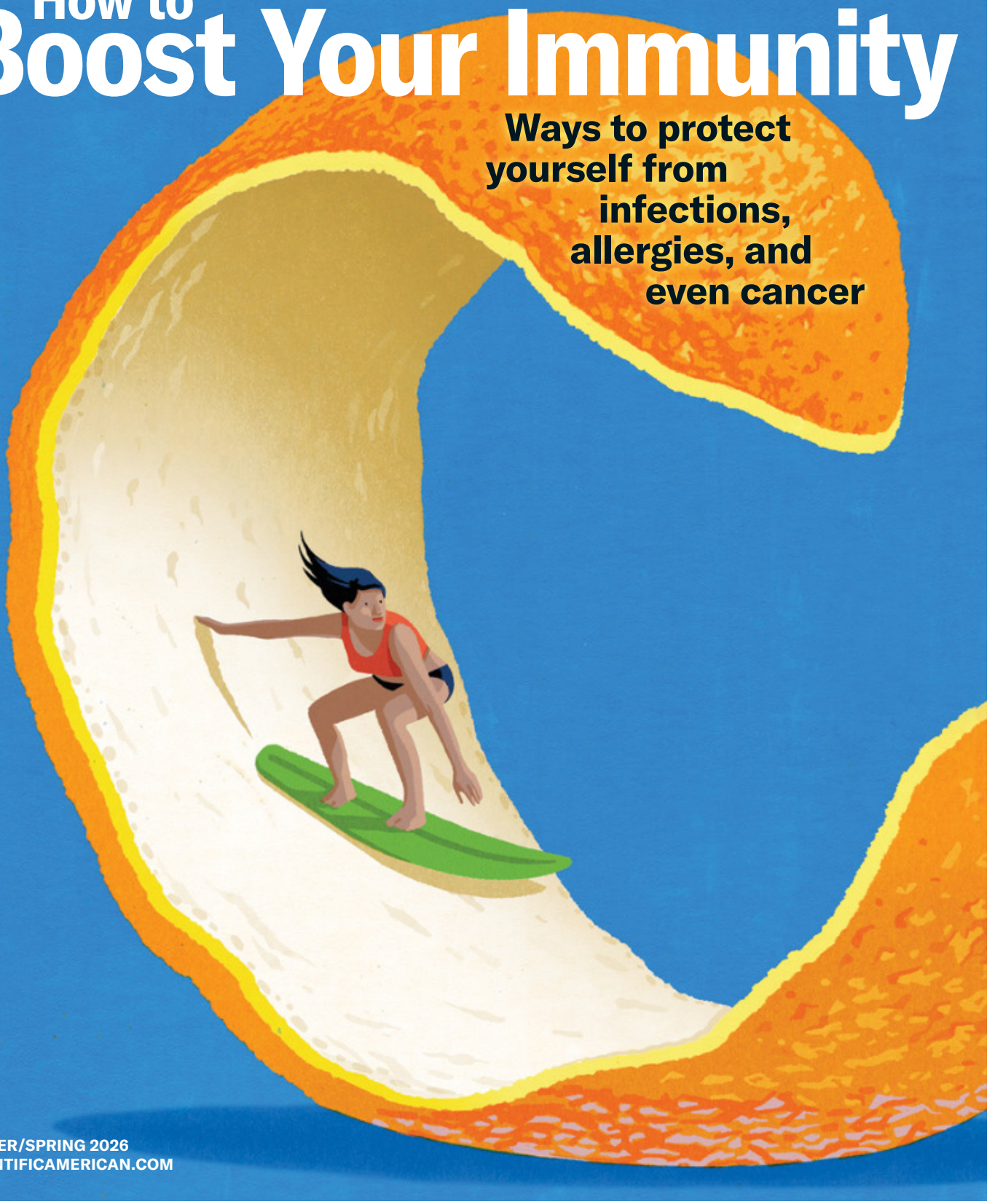
SPECIAL EDITION

SCIENTIFIC AMERICAN

Supplements that really work • A healthy dose of sunlight
Supercharging health with vaccines
New food allergy therapy • Stopping autoimmune disease

How to Boost Your Immunity

Ways to protect yourself from infections, allergies, and even cancer



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Help Yourself

YOU CONTAIN MULTITUDES. Within you there are billions of defenders, ready to protect your health from threats arising both outside and inside your body. This is your immune system, and it consists of an intricate combination of cells and proteins able to spot and destroy cold-causing viruses, infectious bacteria, and even wayward versions of your own cells that are on their way to becoming cancer.

But sometimes, when facing a flu, an allergy, an autoimmune disease such as multiple sclerosis, or a life-threatening tumor, your immune system could use a little help.

It could benefit from an edge, a nudge, some extra resources to keep you healthy. Supplements, surprising treatments, immunity-boosting vaccines and even exercises can help the immune system do its job. The big question is, Which ones work best? Tons of supplements and vitamins that promise to aid immunity line drugstore and supermarket aisles, and friends and family all have their favorite teas and creams they swear will help. Choices can be bewildering.

This is where science comes in. For the stories in this special edition, we looked for immune boosters backed by randomized controlled trials—the best way to compare treatments to see which one is most effective. We also looked for studies involving large groups of people. And we interviewed experts in immunology and in specific illnesses.

Omega-3 fatty acids get a thumbs-up for the way they tamp down damaging inflammation. So does turmeric's yellow ingredient, curcumin. Learn more about these supplements on page 6. Regular use of the former can reduce the risk of heart attack, and the latter can ease osteoarthritis symptoms. Vitamin D, in contrast, isn't the cure-all it was once touted as (*page 14*). It turns out most people make enough on their own because our skin uses sunlight's energy to create the vitamin. Plus, it's in fortified milk and in fish such as salmon.

Supplements, surprising treatments, immunity-boosting vaccines and even exercises can help the immune system do its job.

But vitamin D does seem to reduce the chances of developing some autoimmune diseases such as lupus and psoriasis. And sunlight itself may be a good remedy for autoimmune disease, balancing your immune response to reduce symptoms of multiple sclerosis and type 1 diabetes, as our story on page 22 explains.

Stuffed up by a cold or an allergy? That's usually because of tissue swelling caused by your immune reaction. Your best course might be the over-the-counter decongestant pseudoephedrine (*page 32*). And nasal saline sprays work really well. For food allergies, read on page 56 about new drugs and treatment protocols for the immune system that have dramatically helped children with life-threatening reactions to peanuts. Pet allergies can be relieved by an approach called hyposensitization (*page 72*).

To treat illnesses such as cancer, doctors have harnessed the precision targeting of immune system antibodies to guide chemotherapy directly to cancer cells, as we describe on page 84. But drugs aren't the only treatment. Regular exercise, as straightforward as several hours of brisk walking a week, leads to longer survival for some cancer patients and to more immune cells attacking their tumors (*page 90*).

Puzzles about immunity persist, such as why stimulating one major nerve called the vagus seems to enhance protective effects (*page 100*) and why women get more autoimmune illnesses than men (*page 94*). But scientists are trying to turn information gathered while probing these mysteries into remedies. So more immune system boosts may be coming your way soon.

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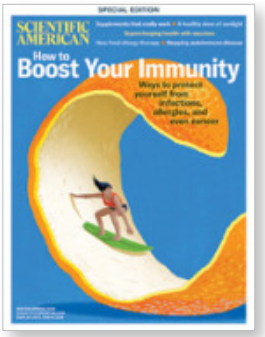
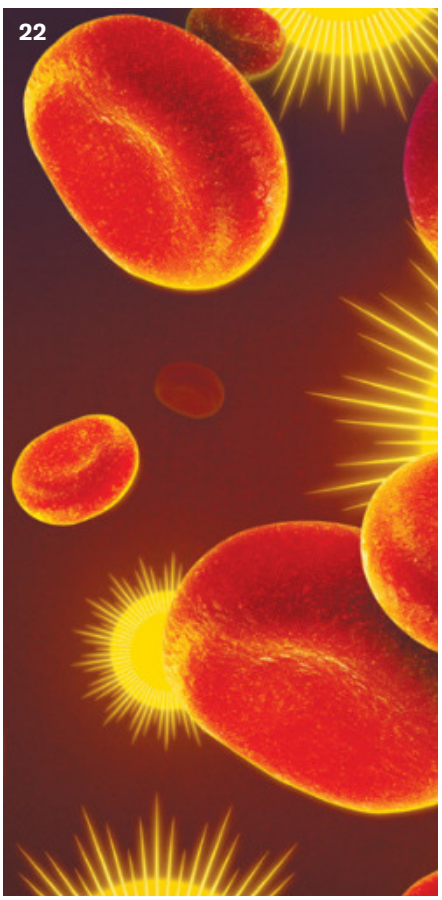
ON THE COVER
ILLUSTRATION
BY PETE RYAN



IMMUNE-STRENGTHENING TREATMENTS AND SUPPLEMENTS



Taylor Callery

SUPERCHARGE HEALTH WITH VACCINES

Cristina Bencina

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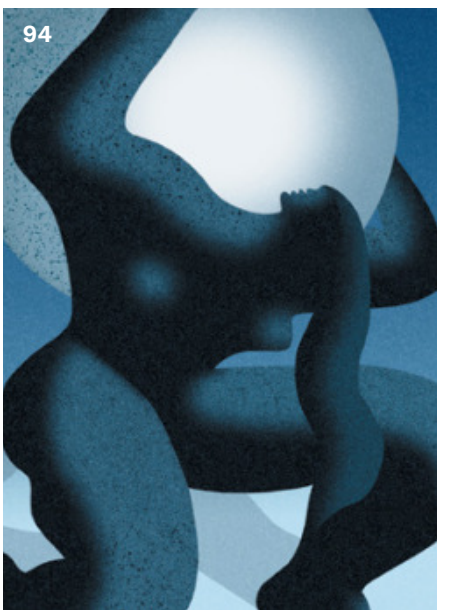
TACKLE ALLERGIES

Andrew B. Myers

CANCER-FIGHTING IMMUNITY

Tavis Coburn

IMMUNE MYSTERIES



Hayley Wall

How to Boost Your Immunity

Some simple, practical steps can raise your resistance to viruses

BY CLAUDIA WALLIS | ILLUSTRATION BY FATINHA RAMOS

FEAR AND FRAUD OFTEN TRAVEL TOGETHER. As coronavirus anxiety began to spread across the land, so did bogus nostrums promising protection from this modern-day plague. As early as March 6, 2020, U.S. regulators began to issue warnings to companies that were promoting false claims, such as this one touting the benefits of drinking a daily dose of silver particles: "It's actually widely acknowledged in both science and the medical industry that ionic silver kills coronaviruses." Um, no.

For people who hope to build up their resistance to coronavirus and infections of all kinds, there are no magic formulas—but there are some science-based steps one can take to maintain a healthy immune system. For starters, don't smoke. Cigarette smokers are much more vulnerable to respiratory infections. Second, make sure you are covering all your nutritional bases with a wide variety of vegetables, fruits, and other elements of a healthy diet. "Eating an optimal diet reduces the risk of getting an infection and reduces the severity of infections," says Wafaie Fawzi, professor of nutrition, epidemiology and global health at Harvard University's T. H. Chan School of Public Health. Third, practice good sleep hygiene so you can raise your chances of adequate nightly rest. And fourth, get regular exercise, which will also help you sleep.

On the dietary front, several nutrients have been tied to improved resistance to viruses. Taking zinc supplements, for example, has been linked to a reduced rate of respiratory infections and shorter duration of related symptoms. Deficiency in zinc, a mineral found in meat, shellfish, nuts and whole grains, is more prevalent in less developed countries, Fawzi notes, but it can occur in wealthier nations, especially during a time of high unemployment and disruptions to the food supply chain.

Vitamins C and D have also been shown to improve resistance to respiratory infections. Perhaps relevant to COVID, vitamin C plays a role in reducing tissue damage from our own immune responses. Oral doses of the vitamin have also been shown to shorten the amount of time in an ICU and on a ventilator for heart surgery patients, according to a 2019 meta-analysis. Could it help COVID patients? Researchers are looking at it, Fawzi says.

Bad Infections? Check Your Genes

Subtle mutations can undermine our ability to fend off a specific bug

BY CLAUDIA WALLIS | ILLUSTRATION BY CELIA KRAMPIEN

BAD LUCK. TERRIBLE MISFORTUNE. That's what we think when we hear about a perfectly healthy child who suddenly dies of influenza, a virus most of us can shake off. But what if it isn't luck? What if this kind of deadly infection turns out to be, well, genetic?

Odd as that sounds, there is a growing body of research that supports the idea. Much of it has been led by Jean-Laurent Casanova, a pediatric immunologist and geneticist at the Rockefeller University. Casanova wanted to unravel those tragic cases of flu, in which a child with no apparent underlying illness wound up in the intensive care unit. He was equally intrigued by other infections that are perfectly survivable or even innocuous for most of us but send some people to their grave.

There are many examples of what Casanova calls "the infection enigma." Herpes simplex viruses, for instance, can cause annoying cold sores and genital lesions in many people, but in rare cases they invade the brain and incite potentially lethal encephalitis. *Candida albicans* is a ubiquitous fungus that typically causes serious harm only to people with a weakened immune system, and yet some otherwise healthy individuals suffer repeated bouts of infection. Even with a dire disease such as tuberculosis, Casanova notes, in places where the TB bacterium is endemic, "everyone inhales it, but not everyone gets sick, and fewer than one in 100 will die of TB." This can't just be the fickle finger of fate, he reasoned.

In some cases, susceptibility to a specific kind of infection—*Candida,* for ex-

As for vitamin D, a 2017 meta-analysis of 25 randomized controlled trials found that vitamin D supplements cut the risk of acute respiratory infection—especially for people with low levels of the vitamin. Rates of deficiency in the U.S. are highest among Black and Hispanic people. Fawzi points out that late winter/early spring, when the pandemic began in the U.S., happens to be when D levels are especially low because we acquire the nutrient mainly via sun exposure.

Fawzi and his colleagues investigated whether vitamin D might help COVID patients, but their results suggested that it didn't improve outcomes. He does suggest taking a basic multivitamin. "A supplement with the recommended daily allowances of vitamins and minerals would be prudent," he says, along with a balanced diet. It might particularly help elderly adults, who are prone to nutritional deficiencies.

As for sleep, scientists have long known that it plays an essential role in bolstering our defenses. Studies show that if you deprive people of sleep after administering a vaccine, they will produce a weaker antibody response than folks who slept. Research suggests that sleep enhances the migration of T cells to the lymph nodes, where they are presented with foreign molecules that trigger antibody production, explains neuroscientist Luciana Besedovsky, who investigates sleep and the immune system at Ludwig Maximilian University of Munich in Germany.

A 2015 study that measured average sleep duration for 164 healthy volunteers and then dripped a rhinovirus into their nose found that those who slept six or fewer hours a night were four times as likely to develop a cold as those who slept more than seven hours. Similarly, a study that followed 57,000 women found that those who slept five or fewer hours nightly were 40 percent more likely to have developed pneumonia over a four-year study period than eight-hour sleepers. Prolonged sleep loss, Besedovsky says, can create a state of low-grade inflammation: "This seems to exhaust your immune system in the long run, so that it may not be able to fight infections that well."

Committing to a regular bedtime and nightly routine that helps you sleep, along with a healthy diet—and perhaps a multivitamin—will not necessarily keep the coronavirus at bay. But these steps have a true silver lining of helping you endure whatever health threats blow your way. ●

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ample—runs in families. This was Casanova's big clue. He hypothesized that some of us harbor genetic mutations, whether inherited or spontaneous, that make us susceptible to a particular germ, much the way certain strains of wheat are genetically vulnerable to a particular blight.

Over the past two decades Casanova, often working with Laurent Abel of Necker Hospital for Sick Children in Paris, and a few other laboratories have identified dozens of single-gene mutations causing this kind of vulnerability. These mutations do not devastate defenses. Instead, Casanova explains, "these are pathogen-specific diseases caused by inborn errors of immunity that are very narrow—sometimes [involving] one virus, one bacterium."

In the case of severe flu, Casanova's team identified three gene defects that raise vulnerability, including two that impact interferons. With herpes simplex encephalitis, one category of mutations lays carriers open to infection in the front of the brain. A second type causes vulnerability to encephalitis in the hindbrain. With flu, children eventually develop antibody protection that compensates for the genetic flaw; the same is probably true for herpes.

Most of these mutations are rare, but Casanova's lab has found a defect that causes vulnerability to TB and is present in one in 600 people of European ancestry and one in 1,000 humans. Casanova and his collaborators have also discovered that inborn errors in the functioning of interferons play a role in increasing vulnerability to COVID.

Taken together, these surprising discoveries are creating a paradigm shift in how we think about severe infection. "This work makes the case that we should shift a little of our attention from the germ to the host, or child," says Isabelle Meyts, a pediatric immunologist at University Hospitals Leuven in Belgium. The findings also expand our understanding of the human immune system, especially defenses that do not depend on white blood cells, notes immunologist Helen Su of the National Institute of Allergy and Infectious Diseases. There is great redundancy built into our germ-fighting systems, so it is shocking to learn that initial protection from a specific bug can depend on a single gene.

This research suggests that doctors should do genetic workups in puzzling cases of serious infection, Meyts says. The results can sometimes guide treatment. For example, Casanova and others have found more than a dozen mutations that disrupt the body's ability to battle non-TB mycobacteria, and all of them mess with interferon gamma—a key immune system activator. Giving such patients this interferon "works beautifully," Casanova says. "It's like insulin for diabetic patients."

A genetic analysis could also enable doctors to counsel relatives on who else is at risk. Crucially, families can come to understand that a loved one died of infection because of a flawed gene. "The fact that they have an answer is a tremendous solace," Su observes. ●

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

SUPPLEMENTS THAT FIGHT INFLAMMATION

Capsules of omega-3 fatty acids show some of the best evidence as anti-inflammatories.

Many products claim to suppress inflammation and disease. Three actually can

BY LORI YOUMSHAJEKIAN

INFLAMMATION HAS TWO FACES. It can be short-lived like the swelling after a twisted ankle or a two-day fever when you get a mild flu, both part of the healing process. Or it can be a longer-lasting and more damaging affliction—chronic, low-grade inflammation that lingers in the body for years without obvious symptoms, silently harming cells. A steady stream of studies has connected this type of chronic inflammation to many serious conditions, including Alzheimer's disease, heart disease, some cancers, and autoimmune illnesses such as lupus.

These findings have begun to reframe how scientists think about disease and some of its causes. They've also created a booming market for supplements promising to lower chronic inflammation. These pills, capsules and powders are projected to become a $33-billion industry by 2027, offering consumers a sense of control over a complex and confusing ailment. Although thousands of products claim to "support immunity" or "reduce inflammation," most lack solid evidence.

Chronic inflammation is damaging because it involves immune system cells and proteins that typically fight short-term battles against bacteria, viruses, and other pathogens. But when these immune system components stay activated for years, they begin to hurt healthy cells and organs. They are intended to break down invading microbes, but over time their ongoing activity can harm blood vessels, for instance, by damaging normal cells that make up the vessels' inner linings or promoting the growth of plaques. That can lead to clots that interrupt or cut off blood flow, increasing the risk of heart attacks and strokes.

We reviewed dozens of studies and spoke with researchers to find out whether any supplements demonstrate anti-inflammatory activity not just in laboratory animals and cultured cells but in human trials. Just three compounds, it turns out, have good evidence of effectiveness: omega-3 fatty acids, curcumin and—in certain ailments—vitamin D.

What is good evidence? We looked for consistent results across several studies that scientists described as large and well designed. Many of the more convincing trials focus on biomarkers that researchers use to track inflammation in the body. These include C-reactive protein (CRP), a molecule produced by the liver when inflammation is active, and cytokines, which are chemical messengers such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), both secreted by immune and fat cells.

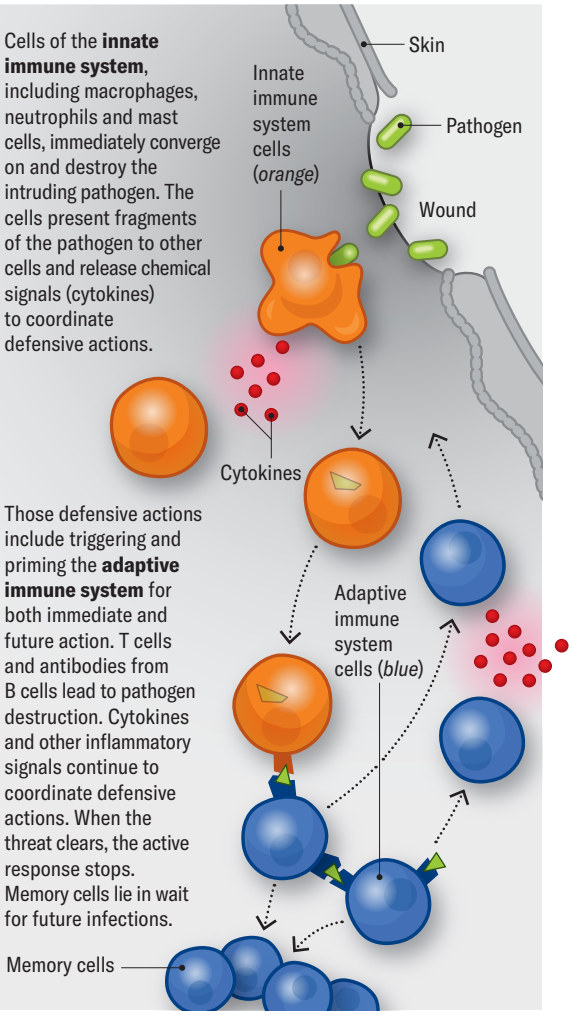
Still, interpreting these markers isn't straightforward. "We don't have a universally accepted or standardized measurement," says Frank Hu, chair of the department of nutrition at the Harvard T. H. Chan School of Public Health. And inflammation involves hundreds of different types of cells and many signal-

Mensent Photography/Getty Images (*preceding pages*)

Good vs. Bad Inflammation

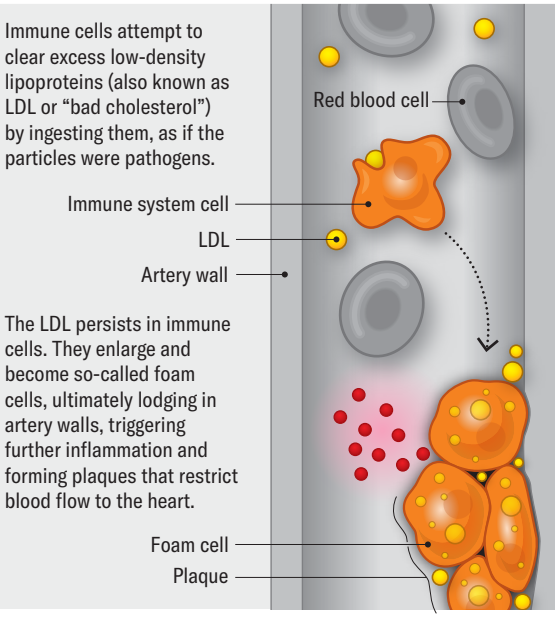
Inflammation is commonly associated with an immune system response to microbial infection or tissue injury. For example, when bacteria enter your body through a cut in your skin, some of your body's immune cells—part of what is called the innate immune system—gather at the site to ward off invaders. They also release signaling proteins called cytokines that call in reinforcements. These additional cells and proteins are known as the adaptive immune system, and they identify and destroy remaining bacteria (*below*). This activity, called **acute inflammation**, is often accompanied by short-term swelling, a fever or mild pain. The acute response generally lasts only hours or days. Similar events occur when you twist an ankle, in which case proteins released by damaged muscle and tendon cells trigger the immune system reaction.

