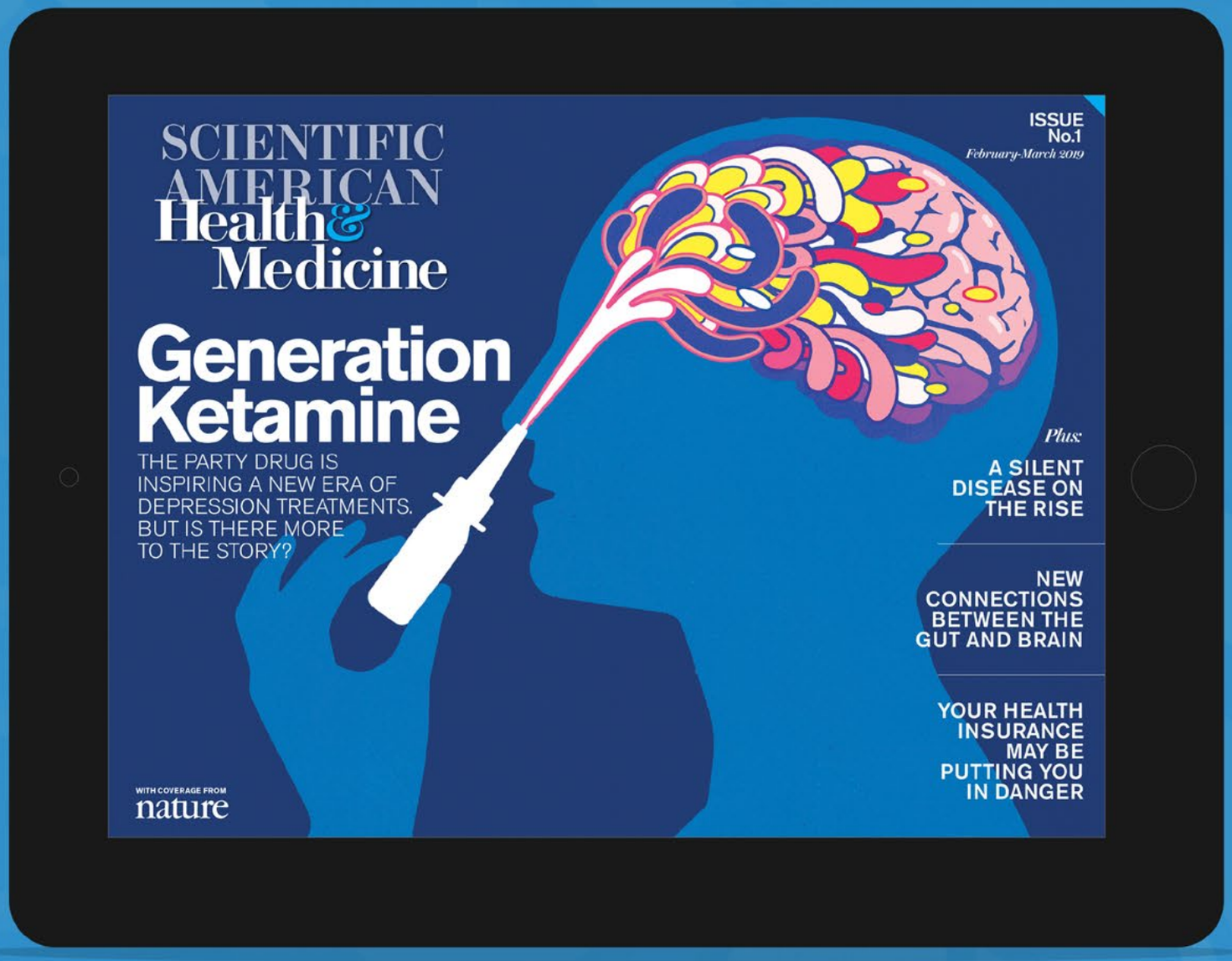


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