ACUTE INFLAMMATORY RESPONSE EXAMPLE:
MICROBIAL INFECTION



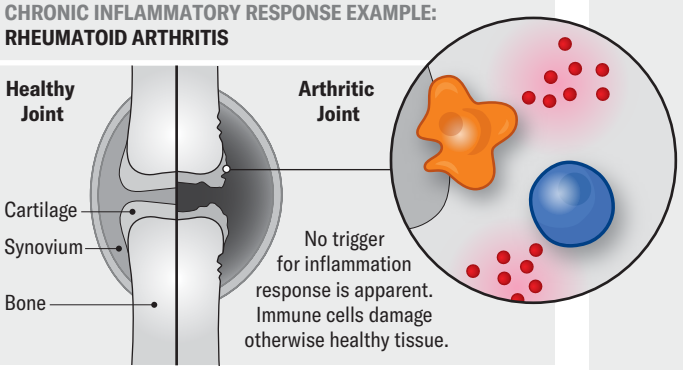
Some forms of inflammation can do more harm than good. In **chronic inflammation,** the same immune system cells are activated, but the response lasts for months or years. In some cases, the threat persists in the system and cannot be cleared by immune cells. For example, macrophages engulf cholesterol particles in the bloodstream. But those particles persist within the macrophages. This leads to bulky plaques on arterial walls and feeds into continued inflammation (*below*).

CHRONIC INFLAMMATORY RESPONSE EXAMPLE:
HEART DISEASE



In other cases, including autoimmune diseases such as rheumatoid arthritis, there's no apparent threat to the body. The inflammatory response targets otherwise healthy organs and cells for an unknown reason. Over time the immune cells can damage healthy tissues, and the ongoing inflammation exacerbates symptoms.

CHRONIC INFLAMMATORY RESPONSE EXAMPLE:
RHEUMATOID ARTHRITIS



To track chronic inflammation—and to learn which anti-inflammatories can reduce it—researchers measure levels of specific cytokines and molecules released by organs during an immune response or an infection.

Graphic by Jen Christiansen

Jim Sugar/Getty Images

ing pathways, adds Prakash Nagarkatti, co-director of the National Institutes of Health Center for Dietary Supplements and Inflammation at the University of South Carolina. This complexity makes it difficult to prove that any supplement works consistently.

The compounds that do show promise will not cure cancer or halt dementia. But they may help quiet the kind of underlying inflammation that has been tied to risks of illness.

AMONG THE HUNDREDS of supplements tested for their effects on human health, omega-3 fatty acids are supported by some of the most compelling evidence. And scientists understand why they work. Two of the main types of omega-3s are eicosapentaenoic acid and docosahexaenoic acid, better known as EPA and DHA. The body metabolizes them into signaling molecules that block the production of certain cytokines and disrupt the nuclear factor κB pathway, which governs the expression of genes tied to inflammation.

Multiple studies suggest that omega-3 supplements can reduce markers of chronic inflammation, Hu says, especially among people with underlying health conditions. A large, carefully controlled trial called VITAL (officially the Vitamin D and Omega-3 Trial), which followed more than 25,000 adults for about five years, found that omega-3 supplements slightly reduced CRP in people

Herring is a rich source of omega-3 fatty acids.

Masanyanka/Getty Images

Egg yolks contain some vitamin D.

who rarely ate fish—fish is a natural omega-3 source, so these people were getting almost all their omega-3s from the supplements. The omega-3 supplements also were associated with a 40 percent reduction in heart attacks among those consuming the least fish. "The people who benefit the most from these supplements are people who start out with lower intake," says JoAnn Manson, an endocrinologist at Harvard Medical School who co-led the study.

Smaller trials have suggested that omega-3 supplementation can reduce certain markers of inflammation—TNF-α, IL-6, CRP and IL-8—especially in people with conditions such as heart failure, Alzheimer's and kidney disease. One 2012 trial found that small amounts—about 1.25 or 2.5 grams per day—lowered IL-6 levels by 10 or 12 percent, respectively, over four months. A similar group got a placebo instead, and their IL-6 levels increased by 36 percent during that period.

But the evidence across various trials is hard to compare. "There is still a question regarding which is the optimal dose and the optimal duration because different studies have used different doses," Hu says. And in healthy people, who have low baseline inflammation, there might be little room for improvement.

RIGOROUS TRIALS HAVE DEBUNKED the once popular idea that vitamin D is a wonder drug for everything from breast cancer to diabetes. For a few autoimmune conditions, however, the vitamin can be helpful. In the VITAL trial, people who took vitamin D daily for five years had a 22 percent lower risk of developing autoimmune diseases such as rheumatoid arthritis, psoriasis and lupus. "High-dose vitamin D has the effect of tamping down inflammation," Manson says. "So conditions that are really directly related to inflammation may benefit."

Lab studies have suggested that vitamin D may interfere with molecular pathways involved with inflammation, in addition to suppressing the production of proinflammatory cytokines. And in a handful of clinical trials in people with autoimmune conditions, vitamin D supplementation appeared to reduce levels of proinflammatory cytokines such as TNF-α, as well as CRP. In one small study of women with type 2 diabetes, a high dose—50,000 international units (IU) every two weeks—reduced CRP. It also increased levels of IL-10, an anti-inflammatory molecule.

A separate study in women with polycystic ovary syndrome (PCOS) found that a combination of vitamin D and omega-3 fatty acids helped to lower CRP levels. And two analyses that grouped together results from several studies back up the idea that the vitamin can cause a significant, though small, reduction in CRP. Another trial in women with PCOS found that a daily dose of 3,200 IU of the vitamin improved patients' insulin sensitivity and liver function. It didn't affect inflammatory markers, however.

Other studies haven't found consistent effects. The VITAL study reported that people who took vitamin D saw a 19 percent drop in CRP levels by the two-year mark, but this difference disappeared by the fourth year. Whether that two-year dip in inflammation translates into long-term benefits remains unclear,

the researchers note. Even then, the findings may also depend on baseline levels. Most people in the VITAL study started with normal levels of vitamin D, Manson says. "People who are already getting reasonable intake may not benefit further from the supplement," she says. A review of other trials looking at inflammation-related biomarkers such as CRP, IL-6 and TNF-α found that vitamin D supplementation at several different doses didn't have a big effect.

As with omega-3s, the varying doses in the different trials may be behind the inconsistent results. Very high weekly doses—40,000 or 50,000 IU—may be necessary. (The recommended daily vitamin D intake for adults is 600 IU.) But high doses carry their own risks, such as too much calcium in the blood.

Although the findings on autoimmune illnesses are intriguing, the American College of Rheumatology still has a conditional recommendation against the use of supplements, instead advocating that people make dietary changes to try to get the recommended vitamins and nutrients from food. Inflammation is central to illnesses such as rheumatoid arthritis, says Arthur M. Mandelin II, a rheumatologist at Northwestern University's Feinberg School of Medicine, but he is interested in vitamin D only as a therapy for patients with demonstrated deficiencies.

THE PIGMENT that gives turmeric its yellow color, curcumin, is another promising compound for fighting chronic inflammation. The substance seems to interfere with the nuclear factor κB pathway, "the apex of inflammatory cascades in the body," explains Janet Funk, a professor of medicine and nutritional sciences at the University of Arizona, who has evaluated hundreds of human trials on the compound.

Funk's review found that the most convincing evidence for curcumin's anti-inflammatory activity was among small clinical trials. People in those trials had preexisting conditions such as metabolic disorders and osteoarthritis. In a few cases, curcumin's effects resembled those of over-the-counter anti-inflammatory drugs such as ibuprofen. "These small trials—and there are a lot of them—all sort of point to it probably being beneficial," Funk says.

The spice turmeric contains curcumin.

Banusevim/Getty Images

Taking omega-3 fatty acid supplements was associated with a 40 percent reduction in heart attacks among people in a trial who ate the least amount of fish.

The caveats in Funk's language, however, reflect the ambiguity of other results. A large Canadian trial found no measurable benefit for inflammation in people who were taking curcumin after surgery, and other trials have been inconclusive. One reason for the inconsistency is curcumin's bioavailability: the substance is poorly absorbed in the gut, rapidly metabolized and quickly cleared from the body. Some supplement manufacturers encase curcumin in nanoparticles to improve its absorption, but these formulations aren't always used in clinical trials, nor are they consistently available over the counter.

Some commercial turmeric and curcumin powders have even been found to contain harmful contaminants such as lead. "People buy turmeric powder based on its color," Funk says. "Partly to make it a more beautiful color, [manufacturers] add lead chromate."

OTHER COMPOUNDS such as flavanols in green tea and dark chocolate or resveratrol in red wine are often promoted as anti-inflammatory agents. But their supporting evidence is weaker, Hu says. They can be hard for the body to absorb, which limits their effectiveness. In the case of resveratrol, the compound is metabolized and cleared so quickly it's unlikely to have any true impact. And even though a recent trial of cocoa flavanols found a promising effect on cardiovascular health, possibly because of reduced inflammation, any benefit might be outweighed by the many extra calories one would consume if they got the compounds by eating chocolate.

Supplements aren't regulated like drugs. The U.S. Food and Drug Administration doesn't require supplement companies to prove that their products improve health, unlike pharmaceutical manufacturers. So there's little financial incentive for these companies to run rigorous clinical trials because, as Funk asks, "What if they find out it doesn't work?"

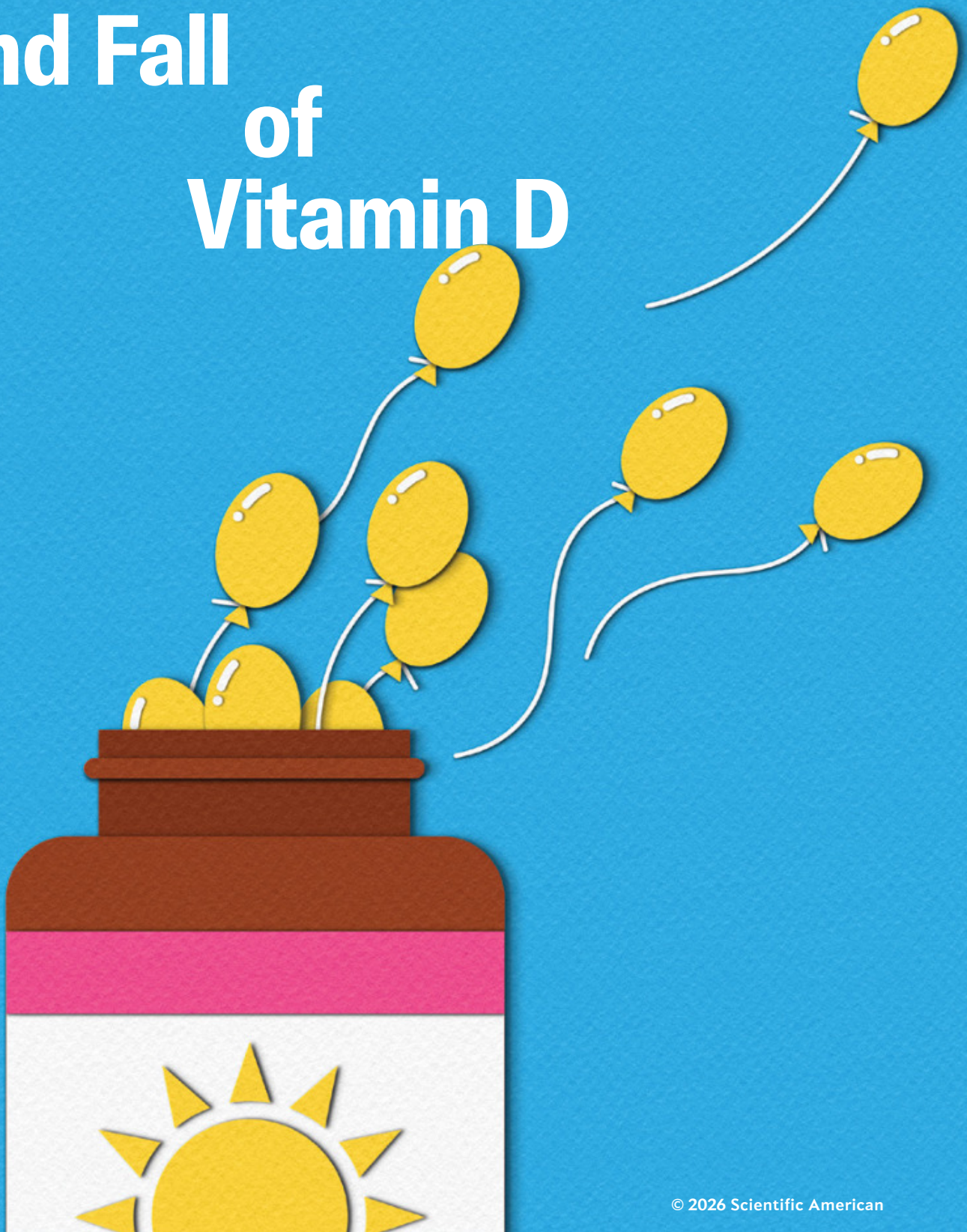
Such trials would also be difficult to run. Supplement ingredients can vary from batch to batch, especially for botanically derived products, in which concentrations depend on where the plants are grown and how the crucial components are extracted. Even when trials are well designed, they can come up against ethical challenges. "You cannot really preselect people on the basis of being deficient or profoundly deficient in these essential vitamins," Manson says, "because once you identify them as being profoundly deficient, you really should be treating them" and not giving half of them placebos in a multiyear trial.

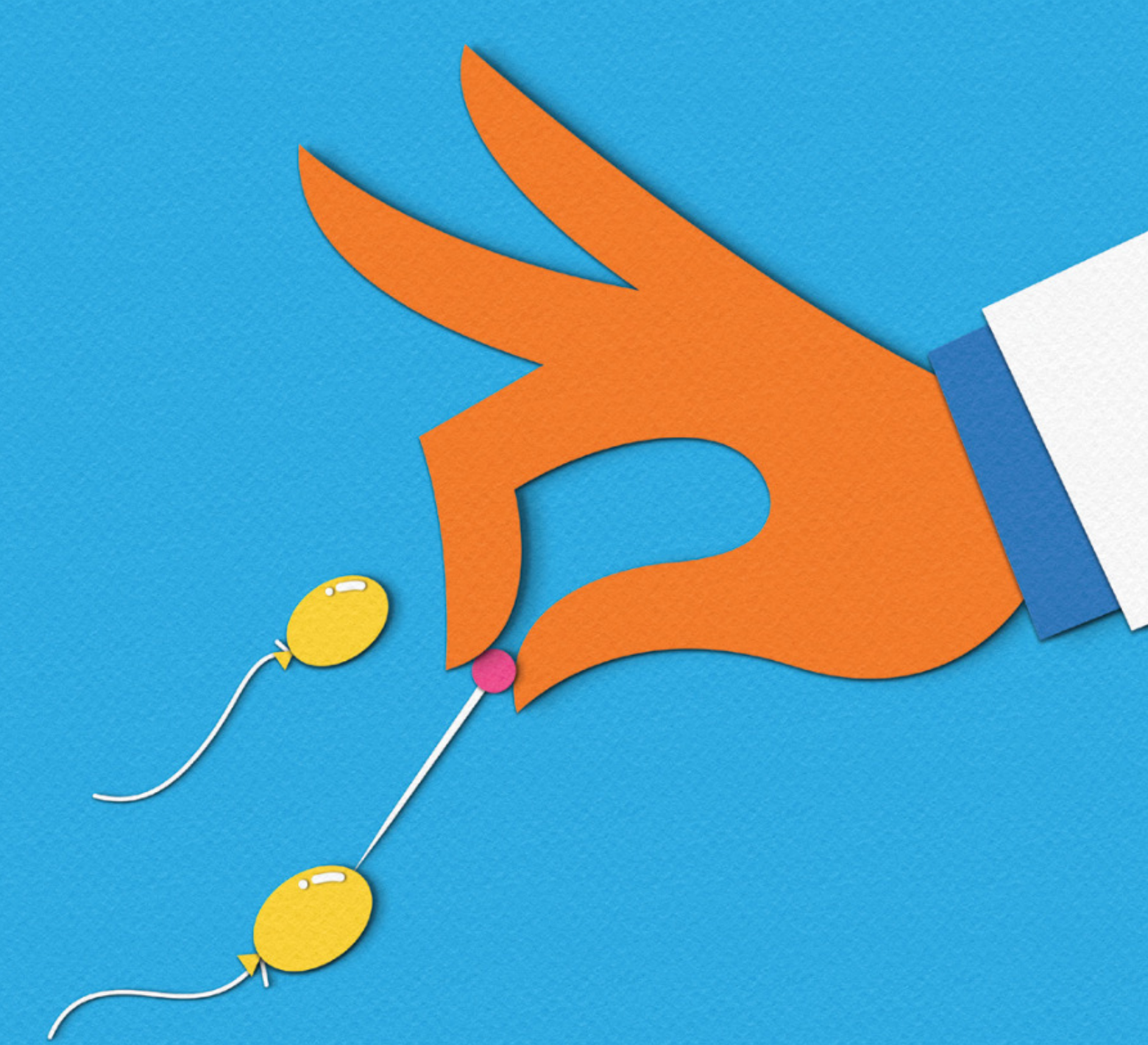
Still, the appeal of supplements is obvious. We all want simple solutions to complex medical problems, especially as we learn more about the damaging effects of chronic inflammation on health. "The patient who spends a good deal of the visit focusing on diets and supplements is also that patient who's very fearful of medication," says Mandelin, the Northwestern rheumatologist. "They're ready to write [the names] down as if there is some magic answer, and unfortunately there isn't."

Instead experts recommend what good medical studies have shown to work: a healthy and balanced diet. Mediterranean-style diets, which are rich in vegetables and whole grains with some fish and poultry, have especially been shown to reduce chronic disease and to promote good health. Regular physical activity helps, too. "Many people think that they can just take a dietary supplement, pop the pill, and that replaces a healthy diet," Manson says. "That is not at all the case." ●

Lori Youmshajekian is a science journalist who reports on consumer health, environmental issues and scientific misconduct. She holds a master's degree in science journalism from New York University and has written for *National Geographic*, *Wired* and *Retraction Watch*, among other outlets.

The Rise and Fall of Vitamin D





Why worries about widespread vitamin D deficiencies—and claims of several health benefits—are overblown

BY CHRISTIE ASCHWANDEN

ILLUSTRATIONS BY ZARA PICKEN

FOR A WHILE VITAMIN D WAS LOOKING LIKE A BONA FIDE HEALTH ELIXIR. It was recognized a century ago as the cure for rickets, a childhood disease that causes weak and deformed bones. Then, in the early 2000s, researchers began amassing a pile of studies suggesting that low vitamin D levels could be a factor in cancer, cardiovascular disease, dementia, depression, diabetes, autoimmune diseases, fractures, respiratory illnesses and Parkinson's disease. It seemed reasonable to think that raising our levels of this simple vitamin—one that our bodies make when lit up by sunshine and that we can get more of from supplements—could cure practically whatever ailed us.

At least two books called *The Vitamin D Cure* were published, along with other books and news reports whose titles include words like "revolution" and "miracle." There was also a growing concern that we weren't getting enough of the vitamin. *Good Morning America* aired a segment that began with reporter Diane Sawyer declaring 100 million Americans were deficient. Her guest was Dr. Oz, who told viewers they could determine their vitamin D level with a simple blood test. Sunshine is the best way to get this vitamin, he said. But if that wasn't enough, he advised cod liver oil or supplements.

Numerous celebrities and vitamin companies raised hopes that vitamin D could be a panacea, says JoAnn Manson, an endocrinologist and epidemiologist at Harvard Medical School and a lead investigator on some of the biggest vitamin D studies to date. Sales of supplements containing the vitamin soared, as did rates of vitamin D testing.

Then the bottom fell out. Although thousands of studies had linked low levels of vitamin D to an assortment of medical conditions, when scientists tried administering it as a means to prevent or treat those problems, the wonder supplement failed miserably. The notion that our lives would be better if we all just raised our vitamin D levels began to look like a fantasy. The idea that vitamin D deficiency was widespread also crumbled. It turned out that notions of what constitutes a deficiency were based on a dubious understanding to begin with. National population sampling showed that most people were already getting enough of the vitamin.

There's no question that vitamin D plays an important role in health. It helps your body absorb and retain calcium and phosphorus; both are critical for building bone. But except for a few subsets of the population (such as breastfed infants and people with particular medical conditions), most people probably don't need supplements.

The story of how vitamin D was discovered, rocketed to miracle status and then returned to Earth illustrates the sometimes jagged path of scientific discovery. It's also a cautionary tale about the need to interpret scientific results with humility. Ultimately it's about the self-correcting nature of science and how knowledge becomes honed over time.

FOR MUCH OF HUMAN HISTORY, people got their vitamin D mostly from the sun. It turns out humans are a little bit like plants—we can turn ultraviolet light into something our bodies need in a process akin to photosynthesis.

When the high-energy rays of UV light—UVB—hit your skin, they start a chain reaction that converts a compound in your skin called a sterol into a vitamin D precursor. This molecule, after a few more steps, becomes a form of the vitamin that promotes calcium absorption from the gut and increases bone mineralization. Vitamin D also seems to bolster the immune system and tamp down inflammation. It does these

things in part by influencing the production of inflammatory compounds and suppressing the buildup of proinflammatory cells. Researchers have studied whether vitamin D can prevent dangerous inflammatory reactions in people with COVID.

Producing vitamin D became increasingly difficult for human bodies during the Industrial Revolution, when smoke and soot darkened the skies and children spent more time in the shade of crowded cities, leading to an increase in rickets. By the late 1800s researchers had documented geographic differences in the prevalence of rickets that pointed to a possible link to sunlight.

In the 1920s Johns Hopkins University biochemist Elmer McCollum identified vitamin D in cod liver oil and gave it its name. German chemist Adolf Otto Reinhold Windaus won a Nobel Prize in 1928 for showing how the body made vitamin D from sunlight. Calling this previously unknown substance a vitamin gave it a sheen of beneficence. The term "vitamin" had been coined by Polish scientist Casimir Funk, who created the word by combining the terms "vita" (Latin for "life") and "amine" (for amino acids, building blocks of life). The word created "an aura of safety and health," says Catherine Price, author of *Vitamania: How Vitamins Revolutionized the Way We Think about Food*.

The practice of fortifying food with vitamin D began when McCollum's former student Harry Steenbock, then at the University of Wisconsin–Madison, discovered that he could produce vitamin D in both rats and their feed by irradiating them with UV light. The rays hit sterol compounds, found in the cells of plants, animals and fungi, and start a conversion process. For instance, exposing chickens to UVB light boosts the vitamin D in their meat and egg yolks. Most of the vitamin D in modern supplements comes from irradiated lanolin, a grease derived from sheep's wool. Steenbock also found that feeding dairy cows irradiated feed or mixing irradiated fat extract into milk raised D levels. Today fortified milk and other dairy products—which also use the lanolin-derived form of the vitamin—are some of the most common dietary sources.

In 1936 the Joseph Schlitz Brewing Company introduced "Sunshine Vitamin D" beer. The ads exclaimed that "beer is good for you—but SCHLITZ, with SUNSHINE Vitamin D, is *extra* good for you. Drink it daily—for health with enjoyment." If it sounds antiquated, consider that in 2022 beer brand Corona launched Corona Sunbrew, a nonalcoholic beer fortified with vitamin D.

The study findings were a shock. Vitamin D did not make a dent in cancer or heart disease, and it did not prevent falls, improve cognitive function or reduce bone fracture risk.

Beer is not, however, a health food. The "natural, evolutionarily appropriate way to get vitamin D is through synthesis in your skin," says Anastassios Pittas, chief of the division of endocrinology, diabetes and metabolism at Tufts Medical Center. But that does not require getting a sunburn. It turns out that you don't need high doses of sun to get sufficient vitamin D. A 2010 study calculated that between April and October, someone in Boston with 25 percent of their skin exposed would need between three and eight minutes of sunlight per day to get enough. Of course, in the winter it might be challenging to find even this amount of sun at some latitudes.

Fortunately, your body is equipped to deal with this kind of variation. Your liver and fat cells store vitamin D for future use, Pittas says. That means you don't necessarily need a big dose every day. Your vitamin D cache generally lasts for about 10 to 12 weeks, so even if you don't have a lot of daily D coming in via sunshine in the winter, Pittas says, you could still have enough circulating from your liver to maintain adequate calcium and phosphorus levels. It's natural to have a winter dip, he says, but that is worrisome only if you're already running low on vitamin D.

INTEREST IN GETTING EXTRA VITAMIN D took off when studies suggested it might lower the risk of heart disease, cancer, diabetes, and a range of other conditions.

The problem is that this evidence came mostly from observational studies, a type of analysis that can't show cause and effect and that might produce misleading results, Manson says. These observational studies looked for associations between vitamin D levels and a particular health issue or compared vitamin D status among people with a condition and those without. For instance, an offshoot of the Framingham Heart Study published in 2008 followed more than 1,700 people without prior cardiovascular disease over about five years and found that people with low vitamin D levels had a higher risk of developing heart disease. The results generated a lot of excitement and hype around vitamin D, Manson says.

Diabetes, too, seemed to track with D levels. A study published in 2010 followed close to 6,100 people in Tromsø, Norway, over a period of 11 years. Their incidence of type 2 diabetes showed an inverse relation with blood levels of vitamin D before their body mass was taken into account: higher D levels were correlated with fewer cases of diabetes. Similarly, a 2011 study of more than 6,500 people in Australia found that the risk of developing diabetes over the course of five years was lowest for the participants with the highest D levels.

All these observational studies have a fundamental weakness: they can identify a co-occurrence between vitamin D and a disease, but they can't prove there is a cause-and-effect relation—or, if there is one, they can't identify in which direction it might go. Think of it this way: there's a strong link between someone's wealth and the price of their car, but that doesn't mean buying an expensive vehicle will make you rich.

"Just because you see an association, that doesn't mean that, okay, if we fix the serum vitamin D level, that's going to fix the problem," says physician Leila Kahwati, associate director of the Research Triangle Institute–University of North Carolina Evidence-Based Practice Center. There might be other factors at play. For instance, people who take vitamin D supplements may be more health-conscious and do other things that protect them from disease, and people who are already in poor health probably spend less time outdoors getting vitamin D from sunlight.

FOR THESE REASONS, randomized controlled trials, in which researchers recruit

a group of participants and then assign them to receive different treatments (or a placebo), are considered the strongest kind of medical evidence, says physician Jodi Segal, associate director of the Center for Health Services and Outcomes Research at Johns Hopkins Bloomberg School of Public Health. A randomized design makes it much more likely that any differences between the study and placebo groups are caused by the intervention rather than by some other variable.

In 2009 Manson and her team embarked on the world's largest and most far-reaching randomized vitamin D trial, called VITAL. The study followed nearly 26,000 generally healthy adults, randomized to receive either 2,000 international units (IU) of vitamin D or a placebo, for an average of 5.3 years. The volunteers were almost evenly split between men and women, and 20 percent of the participants were Black. The study was designed to look at whether vitamin D supplements could prevent cancer or cardiovascular disease.

The results came as a shock. Not only did vitamin D not make a dent in rates of cancer or heart disease, but the trial also found that vitamin D did not prevent falls, improve cognitive function, reduce atrial fibrillation, change body composition, reduce migraine frequency, improve stroke outcomes, decrease age-related macular degeneration, reduce knee pain or even reduce the risk of bone fractures. The finding about fractures "was a real surprise to many people," Manson says.

Extra vitamin D also didn't lower diabetes risk. In a trial published in 2019 in the *New England Journal of Medicine,* Pittas and his colleagues randomized more than 2,400 people at risk for diabetes to take either 4,000 IU of vitamin D or a placebo daily. After two and a half years, a similar number of people in each group went on to develop the disease.

The Vitamin D Assessment Study (ViDA) recruited 5,110 volunteers ages 50 to 84 in New Zealand and randomized them to get either a placebo or 200,000 IU of vitamin D per month—a huge dose much higher than the recommended daily allowance. The study found that levels made no difference in cardiovascular disease, acute respiratory infections, nonspinal fractures, falls and all types of cancer. Other trials found that vitamin D supplementation did not reduce mortality rates or the risk of invasive cancer. These results, along with others coming out of VITAL, led to growing skepticism about vitamin D by around 2020, says Clifford Rosen, an endocrinologist at the Maine-Health Institute for Research.

The ViDA trial did find some modest supplement benefits in people who had started the study with a vitamin D deficiency. But what exactly does "deficiency" mean?

IT DOES NOT MEAN what many doctors think it does, apparently. The widespread notion that much of America is walking around deficient in vitamin D came from what Manson calls a "misinterpretation and misapplication" of the normal levels for vitamin D set by the Institute of Medicine (IOM, now known as the National Academy of Medicine) more than a decade ago.

Here's what happened. In 2011 the IOM convened an expert committee to conduct a thorough analysis of all existing studies on vitamin D and health. Based on this evidence, the committee concluded that the bone-strengthening benefits of vitamin D plateau when blood levels (as measured by a standard vitamin D blood test) reach 12 to 16 nanograms per milliliter. They also found that there were no benefits to having levels above 20 ng/ml. So they set that as the ceiling for their recommendations while noting that the majority of the population is just fine at 16 ng/ml.

According to measurements of vitamin D levels in the general U.S. population collected through the National Health and Nutrition Examination Survey, most people had levels of 20 ng/ml or more in 2011. Levels have actually risen since then, meaning that most people are well within the medical recommendations, says Rosen, who served on the IOM committee.

So where did the idea of mass deficiency come from? First off, 20 ng/ml was erroneously interpreted by some health-care workers as the bare minimum, instead of a level marking good amounts for most people. Recall the IOM found that 16 ng/ml was satisfactory. The implication of the misreading was that people needed more than 20 ng/ml for good bone health, Manson says.

But some of the confusion stems from a second set of guidelines that another medical group, the Endocrine Society, put out around the same time as the IOM standards. Whereas the institute made recommendations for healthy populations, the society's guidelines were aimed at clinicians, particularly those caring for patients at risk for vitamin D deficiency. The makers of these guidelines looked at much of the same evidence that the institute committee reviewed, but they concluded that anything under 20 ng/ml represented "deficiency," and they labeled vitamin D levels of 21 to 29 ng/ml as something they called "insufficiency."

The terms "insufficiency" and "deficiency" have created "a tremendous amount of confusion," says Christopher McCartney, an endocrinologist at West Virginia University. He adds that the Endocrine Society guidelines have been largely taken to mean that everyone needs vitamin D levels of 30 ng/ml or more.

The IOM guidelines don't support that conclusion, and in 2012 the institute committee published a rebuttal paper, "IOM Committee Members Respond to Endocrine Society Vitamin D Guideline." It contended that aspects of the society's guidelines, including the definition of insufficiency, were not well supported by evidence. For instance, the society's guidelines used a 2003 study of only 34 people to support its contention that vitamin D levels above 30 ng/ml are better for calcium absorption. At the same time the society's committee ignored a study of more than 300 people that found that calcium absorption pretty much maxes out at vitamin D levels of 8 ng/ml.

Michael Holick was the lead author of the Endocrine Society guidelines. An endocrinologist at Boston University's medical school, Holick says that the insufficiency standard is justified by an observational study from 2010. It found that about a quarter of the otherwise healthy adult males had evidence of osteomalacia, a bone-softening condition linked to low vitamin D levels. The study didn't find bone problems in people above 30 ng/ml; hence Holick's contention that 30 was the minimum.

The Endocrine Society updated its guidelines in 2024, with McCartney serving as methodologist. He says that the goal with the new guidelines was to focus on randomized trials, not observational ones, and he and his co-workers were careful to call out the evidence gaps that remained.

The committee also took care to avoid outside influence. "Our conflict-of-interest policy is much more transparent and rigorous than I think it has been in the past," McCartney says. Holick, who ran the original guideline-writing group, has advocated

large doses of vitamin D supplements. Although there is no evidence that his judgments were affected by commercial ties, Holick has received at least $100,000 from various companies involved in making vitamin D supplements and tests, according to a 2018 investigation by Kaiser Health News (now KFF Health News) and the *New York Times*. McCartney says that, in part, concerns raised about Holick prompted the Endocrine Society to pay extra attention to ethics.

Holick made a name for himself espousing the health-promoting powers of vitamin D and wrote a book called *The Vitamin D Solution: A 3-Step Strategy to Cure Our Most Common Health Problems*. He has claimed to take 6,000 IU daily and has advised patients to take a minimum of 2,000 to 3,000 IU per day. For comparison, the 2011 IOM report calculated that the average person's daily requirement is 400 IU.

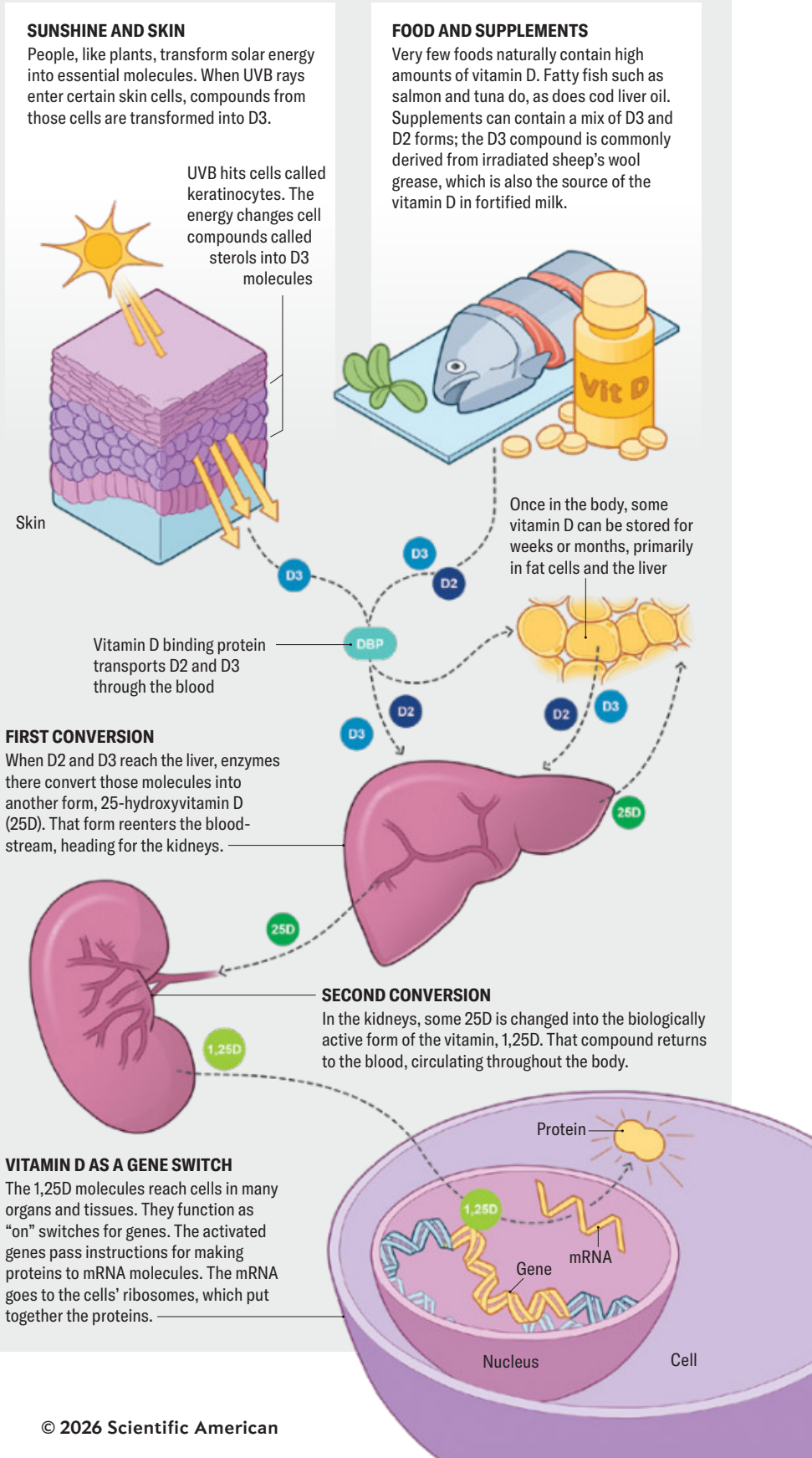
Holick told SCIENTIFIC AMERICAN that it is "not true" that he has conflicts of interest. He acknowledged receiving industry money but said most of the money had "nothing to do with vitamin D" and was instead "associated with me talking about a new drug coming on the market," for patients with chronic hypoparathyroidism.

Still, some in the field see Holick's evangelism for vitamin D as conflicting with his role working on the Endocrine Society guidelines. Rosen says that the guidelines "were driven by Mike. He was the chair of the committee." Rosen trained with Holick and considers him a friend. "He's a good guy," Rosen says. But "just because you hypothesize something doesn't mean you have to stick with it. Michael went to extremes to show that vitamin D had something to do with chronic diseases."

Much of the information put out by companies offering direct-to-consumer testing still claims that anything under 30 ng/ml is low. Athlete Blood Test, for instance, markets blood tests to active people and encourages them to aim for a level of at least 50 ng/ml. While working on this story, I had my vitamin D checked by another testing company, and the laboratory results came back with reference ranges of 30 to 100 ng/ml, implying that anything under 30 was not enough. The lab explanation did note that the IOM's cutoff was 20. (My number was 32.8 ng/ml, which suggests that sunshine really can help—I never take supplements, but I exercise daily outdoors.)

How We Get Vitamin D

Vitamin D helps our bodies absorb calcium for stronger bones. We get it from two slightly different precursor molecules. One is D3, made when sunlight hits our skin cells. The other is D2, which comes from fungi and yeast. Some foods may be fortified with D2. To become active, both molecules go through several conversions in the body.



Graphics consultant: Anastassios Pittas/Tufts Medical Center

Graphic by Now Medical Studios

More than 10 million vitamin D tests are done annually in the U.S., despite the fact that these tests are not recommended by major medical organizations such as the Endocrine Society, the National Academy of Medicine and the U.S. Preventive Services Task Force. Three medical societies have endorsed a recommendation to "not order population-based screening for vitamin D" from Choosing Wisely, an initiative to reduce wasteful medical practices.

Yet the testing goes on. A study published in 2020 examined medical records from a large regional health system in Virginia and found that about 10 percent of the system's patients were tested for D levels, although many of the tests were not indicated by the patients' health conditions. Supporting the idea of the tests being unneeded, 75 percent of the results came back as normal, says study author Michelle Rockwell, an assistant professor of family and community medicine at the Virginia Polytechnic Institute and State University. Furthermore, some of the test results categorized as abnormal may have been considered just fine by the IOM standards; the study used a higher reference range of 30 to 99.9 ng/ml.

Given the VITAL trial's large size and wide scope, many vitamin D researchers hoped it would put many of the purported benefits of vitamin D supplements to rest. "But there's a religiosity around vitamin D," Rosen says. He wrote an editorial in the *New England Journal of Medicine* saying most people can stop taking vitamin D supplements and that the large VITAL study was a "decisive verdict." Even then, Rosen says, he got pushback from colleagues who refused to believe that vitamin D wasn't the panacea they had come to believe. "The evidence is out there," he says. "People don't want to pay attention to it."

ALTHOUGH MOST PEOPLE don't need supplements, there are exceptions. Breast milk does not contain enough vitamin D for infants, so the American Academy of Pediatrics recommends that babies who are breastfed (partially or exclusively) be supplemented with 400 IU a day of vitamin D beginning in the first few days of life to promote stronger bones. In addition, the academy says all infants and children who consume less than 32 ounces of vitamin D–fortified formula or milk per day should also get supplements of 400 IU. Crohn's disease, cystic fibrosis, celiac disease, and certain liver and kidney conditions can cause vitamin D deficiency, so people with these illnesses might also need supplements. People who are hospitalized or who have had gastric bypass surgery may also become deficient.

Typical tests may, however, overestimate vitamin D problems in some people of African ancestry. The standard test measures circulating blood levels of a vitamin D precursor, 25-hydroxyvitamin D, that is bound to a particular protein. A 2013 *New England Journal of Medicine* study found that some people have gene variants that allow circulation of more of the unbound precursor form and less of the bound one. So by focusing on the bound version, the test underestimates total vitamin D availability. The study, which involved more than 2,000 people, found that those who were Black had lower vitamin D levels than white participants according to the standard blood test. Yet those Black people had strong bones and good calcium levels.

Manson is quick to caution that more isn't necessarily better when it comes to vitamin D. "Vitamin D is essential to good health, but we require only small to moderate amounts," she says. She doesn't dissuade people from taking supplements of up to 2,000 IU per day, but she doesn't recommend higher levels because some studies have found that excess vitamin D can increase the risk of dangerous falls—researchers speculate that intermittent high doses affect the central nervous system, which could impair balance. And whether you're taking supplements or not, you are probably getting supplemental vitamin D if you consume dairy products, breakfast cereal, plant milks, or other fortified foods, says Price, author of *Vitamania*.

Despite the disappointing trials on vitamin D, it's not time to dismiss the vitamin completely, Manson says. There's still plenty more to understand. For instance, the VITAL trial showed that among slender or normal-weight people, defined as having body mass indexes of 25 or less, vitamin D supplements appeared to lower the incidence of cancer, cancer deaths and autoimmune disease. This protective effect did not show up among heavier people with higher body masses. Manson cautions that these numbers need to be verified by further work because they are from a smaller subanalysis of the main study. But it's possible that excess body fat may somehow hamper the effectiveness of vitamin D. Obesity itself is a risk factor for both cancer and autoimmune disease, so it's likely that any connection is complex.

Pittas remains convinced that for people at high risk for diabetes, vitamin D can play a role in prevention. His earlier trial did hint that people who received supplemental vitamin D were less likely to develop diabetes: 24.4 percent of them got the disease, versus 26.9 percent of the placebo group. That difference alone was too small to be statistically significant. But when he pooled the results with those of two other randomized trials, he found a

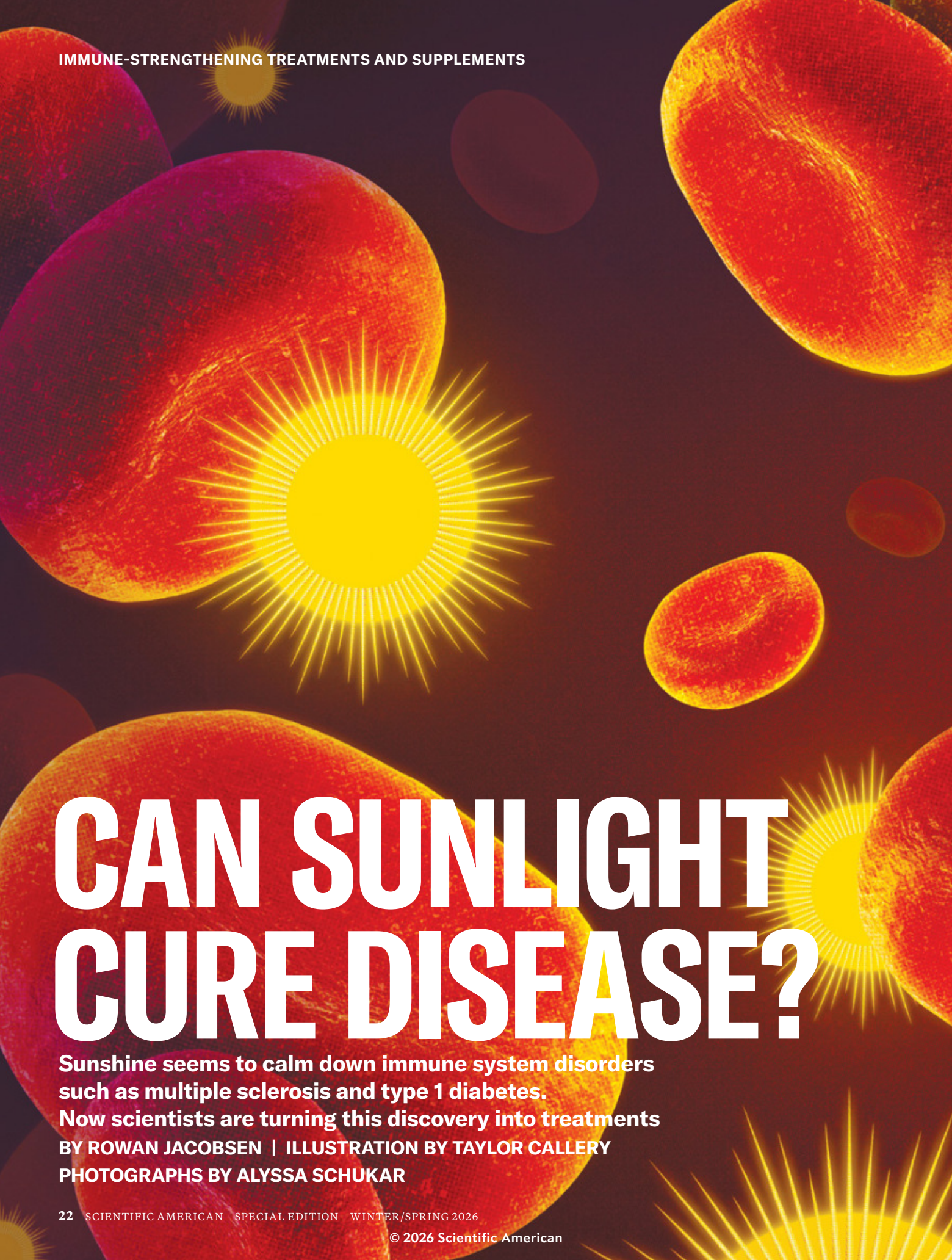
modest but consistent benefit of about a 3 percent reduction in diabetes risk over three years. There are some positive signs for treating COVID, too. Clinical and lab studies have shown that vitamin D has a positive effect on the immune system and can tamp down inflammation. "We saw this in our VITAL trial," Manson says. Holick adds that vitamin D can help downregulate so-called cytokine storms, immune system overreactions that have provoked life-threatening respiratory problems in some COVID patients.

Manson's research group undertook two randomized trials in the past few years to test whether vitamin D can help with COVID. One was designed to investigate whether high-dose vitamin D can reduce the chances of getting the extended and debilitating ailment of long COVID. The other trial looked at whether 1,000 IU of vitamin D per day can reduce the risk of that illness or overall symptom severity.

Vitamins hold a certain allure. They're cheap, they're relatively safe, and there's a sense, emphasized by marketers, that they're "natural" and therefore somehow better than drugs, Rosen says. "There's this magical thinking that vitamins improve health, and some people do feel better" when taking them, he says, pointing to the placebo effect as a potential contributor.

The ups and downs of vitamin D offer a lesson in humility. The relation between the vitamin and disease is far more complicated and nuanced than it first seemed and a reminder that scientific understanding is always evolving. ●

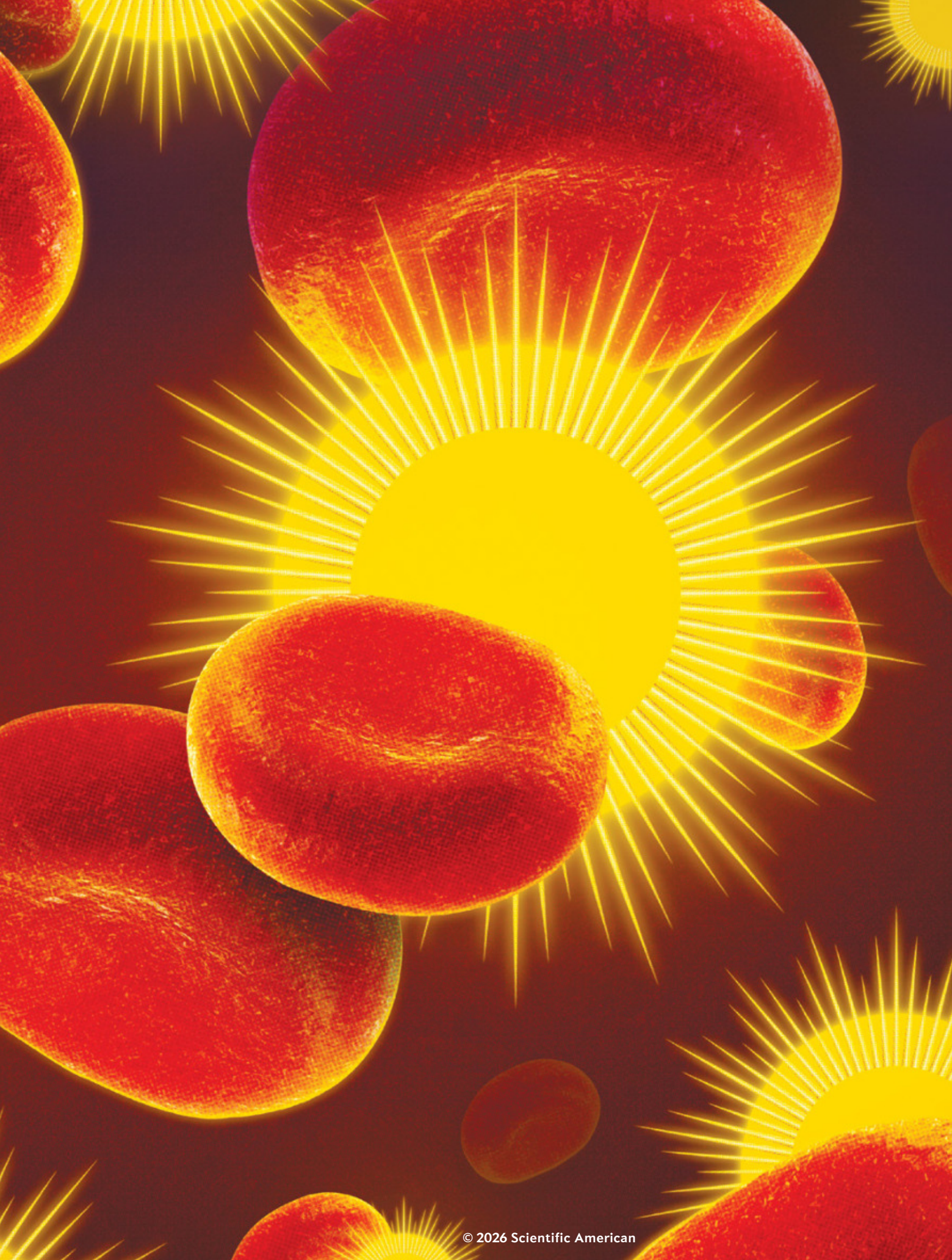
Journalist **Christie Aschwanden,** a frequent *Scientific American* contributor, is author of *Good to Go: What the Athlete in All of Us Can Learn from the Strange Science of Recovery* (W. W. Norton, 2019).



CAN SUNLIGHT CURE DISEASE?

Sunshine seems to calm down immune system disorders such as multiple sclerosis and type 1 diabetes. Now scientists are turning this discovery into treatments

BY ROWAN JACOBSEN | ILLUSTRATION BY TAYLOR CALLERY
PHOTOGRAPHS BY ALYSSA SCHUKAR



EVERY MORNING KATHY REAGAN YOUNG STEPS OUT of the shower in her Virginia Beach home, towels off, dons a pair of protective goggles and stands nine inches from a light box the size of a small space heater. Young presses a button, and the box's bulbs begin to glow a ghostly purple. She briefly bathes her torso in the ultraviolet rays coming from the bulbs, four minutes per side. Then she goes about her day.

That Young can have an ordinary day is remarkable. In 2008 she was diagnosed with multiple sclerosis (MS), a terrible malady in which the body's own immune system attacks the sheaths that insulate the nerves, destroying them bit by bit. Symptoms begin with weakness, spasms, vision and speech problems, intense fatigue, and what Young calls "cog fog"—chronic low-grade cognitive impairment. Flare-ups can lead to periods of motor-control loss and paralysis. Young, an advocate for MS patients and creator of a popular podcast, has suffered through many such episodes. But things improved with the arrival of her light box.

Ultraviolet (UV) light boxes, which emit only a narrow bandwidth of light that is not linked to skin cancer, have been used for years in the treatment of psoriasis. Young got a prescription from her doctor, and the box was sent to her by a medical-device company called Cytokind that was hoping to expand such use to MS and other autoimmune diseases and was looking for some practical patient feedback. She tried out the device and gave them some pointers: make it smaller and easier to hold because MS often makes your hands go numb, and build in timed reminders to overcome the cog fog. Then, to her surprise, she found that her fatigue disappeared a few months after she started using it.

For years Young had been forced to rest in bed many times a day, but that stopped with what she calls her UV-fueled rebirth. "I was in a meeting, and someone said to me, 'Wow, you seem like you're pretty high energy!'" Young says. "And I guess I hadn't really thought about it. And then two days later my daughter said to me, 'Mom, what are you on?' I think we were all a little surprised by how quickly and definitively it happened." Her MS Disease Activity (MSDA) score, which rates MS severity based on the levels of key inflammatory molecules in the blood, was a 1 out of 10, the best possible score, and it stayed low for more than a year. MS has no cure, and Young still suffers from transient pain and tingling, but the return of her vitality has made it all more bearable. "It's incredible," she says. "My friends used to invite me to things, and I'd say yes, but I always canceled because I was wiped out. Well, not anymore."

Young is one of the first people in the U.S. to test UV phototherapy as an MS treatment, but she may be at the forefront of a revolution in how we think about light and a huge class of diseases. Autoimmune diseases such as MS and type 1 diabetes occur when our natural defenses—our immune systems—viciously turn against our own bodies and organs. These illnesses are estimated to affect more than 350 million people worldwide. Treatments have been elusive.

Although only a handful of clinical trials for MS light therapy have been conducted in people, evidence from a number of medical studies now shows that UV light, the highest-energy part of the solar spectrum that reaches Earth's surface, has a surprising ability to calm an immune system that has bolted out of control. The new studies offer tantalizing hints that UV therapy might also work for other autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, Crohn's disease

and colitis. All are more common in people who get very little sun exposure, as are maladies such as Alzheimer's and cardiovascular disease that appear to have some immune system and inflammatory connections.

Now scientists are hoping to decipher the pathways through which UV light causes the immune system to back down from its alarm state. They are tracking the way molecules in the skin such as urocanic acid and lumisterol—which can affect immune system activity—respond to a shot of photons by triggering a cascade of signals that reach every organ in the body. Advocates say this work might lead to a blockbuster drug, an Ozempic for autoimmunity.

Scientists not involved in the light research are more cautious, but they agree that something important is going on. "UV light therapy holds promise," says Annette Langer-Gould, an MS researcher and neurologist at Kaiser Permanente in Los Angeles. But she would like to see rigorous and larger trials on various diseases and a better understanding of the mechanism.

That kind of confirmation could also solve a mystery that has vexed scientists for more than a century: Why do people living in lower-light environments have such high rates of disease?

THE TRAIL THAT LED SCIENTISTS to the discovery of UV light's beneficial effects began with the confirmation of its dangers. In 1974 pioneering researcher Margaret L. Kripke (who would go on to found the department of immunology at MD Anderson Cancer Center in Texas) discovered that she could induce tumors in the skin of mice by exposing the rodents to UV light. But those tumors failed to grow when transferred to the skin of a different mouse. The new host's immune system quickly eliminated them. Ten times she tried, and 10 times the tumors were squelched. When she suppressed the new host's immune system with drugs, however, the tumors took hold. "That was the key!" she later recalled.

But why was the tumor able to grow in the original irradiated mouse? Was the UV light that had induced it also somehow suppressing the mouse's natural immune response? In a series of experiments, Kripke determined that UV radiation was indeed a double whammy. Not only did it damage DNA in skin cells and trigger mutations that could lead to cancer, but it also suppressed the immune system's surveillance of the skin, preventing that system from killing any budding cancers. This finding was a breakthrough in our understanding of how skin cancer develops, but it also seemed nonsensical from an evolutionary perspective. How could it possibly be beneficial for our immune system to relax in the presence of a common carcinogen?

It turns out that immune cells in our skin evolved to walk a fine line. As our primary interface with the outer world, the skin is barraged with potential stressors: heat, cold, wounds, bug bites, mysterious microbes of all kinds. For the first million years that our nonape ancestors spent under tropical African skies, solar radiation was the most common stressor of all. "It's a challenge to the body," says Prue Hart, an immunologist at the Kids Research Institute Australia who has been studying the effects of sunlight on immunity for more than 30 years. "It's the most important environmental insult we have. We evolved to cope with it."

> "UV light calms inflammation in the skin, the nervous system, the pancreas and the gut. Its potential is not fully realized."
>
> —PRUE HART *KIDS RESEARCH INSTITUTE AUSTRALIA*

But if the immune system had reacted to every kiss of sunlight with a full-throated attack, Hart says, we'd have lived in a constant state of inflammation, beset by rashes, hives and cutaneous autoimmune disorders. Instead the system learned to hold its fire.

In prehistoric times, this was the right approach. The damage was usually minor, the skin repaired itself, life went on. The trade-off—especially now that people live long enough for slow-growing tumors to get big and spread to other parts of the body—is that every so often a skin cancer sneaks through. One fascinating confirmation of this idea is polymorphic light eruption (PLE), a common disorder in which patients' immune systems are not suppressed by sunlight. PLE sufferers develop itchy rashes and plaques after sun exposure, but they are less likely to develop skin cancer.

The discovery of UV light's powerful impact on our immune responses launched a brand-new discipline: photoimmunology. Early investigators in this field, such as Kripke, focused on the negative effects of immunosuppression. But they soon found some upsides as well. For example, it finally explained something doctors had noticed for centuries: sunlight soothed psoriasis, a skin condition marked by painful, itchy scales. With the discovery that psoriasis was an autoimmune disease in which the immune system flays the body's own skin cells, it at last made sense. UV light—whether from the sun or a lamp—improved psoriasis by tamping down the inflammatory response.

Remarkably, the effect wasn't just local. Shining light on one patch of inflamed skin could reduce symptoms on other patches. Even more curious, people with psoriasis often suffer from other autoimmune conditions, and sometimes the phototherapy improved their other symptoms as well.

As photoimmunologists probed deeper into the mechanisms, they began to wonder whether the body's response to UV light was more than skin-deep. In the laboratory, they exposed mice to UV radiation and saw their entire immune systems pivot to anti-inflammatory states. In mice with autoimmune diseases, it improved their health. The researchers began comparing notes with epidemiologists, who were documenting signs of the same thing in human populations.

FOR MORE THAN A CENTURY scientists have noticed that many diseases, especially autoimmune and cardiovascular conditions, follow a latitude gradient. Once other confounding factors such as diet, exercise and socioeconomics are accounted for, rates of these diseases rise with latitude. All kinds of causes have been suggested—climate, diet, cosmic rays, something in the water—but nothing fit.

In 1940 a physician at the Medical College of Virginia named Frank Apperly showed that American states and Canadian provinces receiving more solar radiation had higher rates of skin cancer mortality but lower rates of cancer mortality overall. Skin cancer was known to be caused by sunlight, but Apperly suggested that something about the sun was also conferring protection against internal cancers. He didn't know what, but in 1980 Johns Hopkins University epidemiologists Frank and Cedric Garland, two brothers who were analyzing maps of cancer incidence produced as part of the government-led "war on cancer," noticed a strong north-south gradient for colon cancer rates and suggested in a hugely influential paper in the *International Journal of Epidemiology* that vitamin D was responsible.

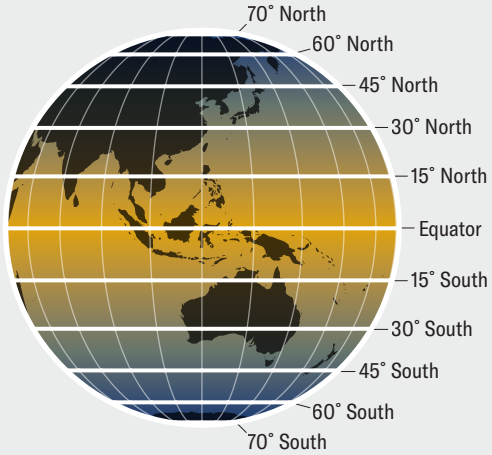
Until then, vitamin D had been known mostly as the micronutrient that prevented rickets. It is produced in the skin with the aid of sunlight, and it helps to deliver calcium to bones, making them resistant to fractures. The Garlands suggested that it might do a lot more than that, and indeed, everywhere scientists looked they discovered an inverse correlation between vitamin D levels and the risk of dozens of diseases, including breast cancer, high blood pressure, diabetes, heart attack, stroke, dementia, depression, and several autoimmune disorders.

Thus began the vitamin D era. Doctors around the world recommended supplementation with this new wonder drug, and they still do for people who are seriously deficient in the substance. But as chronicled in this magazine, rigorous clinical trials have shown that extra D supplementation—using the vitamin as a treatment—doesn't help with any of these diseases. The maladies afflict people who take supplements and people who don't, in equal measure. Most of us get enough D from just a little sunlight or from our diets: fortified dairy products are good sources, for instance, as are fatty fish such as salmon. Whatever sunshine is doing to prevent myriad ailments, it's a lot more complicated than getting the skin to produce a little vitamin D.

The disease with the most dramatic latitude gradient is MS. Prevalence rates are close to zero near the equator and increase by 3.64 cases on average per 100,000 people for each degree of latitude, reaching well over 100 cases per 100,000 people in northern Europe and North America. The gradient exists worldwide and has been growing stronger over time. It even shows up within individual countries, including France, the U.K., Sweden, New Zealand, Canada and the U.S.

Shining Light on Multiple Sclerosis

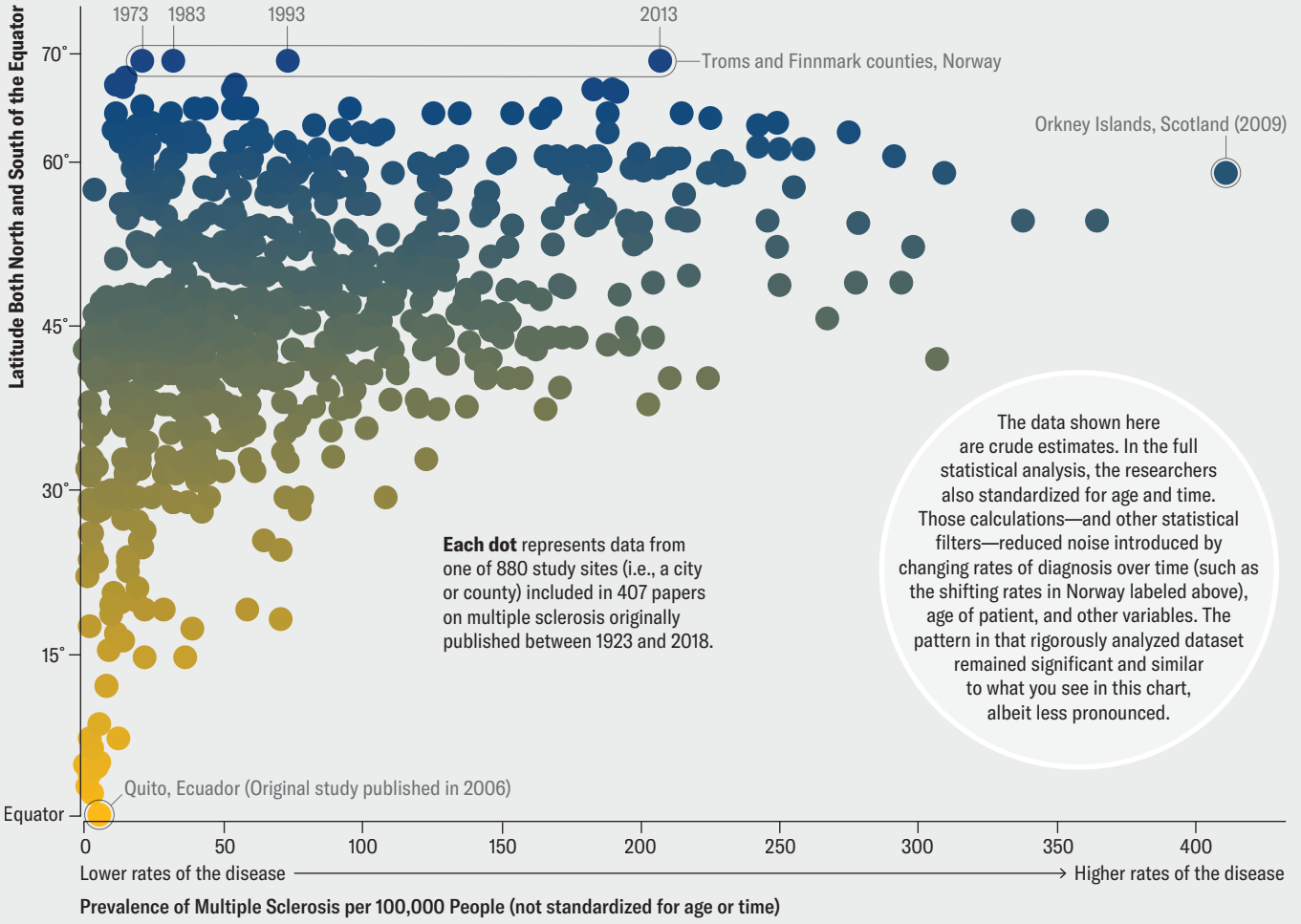
One important clue about sunshine's ability to heal the body came from studies of multiple sclerosis (MS). The disease occurs when a person's immune system attacks protective sheathing around their nerves. Symptoms include difficulty walking, overall weakness, and partial or total loss of sight. MS affects one in 1,000 people worldwide. But it is much more common at higher latitudes, where there is less sunlight, and rarer near the sunny equator. After accounting for confounding factors, scientists think sunlight on skin triggers a reaction that stops wayward immune system activity.



Some of the best data come from Australia, which is one of the only countries to boast a wide range of latitudes, a relatively homogeneous population and a national health-care system with good recordkeeping. A 1981 study found that rates of MS rose from 12 per 100,000 people in tropical Townsville (19 degrees latitude) to 21 in Brisbane (27 degrees), 37 in Newcastle (33 degrees), and a whopping 76 per 100,000 people in Hobart (43 degrees). The latitude connection was reinforced in the early 2000s, when a study of various environmental factors that might contribute to MS onset found rates several times higher in Australia's higher latitudes.

At the time, says epidemiologist Robyn Lucas, an emeritus professor at the Australian National University and one of the leaders of the study, many scientists assumed a lack of vitamin D at the higher latitudes was responsible. "Vitamin D was the flavor of the day. Vitamin D was cancer. Vitamin D was cardiovascular disease," she says. "Vitamin D was autoimmune disease. Vitamin D was everything. And we just thought, 'Yeah, vitamin D.'"

But in 2010 Lucas read a study showing that UV treatments protected mice against MS without affecting their vitamin D levels. Mice are not always good



stand-ins for people, but it was enough to make Lucas curious. "I'd just done the analysis of the vitamin D, and then this paper came out, and I thought, 'Okay, let's have a look at that,'" she says. "So I went back to our data and actually found a much stronger effect for sun exposure."

Since then, Lucas and others have found signs of sunlight's preventive effect on MS everywhere they've looked. People with the most sun damage on the back of the hand—a particularly accurate reflection of lifetime sun exposure—have just one-third the rate of MS compared with those with less. And kids who spent less than 30 minutes a day outside had twice the risk of MS compared with those who spent up to one hour outside and about five times the risk of those who averaged more than an hour outside.

Notably, observational studies like these cannot prove causation. There could be other explanations for the patterns. Perhaps people suffering the earliest symptoms of MS spend more time indoors because they're not feeling well. Maybe something else about high-latitude locations contributes to MS. So epidemiologists looked for other supporting evidence, and they found plenty. Even within the same region, MS relapse rates follow a seasonal cycle—higher in winter, when sun is scarce—and incidence rates correspond closely to birth month, being highest in people for whom it was winter during their first trimester of gestation, when the brain and immune system are developing.

Additional support came from a small clinical trial by Hart. She recruited 20 patients with clinically isolated syndrome, an early-stage version of MS that eventually leads to full MS. Half the subjects received eight weeks of treatment with a narrowband-UV light box similar to the one Kathy Reagan Young uses, undergoing three sessions per week with each session lasting just a few minutes. The other half didn't get light therapy. Within a week of the first treatment, levels of inflammatory proteins in the UV group's blood dropped, and they stayed lower even after the UV sessions ended. Three months after the beginning of the trial, the UV group's disease-severity scores had fallen 13 percent, whereas the control group's had risen 14 percent. These scores correlated with the subjects' self-reported fatigue. A year after the sessions, all the subjects who didn't get UV therapy had developed full-blown MS, but 30 percent of the UV group had been spared.

The fact that the effect lasted for months after the initial UV treatment was intriguing. Immune cells

Source: "Latitude Continues to Be Significantly Associated with the Prevalence of Multiple Sclerosis: An Updated Meta-Analysis," by Steve Simpson, Jr., et al., in *Journal of Neurology, Neurosurgery & Psychiatry*, Vol. 90, No. 11; November 2019 (*data*)

Graphic by Jen Christiansen

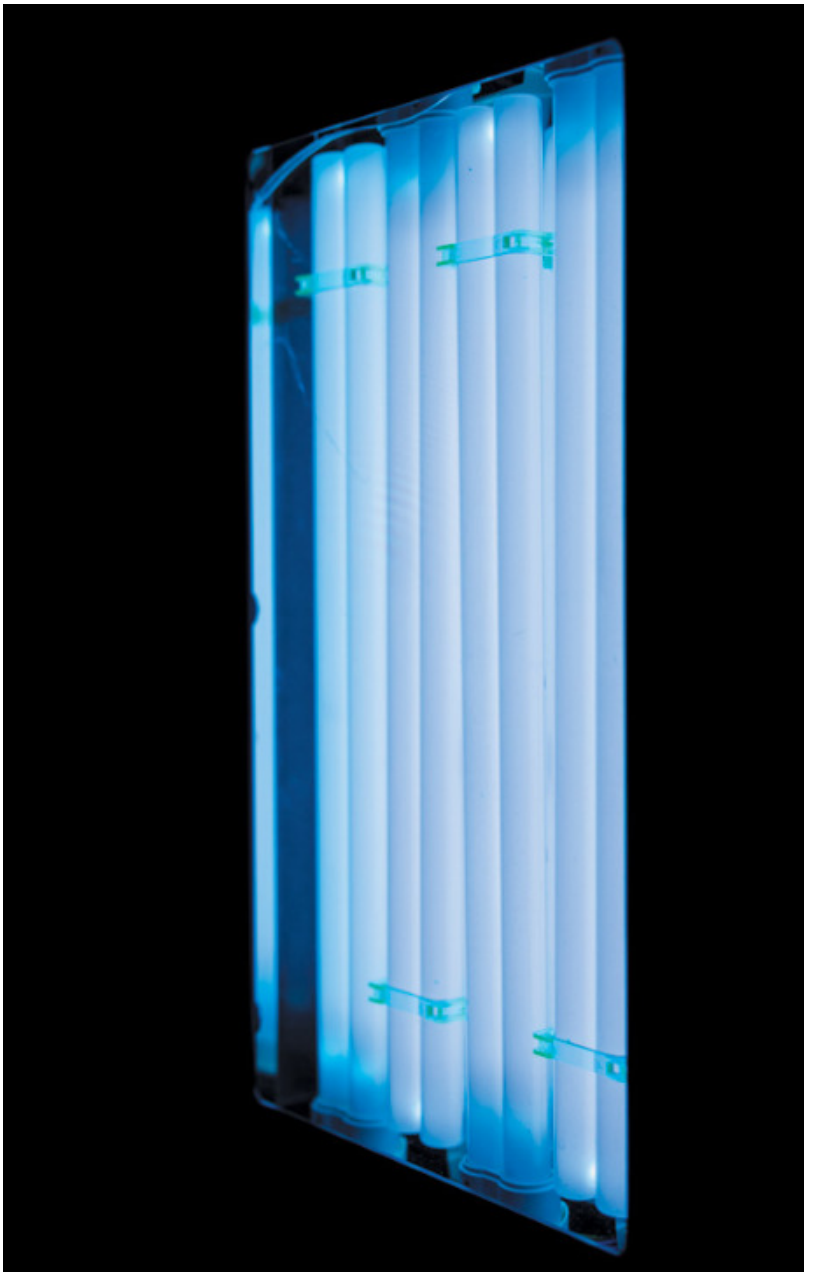
Kathy Reagan Young, who has multiple sclerosis, uses ultraviolet rays from a light box (*right*) for a few minutes every morning. Since she began treatment, her symptoms have eased notably.

are constantly being produced in the bone marrow, and they don't last that long, so the UV hadn't just suppressed the immune cells in circulation; it had reset the system to a more tolerant state. "I think UV is part of our innate immune training," Hart says. "It reprograms subsets of innate immune cells as they evolve out of the bone marrow. They're less inflammatory and more regulatory."

The idea is similar to recent research showing that early exposure to small amounts of allergens can condition the immune system and prevent a hyperactive response later on. "You get this rebalancing," Hart says. "UV light calms inflammation in the skin. But it also then calms inflammation in the central nervous system. It'll calm inflammation in the pancreas and the gut. So I think it's not fully realized the potential it has to be a controller of body homeostasis."

The implications go well beyond MS or even autoimmune diseases. In recent years researchers have learned that many other chronic conditions also have an inflammatory component. Cardiovascular disease is caused in part by immune cells attacking and damaging the walls of blood vessels. Alzheimer's disease is connected to low-grade, smoldering inflammation in the brain. Arthritis, asthma, allergies, diabetes and even depression are thought to have inflammatory components. Something about the modern, indoor, overly hygienic lifestyle may cause our immune systems to lose their healthy set points.

Sun-exposure effects have also been found in some other autoimmune conditions, such as type 1 diabetes, in which the immune system attacks the pancreas, disrupting insulin production. The rate of this disease is threefold higher in southern Australia than in northern



Australia. In the U.S., prevalence is lowest in fall babies, who gestated over the summer. But the difference is most pronounced in northern regions and smallest in sunny spots such as Hawaii and southern California.

Taken together, Lucas says, these findings start to make a very convincing case. "We've now shown it in pediatric MS, we've shown it in Crohn's disease, we've shown it in type 1 diabetes," she says. "There's a consistency of evidence across autoimmune diseases that have a similar immunopathology."

GIVEN THIS CONSISTENCY of evidence, what should we do about it? Although some scientists have argued for increased sun exposure for people at high risk of an autoimmune disease, few health-care providers would ever be comfortable recommending a known carcinogen to their patients. The holy grail, in terms of widespread acceptance, would be to uncover the mysterious molecular pathway through which the skin tells the immune system to relax and then turn it into a biologic—a medication isolated from natural organisms. "What is the Ozempic for autoimmunity?" asks Cytokind co-founder John MacMahon. "Where is it going to come from? Is there something in that photoimmune cascade that can be identified?"

"We don't know what the golden molecule is; we just know it's not vitamin D," Hart says. "So you take a step back and give UV, which gives the skin a chance to make whatever it is." But a pill would be better than a light box as a treatment, MacMahon says. "People prefer pills," he says, and doctors prefer prescribing pills, and pharmaceutical companies definitely prefer making pills.

The problem in finding "whatever it is" is that when

you do shine UV light on the skin and take a peek to see what it makes, you discover a microscopic pharmacopeia. In addition to vitamin D, the skin produces melatonin, serotonin, endorphins, endocannabinoids, cortisol, oxytocin, leptin, nitric oxide, *cis*-urocanic acid, itaconate, lumisterol, tachysterol, and a dozen other vitamin D–like compounds that don't even have names yet.

Most of these molecules are hormones or neurotransmitters, and that should come as no surprise. Although many people tend to think of the skin as nothing but a barrier, it's the largest organ in the body and a vital pole of the neuroendocrine system, in constant conversation with the rest of the body and the brain about how to tune the system to maintain health. It's also a major site for the immune system, stocked with body-defending—or body-attacking, if they go haywire—T cells, macrophages, neutrophils, cytokines, antimicrobial peptides, and other key players.

The way UV light stirs this many-flavored stew is both elegant and complex. For example, the body stocks the skin with a precursor to vitamin D called 7-dehydrocholesterol. When the molecule is hit with the right amount of UV energy, one of its bonds breaks, allowing its atoms to flip to a new configuration. But when hit with *more* UV energy, it flips to a different configuration known as lumisterol, which has been found in the blood in higher concentrations than vitamin D and has known anti-inflammatory and antitumor effects. The skin takes advantage of the bond-breaking power of UV radiation to produce multiple molecules, including *cis*-urocanic acid and nitric oxide, which lowers blood pressure and reduces inflammation throughout the body.

Other skin cells respond to sunlight by increasing production of pro-opiomelanocortin, a protein that is then cleaved by enzymes into three essential molecules: beta-endorphin, a neurotransmitter that causes feelings of well-being and reduces stress hormones; adrenocorticotropic hormone, which triggers the release of cortisol, a steroid that regulates stress and suppresses inflammation; and the alpha form of melanocyte-stimulating hormone, which repairs damaged cells, inhibits proinflammatory molecules and produces melanin to darken the skin.

Immunologist Scott Byrne of the University of Sydney recently discovered six novel lipids—all with names like acylcarnitine and phosphatidylethanolamine, and no, that will not be on the final test—that are produced by the skin in response to UV light and sent down to the lymph nodes under the skin, where various immune cells meet and exchange information. There they signal T cells—the powerful immune warriors that get out of control in people with MS and attack the nervous system—to stay put and stop proliferating. This pathway is separate from the one that suppresses cancer surveillance in the skin, which means it holds the promise of harnessing the good of UV radiation without the bad.

No one fully understands how this biological pachinko game sorts itself out as all these cells and signals bounce off one another, so the quest for the golden molecule will not be completed tomorrow—and is unlikely to have a simple resolution. "Isn't it naive to think one molecule is going to solve all the health conditions controlled by UV?" Hart says. A single cause would certainly be convenient, "but we evolved under the sun for millions of years. It's probably multiple."

Likewise, phototherapy itself is unlikely to deliver all the benefits of full-spectrum sunlight, but it doesn't have to. Its safety, simplicity and affordability mean all it has to do is deliver some benefit. "Phototherapy is so cheap relative to biologics," Hart says. "It's almost a no-brainer as an adjunct treatment for all these inflammatory autoimmune diseases."

That fact alone has drawn the interest of insurance companies. A UV light box costs about $2,000, whereas adalimumab (Humira), a leading biologic drug for various autoimmune diseases, lists for $80,000 a year and must be taken for life. Inspired by that math, along with clinical trials showing phototherapy to be as effective as some medications with fewer side effects, Kaiser Permanente provided 2,200 of its psoriasis patients with free at-home UV light boxes as an experiment. Fewer than a third of them went on to use biologics. Kaiser Permanente now lists at-home UV as a recommended treatment for psoriasis.

But Langer-Gould, the MS expert at Kaiser Permanente, says that although she'd be interested to see whether the light boxes the insurer uses for psoriasis would be helpful for MS, it's too soon to make that leap. "Hart's data are very encouraging," she says. "But the current evidence is not enough to conclude a definitive treatment effect and recommend widespread use. We need at least one more study." That study would have to be a clinical trial large enough to show a significant improvement in patients' underlying conditions. Cytokind is currently pursuing such a study, but the results are probably still years away.

In the meantime, the flexibility of phototherapy will allow Young and other converts to fashion their own healing protocols—independence that becomes all the more precious when you have a debilitating disease. "MS robs you of so much," Young says. "You can't get out of bed, can't go to work, can't clean your house, can't get your groceries. You've got to find rides just to go to the doctor." For now, at least, she has traded all that for busy days of weight training, yoga, charity work, live chats, guided meditations—and a few minutes of UV light every morning. "It's just so empowering," she says. "To find a treatment that lets you actually take care of yourself is kind of amazing." ●

Reporting for this piece was supported by the Nova Institute for Health.

Rowan Jacobsen is a journalist and author of several books, including *Wild Chocolate* (Bloomsbury, 2024). He wrote about how brains are not needed for thinking and problem-solving in *Scientific American*'s February 2024 issue. Follow Jacobsen on X @rowanjacobsen

Young strolls in the sunshine near her Virginia home. Her ultraviolet therapy has let her resume her daily activities and minimized many difficulties and pains created by her multiple sclerosis.

Cold Remedies That Really Work

Snotty, stuffy noses are the hallmark of cold and flu season, but some medications and at-home remedies may offer relief BY MARLA BROADFOOT

RESPIRATORY ILLNESS season is here, and with it typically comes snotty, stuffy noses. In the fall of 2023 a U.S. Food and Drug Administration panel concluded that oral phenylephrine—a common active ingredient in cold and allergy medicines—is useless at clearing up congestion. Now that many over-the-counter drugs officially don't work, what are some other remedies and medications adults and children can turn to?

"It is always a hot topic," says Andrew Lane, a rhinologist and director of the Johns Hopkins Sinus Center. "Whether it's the cold and flu season or allergy season, seems like year-round, congestion is one of the most common things that people come in to see us for."

Lane treats nose and sinus problems and studies how the specialized cells lining the nasal cavity and sinuses participate in the body's immune response—and can contribute to chronic inflammation. He talked with SCIENTIFIC AMERICAN about what causes nasal congestion, as well as what treatments work and why. *An edited transcript of the interview follows.*

What is nasal congestion? What exactly is happening inside our nose when we feel stuffed up?
Basically, congestion is the swelling of the mucous membranes that line the nose.

These mucous membranes help to warm and humidify the air we inhale. The nose is constantly sensing the environment and changing how much air is let through and how much moisture should be added. It does that primarily by dilating or expanding the blood vessels underneath the mucous membranes, which makes the tissue swell.

There's also swelling that occurs from inflammation as the immune system responds to triggers in the environment. For example, when you have an infection, your body needs to bring inflammatory cells to that tissue to fight it off. The blood vessels swell and become kind of leaky, leading to fluid buildup in the tissue. You might also notice your nose looks red when you are congested—the redness comes in part from these swollen and inflamed blood vessels.

So nasal congestion is not caused by the buildup of mucus but is more about swelling and inflammation?
They do go a little bit hand in hand because mucus helps to moisten the air [before it reaches the lungs], and you typically have more mucus production when there's inflammation. But I think of the congestion being more from the stuffiness caused by the swelling of the mucous membranes than from the mucus itself.

What triggers nasal congestion?
The most common causes of nasal congestion are allergies and viral infections, such as those that cause the cold or flu. There's also a form of congestion that has to do with position, where people might complain of being stuffy in one nostril after lying on their side. And then there's congestion that comes from irritants in the environment [such as perfume or smoke].

What oral decongestant medications still work? How about nasal sprays?
Pseudoephedrine is an excellent decongestant that has been around for a long time. It works by constricting the blood vessels, so it counteracts the stuffiness caused by the dilation of vessels that I talked about earlier. [Because pseudoephedrine is chemically related to the stimulant amphetamine], people started making crystal meth out of it, and it was taken off the shelves and put behind the pharmacy counter. That made the medication harder to access, so some people turned to another oral decongestant, phenylephrine. Unlike pseudoephedrine, which can raise blood pressure and make people feel a little hyped up, phenylephrine has fewer side effects—which makes sense because it basically has no effects at all, as the FDA panel concluded. The panel's decision hasn't changed how we treat nasal congestion, because

those of us who prescribe these medications know oral phenylephrine never really worked.

Phenylephrine does work when it is delivered directly to the nose as a spray, however, as does another decongestant called oxymetazoline. The latter is very strong and fast-acting. You should use these sprays only for three days, though—any longer and you risk making things worse. These medications act on adrenergic receptors on the blood vessels that line the nose's mucous membranes. If you take the spray around the clock for many days in a row, those receptors get overstimulated and become resistant to the medication. The effects last less and less, and people keep using it more and more frequently, until they feel like they can't breathe without it. We call that rhinitis medicamentosa, or rebound congestion.

What about nasal steroid sprays?

That's the long game. If you have allergies, then nasal steroid sprays such as fluticasone can help if you use them consistently over a longer period. Steroid sprays work to reduce inflammation, so they're not working directly on blood vessel constriction. In that same vein, if your congestion is caused by an allergy, there are other options, such as antihistamine pills and sprays, that aren't necessarily going to work if your symptoms are instead caused by a cold.

Are there other types of remedies that are effective—such as saline solutions, hot showers, chest rubs or even a comforting bowl of chicken noodle soup?

Saline rinses, which involve moving salt water through your nasal passages, can be helpful because they can hydrate the nose and eliminate irritants that might be driving inflammation. There are good data to show that symptoms are improved with nasal saline. You can deliver saline with a nasal spray, squeeze bottle or neti pot.

Another popular remedy involves steam. I was taught that steam is perfect for your nose because it's already warm and moist, so your nose can relax. But I've also seen studies showing that cool air helps open the nose. There seem to be mixed data, and it depends on the circumstances. Temperature and ambient humidity seem to impact how congested some people are or at least how congested they feel. A hot shower or a bowl of hot soup can create steam, and I think that could act like a decongestant.

Menthol [an ingredient in Vicks VapoRub, Tiger Balm, and other chest rubs] is an interesting one. It does absolutely nothing to any of the objective measures of nasal airflow, but it does improve subjective ones. That's because the nose has temperature-sensitive sensors inside that can detect air movement; menthol tricks the nose into thinking there's a lot of airflow because it creates a cooling sensation, even when there's absolutely no difference in airflow. A bunch of aromatic compounds such as eucalyptus and spearmint have a similar effect.

Another factor that can affect nasal congestion is posture. Your nose will be more congested when you lie down because blood pools in those vessels in the nasal structures and the mucosae [mucous membranes]. If you sleep with your head elevated on a pillow, you'll probably have less congestion. It's just gravity, right? If you twisted your ankle, you would want to prop it up to decrease swelling. Keeping your head up above the level of your heart is going to make your nose less inflamed and less swollen.

Do you have any parting advice for people suffering from nasal congestion?

You're just trying to relieve your symptoms while you wait for the congestion to run its course. Start with things that are least likely to cause side effects, such as saline or chicken soup. There are over-the-counter medications that are effective and generally safe, but some people do experience side effects. If you take a medication once, and it makes you feel sleepy or jittery, just don't take it again.

Nasal congestion only gets concerning if it becomes a persistent problem. In that case, you want to rule out other causes such as nasal polyps or tumors, and you might need a surgical procedure to open the nasal passages. Not everything is just allergies or a cold, so if it doesn't really fit that picture, see a doctor. ●

Marla Broadfoot is a freelance science writer who lives in North Carolina. She has a Ph.D. in genetics and molecular biology and is an adjunct at the University of North Carolina at Chapel Hill. Her feature on postpartum depression was published in our December 2025 issue.

Victoria Kotlyarchuk/Alamy

VIRUS-FREE AIR

Air-cleaning ultraviolet light typically has to be positioned away from people. Devices using shorter UV wavelengths could change this

BY ERIC BENDER

THE BOSTON PIANO BAR where Edward Nardell was singing cabaret songs in 2022 would typically be an ideal setting for airborne diseases to spread. But Nardell and his audience were protected during the COVID-19 pandemic by the far-ultraviolet (UV) lights he had installed to shine down from the ceiling.

Far UV is an emerging form of germicidal UV (GUV) irradiation, a well-established disinfection technology and a growing resource in the battle against pathogens that can spread easily through the air in enclosed spaces.

Indoor air safety begins with ventilation, but it usually can't end there, says Nardell, a physician and researcher in airborne infection at the Harvard T. H. Chan School of Public Health. Ventilation systems that replace air in a room are rarely powerful enough to fully protect against coronaviruses and other easily caught diseases, he explains.

Systems that actively try to clean the air in rooms, such as those using high-efficiency particulate air (HEPA) filters, remove harmful particles more effectively. But they are expensive to install and operate, often noisy, and limited in reach—multiple devices might be needed to cover a room. "That's where the air sanitation with UV comes in," says Donald Milton, an environmental health researcher at the University of Maryland School of Public Health in College Park.

With GUV light, "you can get very high rates of air disinfection with relatively little air movement," Milton says. "And with the newest technology, maybe you don't even have to worry about air movement, because now there are wavelengths that are safer to use, and you can use GUV in the whole room." In crowded spaces such as schools, hospitals and restaurants where diseases can easily spread, GUV can operate unnoticed "even before you know that you've got a problem," Milton says. "That's really critical in keeping these things under control."

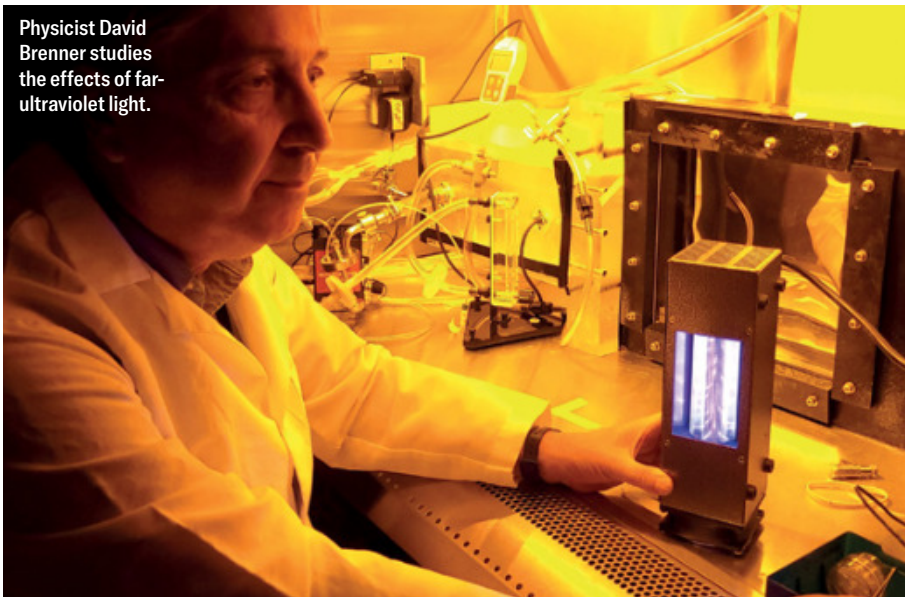
CONVENTIONAL GUV SYSTEMS use mercury vapor lamps, which produce light by passing an electric current through vaporized mercury and are similar to conventional fluorescent bulbs. The lamps emit radiation in the UVC band, with a wavelength of around 254 nanometers. UVC radiation is filtered by the atmosphere, so life on Earth has not evolved to withstand it. The radiation inflicts photochemical damage that mangles nucleic acids—inactivating pathogenic viruses and bacteria, though not necessarily killing them.

The lamps are widely used to disinfect water, clean fruits and vegetables, and sanitize surfaces in spaces such as operating rooms. But because this wavelength can damage human eyes and skin, the light from these systems is kept away from people. That does not mean, however, that it can't be deployed in public spaces. A clever approach developed decades ago, known as upper-room GUV, places the lamps high in a room and takes advantage of rising air currents to inactivate pathogens well away from people.

The technique works well, says William Bahnfleth, an architectural engineer at Pennsylvania State University who focuses on indoor air quality. In a room, air rises from people, equipment and existing ventilation, passes through the radiation zone of the lamps, and then circulates back down into the occupied space.

Although there are no universally accepted and enforced standards for indoor air quality, targets are typically expressed in terms of how often the amount of air in a room is exchanged per hour. The recommendation for examination rooms in U.S. hospitals, for instance, is six air changes per hour. That's a struggle for ventilation systems and typically requires a lot of energy, Bahnfleth says. In contrast, an upper-room GUV system can easily reach the equivalent of two or three times those levels of air exchange for disinfection purposes while using much less energy than a ventilation system. "It's mostly impossible for anything but a hospital or special facility to have six air changes," Nardell says. "GUV is the only method that gives you this incredibly high number of equivalent air changes because you can disinfect such a large volume of air at once."

In a study that applied different combinations of ventilation, filtration, UV and



Physicist David Brenner studies the effects of far-ultraviolet light.

Columbia University Center for Radiological Research

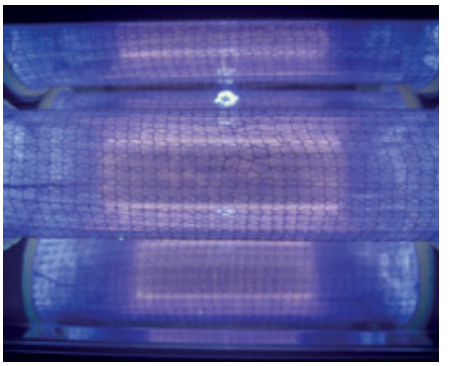
mask wearing in a variety of buildings, including offices, hotels and schools, "the only technology that routinely got the risks down to a reasonably acceptable level was UV," says Shelly Miller, a mechanical engineer and specialist in indoor air quality at the University of Colorado Boulder. "To me that says UV is an incredibly powerful air-cleaning tool that we just are dropping the ball on."

UPPER-ROOM GUV was widely adopted in schools and hospitals following studies in the late 1930s and 1940s led by William Wells, a biologist then at the University of Pennsylvania. Wells and his colleagues showed that upper-room GUV drastically reduced the spread of measles in schools in suburban Philadelphia. Although upper-room GUV is still used in many tuberculosis wards, its use has dropped with the advent of more powerful interventions such as vaccines.

Even though upper-room GUV's conventional UVC light is effective, it is fundamentally limited by the requirement to keep it away from people. Air is cleaned only when it circulates to the top of the room and passes by the GUV light, leaving an opportunity for pathogens to hop to a new host. Shorter wavelengths might help to overcome this limitation.

This is because wavelengths below 254 nm don't penetrate tissues nearly as well, says David Brenner, a physicist specializing in radiological research at Columbia University. Far-UV light with a wavelength of 222 nm doesn't reach beyond the layer of dead cells on the surface of the skin or the film of tears on the surface of the eye. Because bacteria and viruses are much smaller than the thickness of those layers, Brenner and his colleagues reasoned that far-UV radiation could destroy the pathogens without damaging the skin and the eyes. The scientists tested their hypothesis with lamps containing krypton chloride gas, molecules of which release UVC radiation mainly in the 222-nm range under electrical excitation.

Originally aiming to improve disinfection in operating rooms, the Columbia team realized that far-UV radiation might also reduce airborne viral transmission. In a 2018 study, the investigators showed that more than 95 percent of influenza viruses in the air were inactivated when they floated past a low-power far-UV lamp. Brenner's group had already shown that cells in a 3D human skin model and in mice were basically unaffected by such low doses, and other researchers found no evidence of eye damage from 222-nm radiation in rats.



A krypton chloride ultraviolet lamp

Ewan Eadie

When COVID-19 hit, the Columbia scientists ran analogous experiments on strains of coronavirus similar to SARS-CoV-2, again with good results. To scale up their tests, the researchers then collaborated with scientists in the U.K., including a group at Leeds University that had access to a room-size test chamber designed to contain pathogens.

The room-size experiments used *Staphylococcus aureus* bacteria suspended in the air. This microorganism is relatively easy to analyze and is expected to be more robust against UV radiation than coronaviruses, says Ewan Eadie, a medical physicist at the University of Dundee in Scotland and lead author of a paper that outlines the team's findings. "We really had no idea what was going to come out at the end," he says.

The results were excellent. "We got really rapid reduction in the level of pathogens in the room," Brenner says. "Our equivalent air changes per hour were really big, well over 100 equivalent changes per hour."

On the safety side, Brenner and his colleagues reported in May 2022 that they had exposed hairless mice to the radiation for 66 weeks without detecting any skin cancer. They also intended to investigate the risk to the eyes and the mechanisms of how 222-nm radiation damages pathogens.

Despite the promising laboratory tests of far-UV disinfection, there are questions about how well the technology will translate into busy public indoor spaces such as hospitals, schools and restaurants. "The labs are pretty sterile clean conditions," Eadie says. "I'd like to see some real-world data."

In one real-world clinical trial, researchers in Nova Scotia have been examining the use of far-UV light in nursing homes, where it's difficult to prevent the spread of airborne diseases. The controlled study tracked the incidence of COVID and other respiratory viral infections among residents in multiple facilities, half of whom used common areas fitted with far-UV lamps. The other half had placebo lights, identical in appearance but lacking the far-UV output. Results for the trial, which concluded in 2025, are not yet published.

Nardell, meanwhile, chose an airborne-infection research facility in Emalahleni, South Africa, to study COVID. Originally designed to analyze tuberculosis infection, the facility includes a six-bed ward, the air from which is transferred to exposure rooms holding animals that easily become sick with the disease being studied—in this case, hamsters. "Hamsters are the experimental animal of choice for COVID," Nardell says. The study was designed to test the efficacy of far-UV radiation compared with upper-room GUV systems by monitoring the hamsters for signs of sickness.

But companies aren't waiting on peer-reviewed research. Far-UV lamp fixtures are already on the market and being installed around the world—not just in buildings but also on buses and in other infection hotspots. Some devices are even marketed for home use, although Brenner warns consumers to proceed with caution—an appliance delivering the wrong wavelengths can do damage.

Although costs of the fixtures vary widely, Nardell says that $2,000 is a ballpark retail price for a lamp installed by specialists, and the lamps have an expected lifetime of around 15 months if they run continuously. There's hope that far-UV lamps based on light-emitting diodes (LEDs) will eventually provide cheaper and longer-lived alternatives to the gas lamps being used now, but prototype LED far-UV lamps are currently restricted to impractically low levels of power, Eadie says.

In the meantime, Nardell says that in the piano bar where he was performing, the far-UV lamps provided the equivalent of 35 air exchanges per hour, probably making it one of the safest venues for singing on the planet. When he invited Brenner and his colleagues to the bar a few years ago, they enjoyed an evening of cabaret without masks, hoping they would be protected by the invisible light shining on them. "I was pretty nervous and took lots and lots of COVID tests over the next week, but I was fine," Brenner says. ●

Eric Bender is a science writer based in Newton, Mass.

The Staggering Success of Vaccines

Vaccines have been aiding global health for 200 years, and today they are poised to save even more lives from more diseases

BY TARA HAELLE | ILLUSTRATION BY LUISA JUNG

ONCE A WEEK, early in the mornings of 2024, community health worker Kiden Josephine Francis Laja mounts her bicycle and pedals as far as 10 miles away from her small village in South Sudan. Some weeks Laja is doing outreach, spending her day educating a community about which vaccines she can provide and what diseases they prevent. "It's my responsibility to tell the mothers to bring the children for vaccination," she says. She answers their questions and lets them know she'll be back, usually the following week, to vaccinate their children. Late in the evening she mounts her bike and heads home.

When Laja returns with the vaccines, kept in a cooler with ice packs, she will spend the day immunizing anywhere from a few to 200 children against a range of diseases: polio, tetanus, diphtheria, pertussis, hepatitis B, influenza, bacterial meningitis, tuberculosis and COVID. Most people in high-income countries haven't seen the majority of these diseases in decades, but the people of South Sudan know them well. Many have seen family and friends die from them.

During the rest of the week Laja works at the community health center in her village of Pure, monitoring the solar-powered refrigerator and the vials inside. She vaccinates anyone who comes to the facility and metes out drugs for a few maladies such as ulcers, malaria and typhoid. But the village doesn't have antibiotics—or electricity. Villagers grow their own food, raise goats and chickens, and get their water from wells in the ground.

It's not easy work for just $102 a month, especially when it sometimes takes three months for the mother of two to get her pay. When it rains on travel days, she and her outreach pamphlets get soaked. She must regularly check the temperature of the vials in the cooler and replace the ice packs at just the right time to ensure the vaccines don't go bad.

People in South Sudan don't have much, but they have this program. "Vaccines are very important to me and my community and even to my country," Laja says. During a large outbreak of measles that began in 2022 in the country, thousands of children suffered from the disease, and many died, leading to a nationwide vaccination campaign in 2023. "Now in our community you cannot find cases of measles," she says.

Around the globe the measles vaccine has saved nearly 94 million lives over the past 50 years. This and other vaccinations have revolutionized global health. "Immunization is the most universal innovation that we have across humankind," says Orin Levine, president and CEO of the Washington Research Foundation in Seattle. He notes that there are people around the world without access to telephones or even toilets, but they find ways to get their children immunized. "It's the innovation that demonstrates what is possible in terms of delivery of service to everyone everywhere."

A May 2024 study in the *Lancet* estimated that vaccines against 14 common pathogens have saved 154 million lives over the past five decades—at a rate of six lives every minute. They have cut infant mortality by 40 percent globally and by more than 50 percent in Africa. Throughout history vaccines have saved more lives than almost any other intervention. And vaccines' promotion of health equity goes far beyond preventing death. The *Lancet* study found that each life saved through immunization resulted in an average 66 years of full health, without the long-term problems that many diseases cause. Vaccines play a role in nearly every measurement of health equity, from improving access to care, to reducing disability and long-term morbidity, to preventing loss of labor and the death of caretakers.

"We say vaccines are one of humanity's great achievements in terms of having furthered the lifespan and life quality for humanity in the past 50 years," says Aurélia Nguyen, deputy CEO of the Coalition for Epidemic Preparedness Innovations (CEPI), a foundation formed specifically to develop and improve access to vaccines for diseases that lack strong market demand. Of all the different health interventions that exist, she says, "vaccines have the widest reach across the world." The clearest evidence of vaccines' impact on equity is that they are often the first intervention introduced into a community with no other health-care resources.

"When you don't have a health worker or health system, there's nothing. If you have no money, then you want the best bang for the buck, and it's going to be immunization," says epidemiologist Seth Berkley, chief scientific adviser to the Pandemic Center at the Brown University School of Public Health. "For every dollar you invest in immunization, you get $54 of benefit. From a cost-effectiveness point of view, it's

the best investment, so it tends to be the intervention that gets out to those communities first. And once you do that, you have a health worker who's visiting those communities on a regular basis, and then that begins to start the conversation toward more primary health care, and that leads to getting a basic clinic set up. Immunization is the vanguard of the health system."

Every country in the world has an immunization program thanks to the World Health Organization's Expanded Program on Immunization, which was established in 1974. "Every single country and territory" has access to at least some vaccines, says Kate O'Brien, director of the WHO's immunization, vaccines and biologicals department. Poverty, malnutrition, underlying health conditions, overcrowding, human conflict, displacement, and lack of access to medical care, hygiene or sanitation—all of these are risk factors for infectious disease, O'Brien says. Vaccines' ability to reduce disease in the settings most plagued by these problems gives them disproportionate power to improve equity.

THERE MAY BE NO GREATER demonstration of vaccines' power to deliver health equity than their success with smallpox. "The magnitude of the accomplishment of having eradicated smallpox, where absolutely nobody on this Earth gets the disease," O'Brien says, "that's the ultimate in the issue of equity."

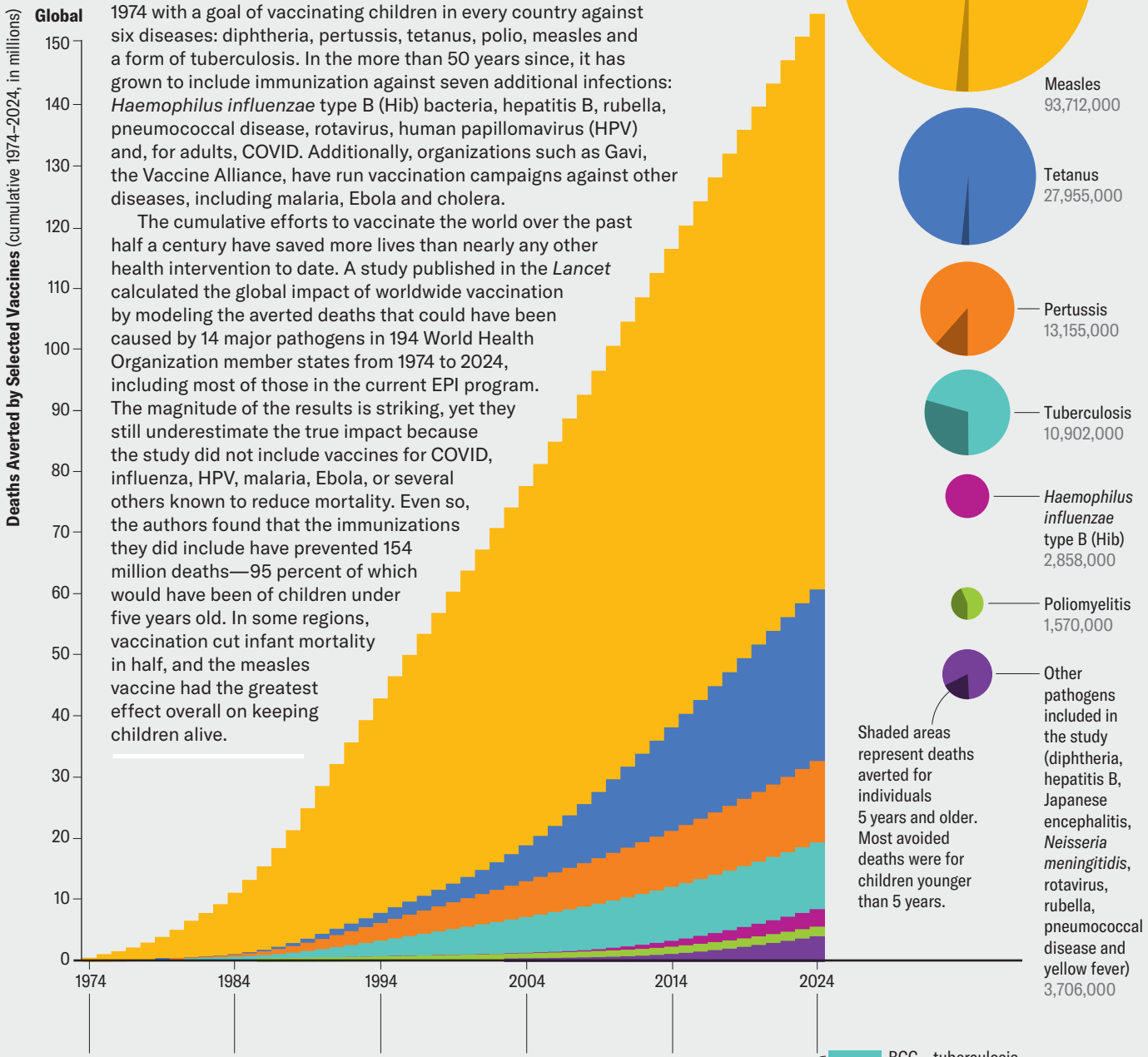
A version of a smallpox vaccine was developed in 1796, and in 1959 global health experts decided to pursue full eradication. In the decade that followed, it became clear that such an ambitious goal would require more than political will. Although smallpox had been eliminated from North America and Europe, frequent outbreaks continued in South America, Africa and Asia.

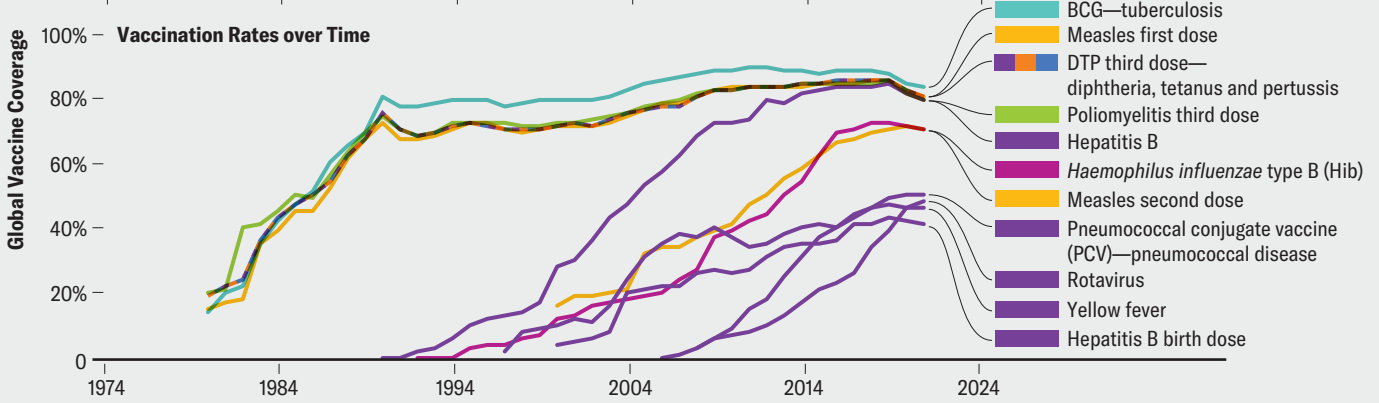
In 1967 the WHO started its Intensified Eradication Program, which prompted a series of innovations. The bifurcated nee-

Millions and Millions Saved

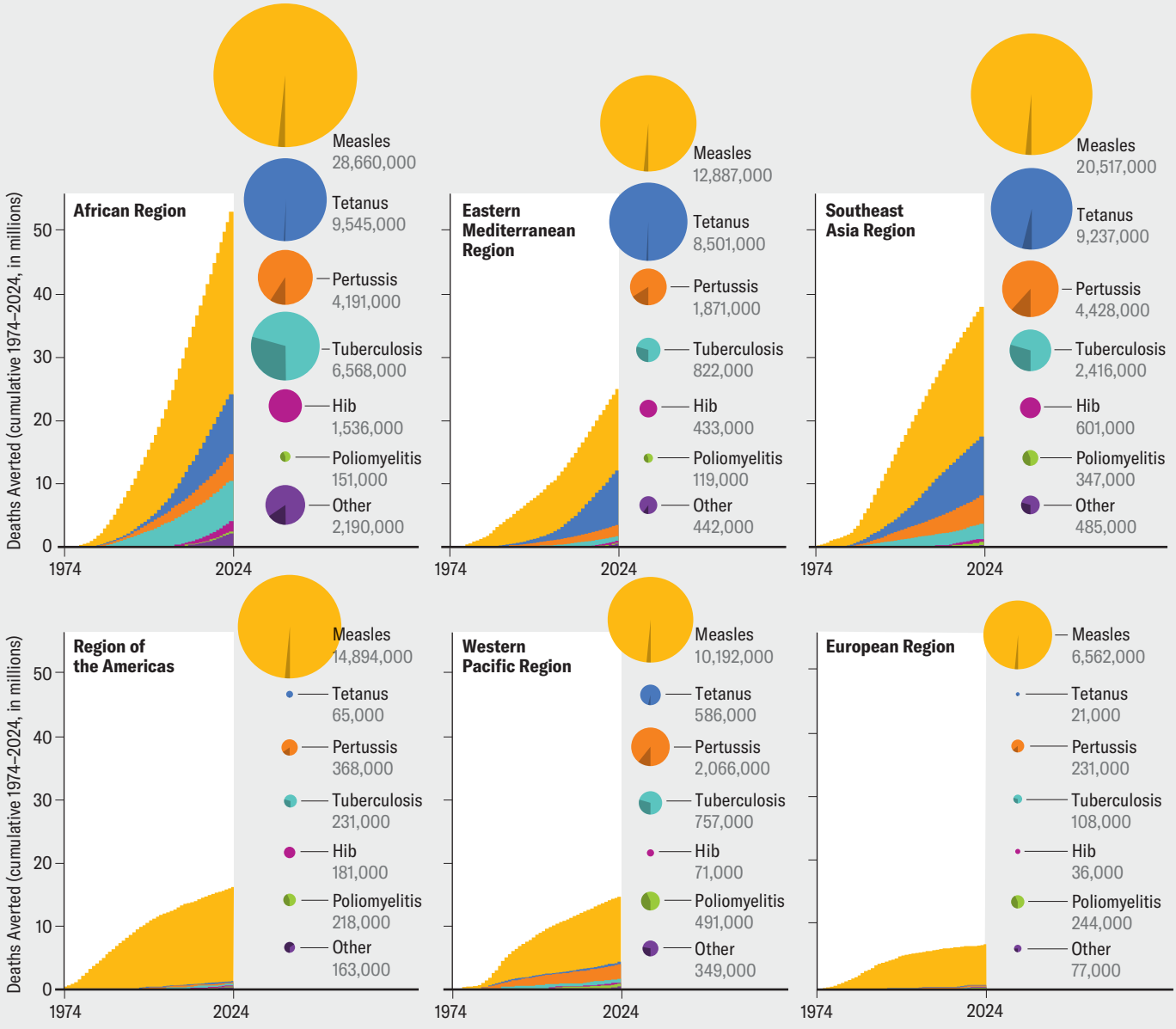
The Essential Program on Immunization (EPI) was developed in 1974 with a goal of vaccinating children in every country against six diseases: diphtheria, pertussis, tetanus, polio, measles and a form of tuberculosis. In the more than 50 years since, it has grown to include immunization against seven additional infections: *Haemophilus influenzae* type B (Hib) bacteria, hepatitis B, rubella, pneumococcal disease, rotavirus, human papillomavirus (HPV) and, for adults, COVID. Additionally, organizations such as Gavi, the Vaccine Alliance, have run vaccination campaigns against other diseases, including malaria, Ebola and cholera.

The cumulative efforts to vaccinate the world over the past half a century have saved more lives than nearly any other health intervention to date. A study published in the *Lancet* calculated the global impact of worldwide vaccination by modeling the averted deaths that could have been caused by 14 major pathogens in 194 World Health Organization member states from 1974 to 2024, including most of those in the current EPI program. The magnitude of the results is striking, yet they still underestimate the true impact because the study did not include vaccines for COVID, influenza, HPV, malaria, Ebola, or several others known to reduce mortality. Even so, the authors found that the immunizations they did include have prevented 154 million deaths—95 percent of which would have been of children under five years old. In some regions, vaccination cut infant mortality in half, and the measles vaccine had the greatest effect overall on keeping children alive.



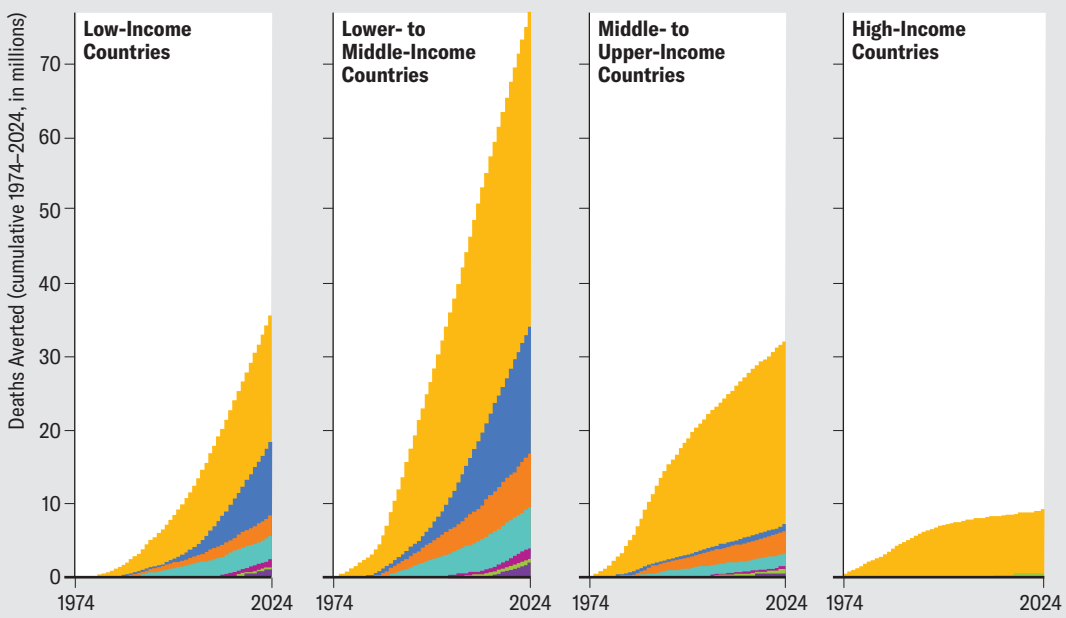


Graphics styled by Jen Christiansen



WHERE IT MATTERS MOST

Vaccines' relative impact on mortality varies by country depending on how affected that country already is by a particular disease and the other major causes of disease there. Vaccine-preventable diseases cause far fewer deaths in high-income countries, where sanitation, hygiene, nutrition, medical infrastructure and health-care access have already substantially improved survival. Meanwhile, vaccines have an outsized impact on preventing deaths in low- and middle-income countries where infectious disease remains a top killer. In short, as the *Lancet* study authors write, "Vaccines promote equity by saving more lives in places where more deaths occur."



Source: "Contribution of Vaccination to Improved Survival and Health: Modelling 50 Years of the Expanded Programme on Immunization," by Andrew J. Shattock et al., in *Lancet*, Vol. 403; May 25, 2024

"Vaccines level the playing field. But frankly, it was a really long road to get to that kind of equity."

—NICOLE LURIE *COALITION FOR EPIDEMIC PREPAREDNESS INNOVATIONS*

dle, which was developed around that time, allowed for smaller doses and required less user expertise for vaccine delivery than the previously favored jet injector. Researchers created a surveillance system to better track disease and vaccinate close contacts of infected people, making mass vaccination campaigns more effective. The last documented case of smallpox occurred in Somalia in 1977, and the WHO declared smallpox officially eradicated three years later.

That success inspired a similarly lofty goal in 1988 that has proved far more challenging: eradicating polio. Since the establishment of the Global Polio Eradication Initiative, cases have fallen 99 percent worldwide, but that last 1 percent is taking decades longer than planned. Public health experts now recognize that very few diseases can be completely eradicated through immunizations. Even so, they aim to decrease vaccine-preventable diseases to such low levels that severe morbidity and mortality are negligible. The WHO's renamed Essential Program on Immunization initially focused on six childhood diseases: polio; measles; disseminated tuberculosis, the form of the disease most common in children; and diphtheria, tetanus and pertussis, for which children receive the combined DTP vaccine. It has since expanded to include vaccines against 13 diseases.

"We have to look backward, in some ways, to realize how far we've really gone," says Lois Privor-Dumm, an adjunct senior associate at Johns Hopkins University. "There has been tremendous progress over the past 50 years, and what is really left is making sure the equity agenda is really a focus."

Now the question is how best to do it. A raft of technological and policy innovations aim to help. Before the WHO's current vaccination program began, fewer than 5 percent of the world's babies had access to routine immunizations. Today 84 percent of infants have received three doses of the DTP vaccine, the metric used to assess global immunization coverage.

"Vaccines level the playing field in terms of who gets these diseases and who doesn't," says Nicole Lurie, U.S. director of CEPI. "But frankly, it was a really long road to get to that kind of equity."

Setbacks through the 1990s led global health leaders to rethink their approach, and in 2000 the WHO, UNICEF, the World Bank and the Gates Foundation collaboratively founded Gavi, the Vaccine Alliance, a public-private partnership working to ensure low- and middle-income countries have access to vaccines against more than 20 infectious diseases. Thanks to Gavi, says Violaine Mitchell, former director of immunization at the Gates Foundation, "now countries not only assume but demand that when a vaccine is introduced in the developed world, it's also made available in the developing world."

Gavi has vaccinated more than one billion children with a routine suite of shots and given a total of 1.8 billion immunizations to people of all ages through campaigns for illnesses such as measles in Ethiopia, Afghanistan and Somalia and yellow fever in Congo, averting more than 17 million deaths through 2022. Since Gavi was established, there has been a 70 percent reduction in deaths from vaccine-preventable diseases in children living in the lower-income countries the alliance supports, and mortality among children younger than five years in those countries has been halved. The pneumococcal and rotavirus vaccines have been particularly significant—pneumonia and diarrhea are among the top global killers of children under five.

But even those impressive numbers don't fully capture the dramatic ways vaccines advance health equity. For example, epidemics of meningococcal meningitis were common in the "meningitis belt," a stretch of 26 countries just south of the Sahara Desert that has the highest rates of meningococcal disease in the world. Up to half of those infected die without treatment; even with treatment, one in 10 people dies. Since the development and distribution of a vaccine against meningitis A, this form of the disease has been nearly eliminated. The vaccine has not only saved lives but prevented long-term effects that meningitis survivors often suffer, including hearing loss, seizures, limb amputations or weakness, scarring, vision problems and cognitive difficulties.

Another example is the human papillomavirus (HPV) vaccine, which can prevent up to 90 percent of HPV-related cancers, including nearly all cervical cancer. Because high-income countries implemented cervical cancer screening programs decades ago, 94 percent of global deaths from cervical cancer in 2022 were in low- and middle-income countries. Gavi programs have vaccinated girls worldwide against HPV, and the organization met its goal of helping to protect 86 million from cervical cancer by 2025. The physical benefits won't be seen for years—it takes up to two decades for an HPV infection to develop into cancer—but the ripple effects of prevention go far beyond saving a single person's life. A death from cervical cancer may mean loss of a family caretaker, loss of income, and difficulty meeting children's continuing health needs. "The tsunami effect of losing a mother to children, especially for those who are not economically stable, is devastating to a family," O'Brien says. "Their lives are entirely dependent on the survival of that person."

VACCINATION CAN BE A KEY entry point to additional health care. The late William Foege, a former director of the U.S. Centers for Disease Control and Prevention, who was instrumental in leading smallpox eradication and in setting up Gavi, called vaccines "the tugboat" for preventive care.

When health workers arrive to vaccinate children in a community, they can assess other children's growth trajectories and nutritional issues, provide vitamin A supplements where there are deficiencies, distribute deworming tablets, monitor mosquito-borne diseases and check on additional needs. "If you manage to reach a child and give them a measles vaccine, then you may be able to give their mother maternal services," Nguyen says. "It's a perfect time to say: Are you sleeping under a bed net? Do you need a bed net? What are you doing for family planning?" Mitchell says. "All those conversations can come about because of the contact between the caregiver and the health worker that wouldn't [otherwise] happen."

In 1985 Rotary International launched its PolioPlus program, which used vaccination campaigns as an opening for other health interventions. "When Rotary and its partners added other things to improve the health systems of countries, it was a game changer," says Stella Anyangwe, a former Rotary International EndPolioNow coordinator and former WHO official. By strengthening laboratory systems, the cold-chain network of refrigerated storage necessary for transporting the vaccine, and overall disease surveillance, she says, improving systems for polio eradication "strengthened the health systems in general." In short, Levine says, "immunization is an innovation that is pulling other innovations along."

It can also free up valuable time and resources in health care. As infectious disease incidence falls, health workers and hospital beds become available for people with other conditions. This may already be happening with malaria. In Burkina Faso, about two out of every five visits to a health-care provider in 2024 were for malaria, which historically accounts for more than 60 percent of the country's hospitalizations. Similarly, malaria cases make up about half of hospitalizations in Cameroon; most of those patients are children under five who are eligible for the malaria vaccine. Although current malaria vaccines don't prevent infection altogether, they reduce severe disease by 30 percent and all-cause mortality by 13 percent. Gavi began rolling out vaccination campaigns against malaria in 2023, providing 18 million doses to a dozen African countries, and malaria deaths have already begun falling. "You can imagine how much that's going to free up capacity for health-care workers to focus on other [issues]," Nguyen says.

Vaccines help countries with fewer resources protect themselves from disease. Outbreaks disproportionately affect poorer areas: the 2014–2016 Ebola epidemic in West Africa, for example, devastated the region's health-care infrastructure. Since the development of an Ebola vaccine in the late 2010s, subsequent outbreaks have remained comparatively small. And the outbreak of mpox, which led the WHO to declare a global public health emergency in August 2024, was managed with vaccines that had become available only in the past few years.

Gavi now supports stockpiles of outbreak-specific vaccines for cholera, yellow fever, meningococcal disease and Ebola so the countries most affected can focus their health-care resources on chronic disease, snakebites, cancer and HIV, among other conditions.

IN LATE 2019, when a novel coronavirus detected in Wuhan, China, kicked off one of the largest, deadliest pandemics in a century, everyone looked to the same solution: a vaccine. COVID's devastation hit poorer countries with less developed health-care systems particularly hard, and in wealthier countries people from underserved and low-income communities suffered higher rates of illness, death and economic hardship. It was clear that a COVID vaccine would be the most equitable solution.

The U.S. quickly directed $10 billion toward vaccine development, and dozens of other countries allocated what they could. The effort broke every record for the fastest vaccine development. The Chinese CDC released the sequence of SARS-CoV-2 on January 10, 2020, and just 11 months later, on December 8, 2020, the first COVID vaccine was administered outside of a clinical trial.

Officials at Gavi, UNICEF, WHO and CEPI quickly organized Covax, an international effort to accelerate COVID vaccine development and "to guarantee fair and equitable access for every country in the world," according to the WHO. Covax delivered nearly two billion vaccines to more than 140 countries in the two years after the vaccines' introduction, "by far the fastest, largest and most effective public health rollout in history," a Gavi spokesperson says. A 2022 study in the *Lancet Infectious Diseases* estimates that COVID vaccination worldwide prevented 19.8 million excess deaths, 7.4 million of those in Covax countries.

The challenges were steep and vaccine distribution contentious. "At no point did a richer country with access to vaccine doses choose to slow down its rollout to make doses available for people at higher risk in lower-income countries," Levine says. "That's vaccine nationalism, and it undermined the success of hardworking folks at Covax."

Those problems have prompted a lot of reflection and a lot of new action. The organizations behind Covax have set their sights on improving vaccine equity during future pandemics. Because Africa lacked vaccine access and had few manufacturing capabilities of its own, these efforts are particularly focused on boosting the continent's vaccine-manufacturing capabilities. The Africa CDC has partnered with other organizations to create the Partnerships for African Vaccine Manufacturing with a goal of making 60 percent of its needed vaccines by 2040. In June 2024 Gavi launched the African Vaccine Manufacturing Accelerator, a financing program developed with the Africa CDC and African Union to put up to $1.2 billion over the next decade toward building up the continent's vaccine-manufacturing capacity.

In the more than 25 years since Gavi was launched, it has made substantial progress in advancing equity in vaccine manufacturing. In 2000 four of its five vaccine suppliers were in wealthy countries. Today most of its 20 or so suppliers are in developing countries. "It opened up a marketplace for large-scale, low-cost manufacturing in India, in Brazil, in China and in Indonesia," says Berkley, the Brown University adviser.

It will still be immensely challenging to get vaccines into the arms and mouths of people who need them most. Health workers must find and immunize zero-dose children—children who have yet to receive vaccines of any kind, like the ones Laja sees in South Sudan. And low-income countries must acquire the financing and build the infrastructure to facilitate that process. Then Laja and her peers must educate people so fear does not become a barrier to access.

Workers such as Laja are part of the global workforce that the WHO, Gavi, UNICEF, the Gates Foundation, Rotary, and other organizations have trained to use vaccines against disease and health disparities. In 2024 Laja completed training in preparation for South Sudan's malaria-vaccine rollout. In 2022 there were almost 7,000 malaria deaths in South Sudan; the disease is a top killer of young children in the country. The previous year South Sudan's malaria fatalities accounted for more than 1.2 percent of the total worldwide.

Laja is eager to see the vaccines' impact on her community and in the villages she visits, where parents will walk for miles from outlying areas to meet her. "There are very few things women and caretakers will walk hours and hours for, but vaccines are still one of them," Mitchell says. "People will literally drop everything to come and vaccinate their child."●

Tara Haelle is a Dallas-based science journalist whose specialties include infectious disease, medical research and health disparities.

Annual Shots Protect against Severe COVID

A recent study shows that receiving an updated COVID vaccine reduced people's risk of severe disease and death in all age groups, regardless of immunity from prior infection or vaccination BY SARA NOVAK

A STUDY PUBLISHED IN OCTOBER 2025 in the *New England Journal of Medicine* showed that mRNA COVID vaccines for the 2024–2025 season reduced people's risk of emergency department visits by 29 percent, their risk of hospitalization by 39 percent and their risk of death by 64 percent. Of the nearly 300,000 U.S. participants in the study, 35 percent received the Pfizer vaccine (COMIRNATY), and 64 percent received the Moderna vaccine (Spikevax). According to the study's authors, COVID vaccination was effective in all age groups and "in persons with or without major chronic conditions."

The research is in line with what scientists have seen in previous years. "The vaccine is efficacious, particularly against severe disease," says Stanley Perlman, a coronavirus researcher and a professor of microbiology and immunology at the University of Iowa, who was not involved in the study. And he and other experts expect the 2025–2026 COVID vaccines' performance will follow suit. The study's authors declined to comment on the findings.

The COVID vaccines' effectiveness against symptomatic disease has generally waned since the first year they became widely available: the 2024–2025 shots offer 29 to 64 percent protection, compared with the 94 percent protection given by the vaccines in 2019. This dip, however, is expected in a population with some prior immunity, Perlman says. Nisha Viswanathan, an internal medicine doctor and medical director of the University of California, Los Angeles, Long COVID program, who was not involved in the study, agrees that changes in immunity—and the subsequent response to the vaccines—were anticipated as more people were exposed to the COVID-causing virus through either prior infection or vaccination.

The new research also "calls into question the idea that younger individuals and those without risk factors don't need the vaccine," Viswanathan says. Instead the data show that the shot, though most effective for older individuals and those with comorbidities, "was also protective in those without risk factors," she says. Additionally, Viswanathan says that the study design made the evidence "more compelling" because the authors included enough women and younger individuals, which made the results more balanced and provided a fuller picture of vaccine effectiveness for all cohorts. The Centers for Disease Control and Prevention recommended the current season's COVID shots to adults aged 65 and older and those with underlying health conditions that increase risk of severe disease but decided that vaccination for healthy people older than six months should be based on shared clinical decision-making.

Luis Alvarez/Getty Images

Although the research includes only data for last season's vaccines, Perlman contends that the findings are still relevant to the current season. The virus that circulated in 2024, just like the one that is circulating now, derives from a single precursor virus called JN.1. Both variants are similar in terms of severity. Because vaccine manufacturers base their formulas on the circulating variant, it's expected that the current COVID shots will stack up similarly to last season's.

Real-world data on effectiveness for the new COVID vaccine are still limited, but researchers can make some predictions based on neutralizing antibody levels, known as titers, which indicate the strength of the immune system's protective response to the virus the vaccines are based on. Both of the 2025–2026 mRNA vaccines, Spikevax and COMIRNATY, target the LP.8.1 variant. COMIRNATY showed a fourfold increase in neutralizing antibody titers above baselines levels, whereas Spikevax showed an eightfold increase. Higher titers generally signify that a formula provides better immune protection, especially against severe disease. Perlman says Spikevax's higher titers could be the result of the vaccine including a larger amount of synthetic mRNA molecules. Still, he adds, a twofold difference will not offer meaningfully more protection for most people.

Just 21 percent of the adult U.S. population got vaccinated against COVID last season—a proportion that has been steadily declining. With less vaccine-induced immunity, Perlman says, more people "would benefit even more from getting vaccinated now." ●

Sara Novak is a science writer based on Sullivan's Island, S.C. Her work has appeared in *Discover, Sierra Magazine, Popular Science* and *New Scientist,* among other publications. Follow Novak on X @sarafnovak

THE LONG SHOT

After decades of frustration, scientists finally have successful vaccines and treatments for the respiratory disease RSV

BY TARA HAELLE | ILLUSTRATION BY CRISTINA BENCINA

FOR MANY PEOPLE, an infection with respiratory syncytial virus, or RSV, is little more than a troublesome cold. But the virus poses a serious danger to babies, older adults and immunocompromised people. The disease is the leading cause of hospitalization in infants in the U.S. and was particularly bad in recent seasons. An estimated 58,000 to 80,000 children under five years old and 110,000 to 180,000 older adults in the U.S. are hospitalized with RSV every year. As many as 300 infected infants die annually, along with up to 10,000 older adults.

After a decades-long search, vaccines for RSV are at last here. Scientists have been working on the shots since soon after the virus was discovered in 1956. But some disastrous clinical trials in the 1960s and dozens of other failed attempts stymied progress for many years. Now three RSV vaccines for older adults have been approved by the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention. A vaccine for pregnant people, designed to protect infants after birth, was approved by the FDA in August 2023 and publicly recommended by the CDC a month later. The breakthrough leading to these developments happened once researchers solved a 50-year-old mystery about the virus by examining the shape of its proteins. The discovery has ushered in a new era of vaccine development using designs based on the structure of proteins—the same approach that enabled the rapid development of a COVID vaccine.

Until recently, the main ways to prevent RSV infection were the typical hygiene practices used to prevent common colds, such as wearing a face mask, washing one's hands and avoiding sick people. There was also one medication: palivizumab, a short-acting monoclonal antibody that provides passive immunity (protection with antibodies created outside a person's own body) to infants for up to one month at a time. But palivizumab, which was approved in 1998, required multiple doses that cost more than $1,800 each. The drug was licensed for preterm infants born before 35 weeks who were younger than six months at the beginning of the RSV season, which starts in the fall. The American Academy of Pediatrics stopped recommending the antibody's use in 2025, however, and it was discontinued in the U.S. at the end of that year.

THIRTY YEARS BEFORE THAT DRUG DEBUTED, scientists were already working on an RSV vaccine intended to save lives. To their horror, it took lives away. In 1966 four clinical trials tested a vaccine made with an inactivated form of the virus in children who had never gotten RSV before. In one of the studies, 80 percent of the vaccinated children were hospitalized when they later contracted the virus, and two toddlers—a 14-month-old and a 16-month-old—died.

Typical hospitalization rates for children with RSV are in the single digits, says Ruth Karron, a pediatrician and director of the Johns Hopkins Vaccine Initiative. Otherwise healthy children do sometimes die from the virus, but that is most likely to occur in the first six months of life, so the deaths of toddlers were especially telling.

"As you can imagine, this sort of stopped vaccine development for a very long time," Karron says. "You took a pathogen that, even then, didn't kill that many children, and it killed children."

The disaster was traced to a phenomenon called antibody-dependent enhancement, in which the body produces antibodies that don't adequately protect it and instead exacerbate the infection. Antibody-dependent enhancement had occurred with an early version of a measles vaccine in the 1960s that was later pulled from use, and it has since been reported with the dengue fever vaccine.

But the mechanism that causes this problem varies depending on the pathogen. With dengue, for example, there are four types of the virus, and antibodies to one do not protect completely against all the others. So when a person develops antibodies in response to one dengue serotype and then becomes infected with another, the body tries to fight the second infection with the antibodies from the first and fails, while the infection worsens. The problem with RSV was that scientists didn't know what caused its antibody-dependent enhancement.

For the next two decades RSV vaccine progress stagnated. Researchers developed multiple live attenuated vaccines using virus that was weakened instead of neutralized, or deactivated. These didn't cause enhanced disease, but they also didn't make it far in clinical trials. "The problem with live attenuated vaccines is that you've got a relatively small therapeutic window, meaning if they're not attenuated enough, they will cause disease. Too attenuated, and they won't be immunogenic enough to cause immunity," says Barney Graham, a vaccinologist and senior adviser for global health equity at the Morehouse School of Medicine, who has spent his career studying RSV vaccine development for children but was not involved in those devastating early trials. "When you start putting it into lots of children, who have so much variability themselves, it's hard to get that therapeutic window to fit all of the children," says Graham, who was also instrumental in developing a COVID vaccine.

Before RSV vaccine research could lead anywhere fruitful, researchers needed to know what had gone so wrong in the 1960s trials to cause antibody-enhanced disease. The mystery wasn't solved until 2009, when Fernando P. Polack, founder of the Infant Foundation in Argentina, and his team published a study in *Nature Medicine* describing experiments with mice that demonstrated how the antibodies produced by the vaccinated children's immune systems bound to RSV but did not neutralize it.

With those antibodies failing to neutralize the virus, it proliferated, resulting in a lot of ineffective antibodies and a lot of viral antigens clumping together with those antibodies, Graham says. These clumps built up in the tissue, attracting immune system proteins that caused a cascade leading to inflammation. That inflammation damaged lung tissue and created mucus that constricted the airways and made the children sicker than they would have been with no preexisting antibodies. But a big question remained: Why didn't those antibodies adequately neutralize the virus? As it turned out, a serendipitous meeting would lead to an answer to that question and the final steps necessary to make RSV vaccines a reality.

In 2008 JASON MCLELLAN, now a molecular biologist at the University of Texas at Austin, had just begun a postdoctoral fellowship at the National Institutes of Health Vaccine Research Center, where he met Graham. Graham, who was leading RSV vaccine efforts there, learned that McLellan, who specialized in mapping the atomic structure of proteins, wanted to work on something "a little off the radar," Graham says. "Well, we have no structural information on RSV yet," he told McLellan. Graham was particularly interested in the "F protein," the antigen that was the main target for RSV vaccine development.

The idea piqued McLellan's interest. "It became clear that RSV was one of the major childhood pathogens for which we didn't have a vaccine, so working on a vaccine that can help save the lives of babies and young children was very motivating," he says. The pair's goal—discovering the F protein's structure—would become the key to creating a successful vaccine. But the F protein isn't stable: when it fuses with a cell, allowing the virus to enter and hijack the cell to reproduce, it changes shape. Antibodies against the so-called postfusion shape—the ones produced by the immune systems of the children in the 1960s trials—don't fully neutralize the circulating form of the virus *before* it binds to cells, known as the prefusion form. But if a vaccine could induce antibodies against this form, they should bind properly with the virus's active form. The trick was to figure out what that prefusion protein looked like and how to lock it into that shape.

To do that, the two researchers first took a harder look at the other form, the postfusion protein. "That's the one that's easy to make; it's stable, and so it's relatively easy to work with," Graham says. Knowing the structure of both the prefusion and postfusion proteins would enable Graham and McLellan to understand how the protein morphs between the two shapes. By 2010 McLellan had determined the structure of the postfusion protein using x-ray crystallography. Next, to decipher the prefusion protein, his team needed to find an antibody that neutralized the virus without binding to the postfusion protein.

In collaboration with researchers at Xiamen University in China, McLellan and Graham screened more

than 13,000 mouse antibodies until they found one that effectively neutralized RSV's prefusion F protein without binding to the postfusion one. The winning antibody was about 50 times more potent at neutralizing the virus than palivizumab, the FDA-approved antibody against RSV. The finding suggested previous vaccine candidates had failed because none produced antibodies potent enough to neutralize the virus.

The researchers then used a similar human antibody to determine the F protein's structure. "After we had that structure, everything really fell in place," Graham says. "All of a sudden, we had a new, very vulnerable target on the virus for making a vaccine."

Now, finally able to see exactly where the antibodies attached to the protein, McLellan and the team substituted two amino acids in the sequence that encodes the F protein to create a covalent bond that effectively "stapled" the protein together, preventing it from pulling apart into its postfusion shape. They published their method in late 2013, then spent the next few years growing human cells that would produce the prefusion protein and learning how to purify it for use in a vaccine.

The first small clinical trials to evaluate the vaccine's safety began in 2017 and produced encouraging results two years later. By then, "RSV vaccines had a life of their own," Graham says, as the pharmaceutical industry took over their development.

McLellan, meanwhile, turned his focus to coronaviruses. The RSV work would ultimately pave the way for determining the spike protein structure of SARS-CoV-2, the virus that causes COVID, and enable Moderna, Pfizer, and other companies to develop a COVID vaccine in record time. The era of protein-structure-based vaccine design—starting with figuring out a pathogen's protein structure and building a vaccine around it—had begun.

THE PHARMACEUTICAL COMPANIES that took the lead in developing vaccines based on this science were GSK and Pfizer. The fda approved GSK's Arexvy, the first RSV vaccine for adults 60 and older, on May 3, 2023, and then approved Pfizer's Abrysvo for the same age group on May 31. GSK said its vaccine is 94 percent effective against severe disease and 83 percent effective against symptomatic disease in adults 60 and older. Pfizer said its vaccine is 86 percent effective against severe disease with at least three symptoms and 67 percent effective against symptomatic disease with at least two symptoms in adults age 60 and older. A CDC advisory panel voted in favor of recommending that people in that age group may get an RSV vaccine in consultation with their health-care provider but stopped short of recommending it for all older adults. Both vaccines are now available for people 50 and older who are at increased risk of severe RSV disease.

The more challenging need was a vaccine to protect newborns, especially because the immune systems of babies less than four months old are too immature to respond to most vaccines and develop the immune memory needed to fight a disease. Researchers used the same approach that protects newborns from flu and pertussis—administering a vaccine during pregnancy so the parent's antibodies will cross the placenta to the fetus. An RSV vaccine would protect infants for the first six months after birth, when babies are most at risk for serious complications from the disease.

The fda's Vaccines and Related Biological Products Advisory Committee voted in May 2023 to recommend fda approval for Pfizer's parental RSV vaccine candidate, and the fda approved it in August 2023. Pfizer has said its RSV vaccine for pregnant people is 82 percent effective against severe RSV in newborns for up to three months and 69 percent effective through six months. The committee was impressed with the vaccine's effectiveness, but some members had reservations about its safety data.

The FDA advisory panel voted unanimously in favor of the Pfizer vaccine's effectiveness and 10 to 4 in favor of the vaccine's safety. The primary reason for the four nay votes for safety was that the premature birth rate was slightly higher in the vaccinated group but not statistically significantly so. "I think the four votes were really just an abundance of caution," Graham says. "They weren't saying it wasn't safe. They said they wanted more information before they said yes," although it's not easy to get that additional information until studies are conducted in the general population.

GSK stopped its own trial of a vaccine for pregnant people because infants born in the vaccine group were 38 percent more likely to be born premature.

Beyond vaccines, AstraZeneca and Sanofi announced in March 2022 that nirsevimab, a prophylactic monoclonal antibody drug similar to palivizumab, is 75 percent effective against cases of RSV that require medical care in infants younger than one year with no history of RSV—and the protection lasts five months, which is about the length of a typical RSV season. Europe approved nirsevimab in November 2022, and the fda approved it in July 2023. A similar long-acting monoclonal antibody made by Merck, clesrovimab, was approved by the FDA in June 2025.

One challenge will be assuring the protection of children in low-income families, who are already more vulnerable to worse outcomes from RSV. The U.S. Vaccines for Children program ensures all eligible children can access vaccines recommended by the cdc, even if they lack insurance. That program now covers nirsevimab and clesrovimab, but it doesn't include vaccines for pregnant adults.

Insurance companies also recently expanded coverage to include nirsevimab and clesrovimab. Infants, like older adults, now have highly effective options to reduce their risk of RSV for the first time in the half a century since scientists began the effort. ●

Tara Haelle is a Dallas-based science journalist whose specialties include infectious disease, medical research and health disparities.

NO MORE NEEDLES

Gentle nasal sprays are being tested as vaccines against COVID, the flu, RSV, and more. They may work better than shots in the arm BY STEPHANI SUTHERLAND

ILLUSTRATION BY SAM FALCONER

ALYSON VELASQUEZ HATES NEEDLES. She never liked getting shots as a kid, and her anxiety only grew as she got older. "It really ballooned in my teens and early 20s," she says. "It became a full-blown phobia." She would panic at the sight of a needle being brought into an exam room; more than once she passed out. Velasquez says that she took an antianxiety medication before one appointment yet still ran around the room screaming inconsolably "like I was a small child; I was 22." After that episode Velasquez, now 36 years old, quit needles completely. "No vaccinations, no blood work. For all of my 20s it was a no-go for me," she says.

Then COVID showed up. "It finally hit a point where it wasn't just about me," Velasquez says. "It felt so selfish not to do this for the greater public health and the safety of our global community." So she got vaccinated against the SARS-CoV-2 virus in 2021, although she had to sit on her husband's lap while he held her arms. "It was a spectacle. The poor guy at CVS ... he did ask me, 'Are you sure you want to do this?'" She very much did. "I'm very pro-vaccine. I am a rational human. I understand the necessity of [getting] them," she insists. But today she still struggles with each injection.

Those struggles would end, however, if all her future vaccinations could be delivered by a nasal spray. "Oh, my God, amazing!" Velasquez says.

The amazing appears to be well on its way. Vaccines delivered through the nose are now being tested for several diseases. In the U.S., clinical trials are showing success. Two of these vaccines have generated multiple immune system responses against the COVID-causing virus in people who received them through a puff up the nose; in 2024 their makers received nearly $20 million from Project NextGen, the Biden-Harris administration's COVID medical initiative. Researchers are optimistic that a nasal spray delivering a COVID vaccine could be ready for the U.S. as soon as 2027. Although many recent efforts have focused on inoculations against SARS-CoV-2, nasal vaccines could also protect us against the flu, respiratory syncytial virus (RSV), and more.

A few nasal vaccines have been introduced in the past, but they've been beset by problems. The flu inoculation FluMist has not gained popularity because of debates about its effectiveness, and a different vaccine was pulled from the market decades ago because some people had serious side effects. In China and India, nasal vaccines for COVID have been approved because those countries prioritized their development during the pandemic, whereas

the U.S. and other wealthy nations opted to stick with arm injections. But this new crop of vaccines takes advantage of technology that produces stronger immune responses and is safer than preparations used in the past.

In fact, immunologists say these spritzes up the nose—or inhaled puffs through the mouth—can provide faster, stronger protection against respiratory viruses than a shot in the arm. That is because the new vaccines activate a branch of the immune system that has evolved for robust, rapid responses against airborne germs. "It may be more likely to really prevent infection from getting established," says Fiona Smaill, an infectious disease researcher at McMaster University in Ontario. Such inoculations may also help reduce the enormous inequities in vaccine access revealed by the pandemic. These formulations should be cheaper and easier to transport to poor regions than current shots.

But nasal vaccines still face technical hurdles, such as how best to deliver them into the body. And unlike injected vaccines, which scientists can measure immune responses to with blood tests alone, testing for immunity that starts in nose cells is more challenging. But researchers working in this field agree that despite the hurdles, nasal formulations are the next step in vaccine evolution.

TRADITIONAL VACCINES injected through the skin and into an arm muscle provide excellent protection against viruses. They coax immune cells into making widely circulated antibodies—special proteins that recognize specific structural features on viruses or other invading pathogens, glom on to them and mark them for destruction. Other immune cells retain a "memory" of that pathogen for future encounters.

Intramuscular injection vaccines are good at preventing a disease from spreading, but they do not stop the initial infection. A nasal spray does a much better job. That's because sprays are aimed directly at the spot where many viruses first enter the body: the nose and the tissue that lines it, called the mucosa.

Mucosa makes up much of our bodies' internal surfaces, stretching from the nose, mouth and throat down the respiratory tract to the lungs, through the gastrointestinal tract to the anus, and into the urogenital tract. Mucosa is where our bodies encounter the vast majority of pathogenic threats, Smaill says, be it flu, COVID, or bacterial infections that attack the gut. This tough, triple-layered tissue is specialized to fight off invaders with its thick coating of secretory goo—mucus—and with a cadre of resident immune cells waiting to attack. "Mucosa is really the first line of defense against any infection we're exposed to," Smaill says.

Mucosal immunity not only prepares the immune system for the fight where it occurs but also offers three different types of protection—at least one more than a shot does. Both nasal vaccines and shots mobilize immune messenger cells, which gather the interlopers' proteins and display them on their surfaces.

Nasal sprays aim directly at the spot where most viruses first enter the body: the nose.

These cells head to the lymph nodes, where they show off their captured prize to B and T cells, which are members of another part of the immune system called the adaptive arm. B cells, in turn, produce antibodies, molecules that home in on the foreign proteins and flag their owners—the invading microbes—for destruction. Killer T cells directly attack infected cells, eliminating them and the microbes inside. This provides broad protection, but it takes time, during which the virus continues to replicate and spread.

That's why a second type of protection, offered only by the mucosal tissue, is so important. The mucosa holds cells of the innate immune system, which are the body's "first responders." Some of these cells, called macrophages, recognize invasive microbes as foreign and swallow them up. They also trigger inflammation—an alarm sounded to recruit more immune cells.

Another part of this localized response is called tissue-resident immunity. These cells don't have to detect telltale signs of a pathogen and make a long journey to the infected tissue. They are more like a Special Forces unit dropped behind enemy lines where a skirmish is occurring rather than waiting for the proverbial cavalry to arrive. This localized reaction can be quite potent. Its activation is notoriously difficult to demonstrate, however, so historically it's been hard for vaccine makers to show they've hit the mark. But it turns out that one type of antibody, called IgA, is a good indicator of mucosal immunity because IgAs tend to predominate in the mucosa rather than other parts of the body. In an early trial of CoviLiv, a nasal COVID vaccine produced by Codagenix, about half of participants had detectable IgA responses within several weeks after receiving two doses. That trial also showed the vaccine was safe and led to NextGen funding for a larger trial of the vaccine's efficacy.

It's possible an inhaled vaccine may provide yet one more layer of protection, called trained innate immunity. This reaction is a bit of a mystery: although immunologists know it exists and appears also to be produced by intramuscular injections, they can't quite explain how it works. Immune cells associated with trained innate immunity seem to have memory-like responses, reacting quickly against subsequent infections. They also have been found to respond against pathogens entirely unrelated to the intended vaccine target. Smaill and her colleagues found that when they immunized mice with an inhaled tuberculosis vaccine and then challenged them with pneumococcal bacteria, the mice were protected. In children, there is some evidence that a tuberculosis vaccine, in the arm, generates this type of broad response against other diseases.

Akiko Iwasaki, an immunologist at Yale University who has carried out research on nasal vaccines for COVID, sees two major potential benefits to nasal immunity in addition to better, faster, more localized protection. First, attacking the virus in the nose could prevent the disease from being transmitted to others by reducing the amount of virus that people breathe out. And second, Iwasaki says, the spray may limit how deeply the infection moves into the body, so "we believe that it will also prevent long COVID." That debilitating postinfection condition, sometimes marked by signs of entrenched viral particles, disables people with extreme fatigue, chronic pain, a variety of cognitive difficulties, and other symptoms.

MAKING A NEW VACCINE is hard, regardless of how you administer it. It needs to raise an immune response that's strong enough to protect against future invasions but not so strong that the components of that response—such as inflammation and fever—harm the host.

The lining of the nose puts up its own barriers—literal, physical ones. Because the nasal mucosa is exposed to so many irritants from the air, ranging from pet hair to pollen, the nose has multiple lines of defense against invading pathogens. Nostril hair, mucus, and features called cilia that sweep the nasal surface all aim to trap small foreign objects before they can get deeper into the body—and that includes tiny droplets of vaccine.

And lots of small foreign particles—often harmless—still make it through those defenses. So the nose has developed a way to become less reactive to harmless objects. This dampened reactivity is called immunological tolerance, and it may be the biggest hurdle to successful development of a nasal vaccine. When foreign particles show up in the bloodstream, a space that is ostensibly sterile, immune cells immediately recognize them as invaders. But mucosal surfaces are constantly bombarded by both pathogens and harmless materials. The immune system uses tolerance—a complex series of decisions carried out by specialized cells—to determine whether a substance is harmful. "This is very important because we can't have our lungs or gastrointestinal tract always responding to nonharmful foreign entities that they encounter," says Yale infectious disease researcher Benjamin Goldman-Israelow. For example, inflammation in the lungs would make it hard to breathe; in the gut, it would prevent the absorption of water and nutrients.

These barriers may hamper the effectiveness of a nasal flu vaccine that's been around for a while, called FluMist in the U.S. The inoculation is safe, says infectious disease scientist Michael Diamond of Washington University in St. Louis, but it faces a problem similar to that of injected flu vaccines: it isn't very effective at warding off new seasonal flu strains. This might be because flu strains are so common, and people are frequently infected by the time they are adults. Their immune systems are already primed to recognize and destroy familiar flu particles. FluMist is built from a live flu virus, so immune cells probably treat the vaccine as an invader and demolish it as soon as it shows up in the nose, before it has a chance to do any good. This preexisting immunity isn't such an issue in children, who are less likely to have had multiple flu infections.

In other vaccines, researchers often use adjuvants, special agents that attract the attention of immune cells, to boost a response. Some nasal vaccines use adjuvants to overcome tolerance, but in the nose, adjuvants can pose unique dangers. In at least one case, a nasal adjuvant led to disastrous consequences. An intranasal vaccine for influenza, licensed in Switzerland for the 2000–2001 season, used a toxin isolated from *Escherichia coli* bacteria as an adjuvant to provoke a reaction to the inactivated virus. No serious side effects were reported during the trial period, but once the vaccine was released, Swiss officials saw a concerning uptick in cases of Bell's palsy, a disease that causes weakness or paralysis of the facial muscles, often leading to a drooping or disfigured face. Researchers at the University of Zurich estimated that the adjuvanted flu vaccine had increased the risk of contracting Bell's palsy by about 20 times, and the vaccine was discontinued. "We need to be cautious about using adjuvants like that from known pathogens," says pharmaceutical formulations scientist Vicky Kett of Queen's University Belfast in Northern Ireland.

To get around the challenges posed by the nose, some researchers have explored vaccines inhaled through the mouth. Smaill is involved with one of them. She and her McMaster colleagues aerosolized their vaccine for COVID into a fine mist delivered by a nebulizer, from which it rapidly reaches the lungs. Experiments in mice have shown promising results, with mucosal immunity established after administration of the vaccine.

Another vaccine strategy is to use a harmless virus to carry viral genes or proteins. Researchers at the Icahn School of Medicine at Mount Sinai in New York City selected a bird pathogen, Newcastle disease virus (NDV). "It's naturally a respiratory pathogen," so it infects nasal cells, says Michael Egan, CEO and chief scientific officer of CastleVax, a company that formed to develop the NDV vaccine for COVID. A small early clinical trial showed that the CastleVax vaccine was safe and caused robust immune responses in people. "Those results were very promising," Egan says. People who received the vaccine also produced antibodies that indicated multitiered mucosal immunity, not simply the adaptive immunity resulting from a shot in the arm.

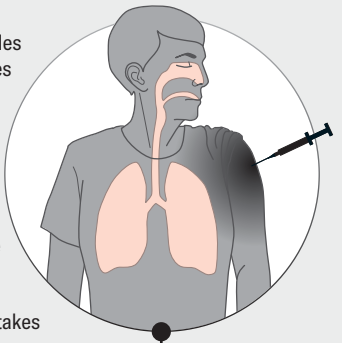
Following that trial, the CastleVax project received NextGen funding, and results from a trial of 10,000 people are expected in 2026. Half of those people received a messenger RNA (mRNA) injection, and half got the new NDV nasal spray. The data should show whether the new nasal vaccine can do a better job of

The Vaccine Advantages of a Puff Up the Nose

As kids and adults, we become very familiar with the vaccine needle. Jabs for measles, mumps, COVID, flu, polio, and more protect people against all kinds of diseases. The injection starts in the arm but triggers an immune response that travels the body. It kicks in, however, after an infection starts. A new type of vaccine is emerging, though, for viruses and bacteria that we breathe. It meets the threat at the earliest moment: in the nose and mouth. These nasal or inhaled vaccines could stop pathogens almost before they get started.

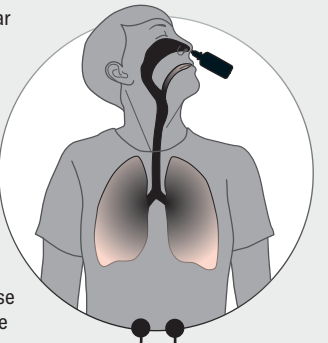
A SHOT IN THE ARM

Traditional vaccines go into an arm muscle. The vaccines carry molecules that are part of a germ or sometimes a badly weakened or killed version of the germ itself. The goal is to introduce these targets to what's called the adaptive immune system. This system essentially trains cells and proteins to recognize the invader. The adaptive system retains a memory of the germ and travels through the body looking to attack it. This response takes time, however.



A SPRAY UP THE NOSE

Nasal vaccines stimulate a particular tissue: the mucosa. It lines the insides of our noses and mouths, stretching down to the lungs and through our gastrointestinal tracts. In addition to adaptive immune cells, the mucosa holds "first responder" cells that immediately attack germs. They are part of what's called the innate immune system. And nasal vaccine sprays contain parts of those germs, to trigger innate and adaptive immune responses.



A A B

SYSTEMIC/ADAPTIVE IMMUNITY

1 A vaccine is introduced to the body.

Vaccine particle

2 Specialized immune cells take up the vaccine material.

3 The aptly named antigen-presenting cells travel to a lymph node via the circulatory system.

Antigen

Antigen-presenting cell

Lymph node

Killer T cell

Helper T cell

Activated B cell

B cell

Memory cells

4 In the lymph node, antigens are presented to helper T cells. Helper T cells engage additional immune cells, priming them for later action.

RESIDENT MUCOSAL IMMUNITY

Vaccine particle

Mucosal epithelial cell

sIgA

Antigen-presenting cell

Helper T cell

1 Vaccine is introduced to the body—directly into a mucosal area.

2 Resident antigen-presenting immune cells take up the vaccine material, then display fragments on their surface to resident helper T cells in the mucosa-associated lymphoid tissue.

3 Helper T cells engage additional immune cells already on site, causing them to secrete a mucosal-specific antibody called sIgA, as well as priming the cells for later action.

SUBSEQUENT EXPOSURE TO A VIRUS

Virus-disabling antibodies from B cells

Virus

Infected host cell

Killer T cell

5 When the target virus enters the body—often through the nose—primed immune cells and antibodies released from activated B cells travel from lymph nodes to the site via the circulatory system. Antibodies disable the virus, and killer T cells destroy host cells, preventing further replication.

SUBSEQUENT EXPOSURE TO A VIRUS

Virus

sIgA

Infected host cell

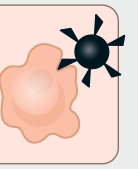
Killer T cell

Activated B cell

4 When the target virus enters the body via the same mucus-lined route, the primed immune cells and sIgA are already in position, ready to disable the virus and destroy infected cells.

TRAINED INNATE IMMUNITY

Some research indicates that nasal vaccines also prime cells of the innate branch of the immune system—including macrophages—to be more efficient at destroying subsequent viruses unrelated to the target pathogen.



Source: Florian Krammer/Icahn School of Medicine at Mount Sinai and Medical University of Vienna, Austria (*consultant*)

Graphic by Jen Christiansen

> "We're expecting to see fewer breakthrough infections in people who got the vaccine up the nose."
> —MICHAEL EGAN *CASTLEVAX*

preventing infection than the mRNA injections. Egan has high hopes. "We're expecting to see a lot fewer breakthrough infections in people who got the vaccine up the nose by virtue of having those mucosal immune responses," he says.

Florian Krammer, one of the Mount Sinai researchers behind the vaccine, engineered NDV particles to display a stabilized version of the spike protein that's so prominent in SARS-CoV-2. "You end up with a particle that's covered with spike," he says. Spike protein in the bloodstream can raise an immune response. But the NDV vaccine works in another way, too. The virus particle can also get into cells, where it can replicate enough times to cause virus particles to emerge from the cells, provoking another immune reaction. Before moving into human trials, however, researchers had to complete clinical trials to establish that the Newcastle virus is truly harmless because the nose is close to the central nervous system—it has neurons that connect to the olfactory bulb, which is part of the brain. Those trials confirmed that it is safe for this use.

This type of caution is one reason a COVID nasal vaccine approved in India hasn't been adopted by the U.S. or other countries. The inoculation, called iNCOVACC, uses a harmless simian adenovirus to carry the spike protein into the airway. The research originated in the laboratories of Diamond and some of his colleagues at Washington University at the start of the pandemic, when they tested the formulation on rodents and nonhuman primates. "The preclinical data were outstanding," Diamond says. Around the time he and his colleagues published initial animal results in *Cell* in 2020, Bharat Biotech in India licensed the idea from the university. In a 2023 phase 3 clinical trial in India, the nasal vaccine produced superior systemic immunity compared with a shot.

Diamond says American drug companies didn't pursue this approach, because "they wanted to use known quantities," such as the mRNA vaccines, which were already proving themselves in clinical trials in 2020. As the pandemic took hold, there was little appetite to develop nasal vaccine technology to stimulate mucosal immunity while the tried-and-true route of shots in the arm was available and working. But by 2024 an inhaled vaccine using technology similar to iNCOVACC's was being developed for approval in the U.S. by biotech company Ocugen. Both inhaled and nasal forms of the vaccine have been cleared for clinical trials as part of Project NextGen. These new vaccines are using classical vaccine methods based on the virus rather than using new, mRNA- based technology. The mRNA preparations were developed specifically for intramuscular injections and would have to be significantly modified.

Codagenix, which is developing CoviLiv, sidestepped the need for a new viral vector or an adjuvant by disabling a live SARS-CoV-2 virus. To make it safe, scientists engineered a version of the virus with 283 mutations, alterations to its genetic code that make it hard for the virus to replicate and harm the body. Without all these genetic changes, there would be a chance the virus could revert to a dangerous, pathogenic form. But with hundreds of key mutations, "statistically, it's basically impossible that this will revert back to a live virus in the population," says Johanna Kaufmann, who helped to develop the vaccine before leaving Codagenix for another company in 2024.

BECAUSE MOST PEOPLE on the planet have now been exposed to SARS-CoV-2—in the same way they're regularly exposed to the flu—some nasal vaccines are being designed as boosters for a preexisting immune response that is starting to wane. For example, Yale researchers Iwasaki and Goldman-Israelow are pursuing a strategy in animals deemed "prime and spike."

The idea is to start with a vaccine injection—the "prime" that stimulates adaptive immunity—then follow it a few weeks later with a nasal puff that "spikes" the system with more viral protein, leading to mucosal immunity. In a study published in 2022 in *Science,* Iwasaki and her colleagues reported that they primed rodents with the mRNA vaccine developed by Pfizer and BioNTech, the same shot so many of us have received. Two weeks later some of the mice received an intranasal puff of saline containing a fragment of the SARS-CoV-2 spike protein. Because the animals had some preexisting immunity from the shot, the researchers didn't add any adjuvants to heighten the effects of the nasal puff. Two weeks later researchers detected stronger signs of mucosal immunity in mice that had received this treatment compared with mice that got only the shot.

"Not only can we establish tissue-resident memory T cells" to fight off the virus in the nose, Iwasaki says, but the prime-and-spike method also produces those vigorous IgA antibodies in the mucosal layer. "And that's much more advantageous because we can prevent the virus from ever infecting the host," she notes. The study suggests that this approach might also lessen the chances of transmitting the disease to others because of the lower overall viral load. Experiments in hamsters demonstrated that vaccinated animals shed less virus, and they were less likely to contract COVID from infected cage mates that had not been vaccinated themselves.

ALTHOUGH MANY OF THE NEW vaccine strategies are aimed at COVID, nasal vaccines for other diseases are already being planned. Kaufmann, formerly of Codagenix, says the company currently has clinical trials un-

derway for nasal vaccines against flu and RSV. CastleVax's Egan says "we have plans to address other pathogens" such as RSV and human metapneumovirus, another leading cause of respiratory disease in kids.

Vaccines that don't need to be injected could clear many barriers to vaccine access worldwide. "We saw with COVID there was no vaccine equity," Smaill says. Many people in low-income countries never received a shot; they were still going without one years after the vaccines debuted.

In part, this inequity is a consequence of the high cost of delivering a vaccine that needs to stay frozen on a long journey from manufacturing facilities in wealthy countries. Some of the nasal sprays in development don't need deep-cold storage, so they might be easier to store and transport. And a nasal spray or an inhaled puff would be much easier to administer than a shot. No health professional is required, so people could spray it into their noses or mouths at home.

For these reasons, needle-free delivery matters to the World Health Organization. The WHO included the Codagenix nasal spray in its Solidarity Trial Vaccines program to improve vaccine equity. The CoviLiv spray entered phase 3 clinical trials around the world as part of this effort. "The fact that the WHO was still interested in a primary vaccination trial in the geographies it's passionate about—that's indicative that there is still a gap," Kaufmann says. CoviLiv was codeveloped with the Serum Institute of India, the world's largest maker of vaccines by dose. The partnership enabled production at the high volume required for Solidarity.

The CastleVax vaccine with the NDV vector provides another layer of equity because the facilities required to make it already exist in many low- and middle-income countries. "The cool thing is that NDV is a chicken virus, so it grows very well in embryonated eggs—that's exactly the system used for making flu vaccines," Krammer says. For example, for a clinical trial in Thailand, "we just shipped them the seed virus, and then they produced the vaccine and ran the clinical trials," he says. Many countries around the world have similar facilities, so they will not need to depend on pharma companies based in richer places.

Even high-income countries face barriers to vaccination, although they may be more personal than systemic. For very many people, the needle itself is the problem. Extreme phobia such as Velasquez's is uncommon, but many people have a general fear of needles that makes vaccinations stressful or even impossible for them. For about one in 10 people needle-related fear or pain is a barrier to vaccinations, says C. Meghan McMurtry, a psychologist at the University of Guelph in Ontario. Needle fear "is present in most young kids and in about half of adolescents. And 20 to 30 percent of adults have some level of fear." A review of studies of children showed that "concern around pain and needle fear are barriers to vaccination in about 8 percent of the general population and about 18 percent in the vaccine-hesitant population," McMurtry adds.

Some people are wary of injected vaccines even if they're not afraid of needles, Kett says; they see injections as too invasive even if the needle doesn't bother them. "We're hopeful that something administered by the nasal route would be less likely to come across some of those issues," Kett says.

In the U.S., however, sprays and puffs won't be available until they are approved by the Food and Drug Administration, which requires clear evidence of disease protection. As Diamond points out, standards for such evidence are well established for injections, and vaccine makers can follow the rule book: regulations point to particular antibodies and specific ways to measure them with a simple blood test. But for nasal vaccines, Iwasaki says, "we don't have a standard way to collect nasal mucus or measure antibody titers. All these practical issues have not been worked out."

Iwasaki has also faced frustrations because of a restriction by the U.S. Centers for Disease Control and Prevention that has stopped researchers from using existing COVID vaccines in basic research to develop new nasal sprays. The rule was set in 2020, when COVID injections had just been developed and were in short supply; people had to wait to get vaccinated until they were eligible based on factors such as age and preexisting conditions. "That made sense back then, but those concerns are years old; things are different now," Iwasaki says. Even when excess vaccine was being thrown out, she says, she and her colleagues could not get access to the expired vials.

Today scientists want to contrast the effectiveness of nasal formulations with injections already in use. "Those comparisons are really important for convincing the FDA that this is a worthy vaccine to pursue," Iwasaki says. But the restriction held up studies by her company, Xanadu, slowing down work. (The CDC did not respond to a request for comment.)

Despite the bureaucratic and scientific hurdles, the sheer number of nasal vaccines that have entered clinical trials encourages Iwasaki and other scientists pursuing the needle-free route. They say it seems like only a matter of time before getting vaccinated will be as simple as a spritz up the nose.

Velasquez, for one, can't wait for that day to arrive. The circumstances that finally forced her to reckon with her fear of needles (a global pandemic, the prospect of parenthood and the numerous blood tests that accompanied her pregnancy) were so much bigger than her. If not for them, she might still be avoiding shots. "So having vaccines without needles—I would get every vaccine any doctor wanted me to get, ever. It would be a complete game changer for me." ●

Stephani Sutherland is a neuroscientist and science journalist based in southern California. She wrote about the causes of long COVID in our March 2023 issue.

THE END OF FOOD ALLERGIES?

New treatments can free millions from peanut allergy's deadly threat and hold hope for other foods

BY MARYN MCKENNA | PHOTOGRAPHY BY ANDREW B. MYERS

ANABELLE TERRY, A SLENDER, self-possessed girl in her early teens, has heard the peanut butter story her entire life. At two and a half she ate nuts for the first time. Her mother, Victoria, had made a little treat: popcorn drizzled with melted caramel, chocolate and peanut butter. Anabelle gobbled it down. "And afterward, I felt really sick," she says. A few minutes later she vomited on the kitchen floor.

There was more trouble ahead. A visit to an allergist confirmed that Anabelle was severely allergic to the peanut butter in the dessert, as well as to most other nuts. It began a life upheaval familiar to families of kids with allergies: learning to decode labels, to carry an EpiPen, and to interrogate friends and their parents about the ingredients in a birthday cake.

Every once in a while, there would be a slip-up. It might be a snack that someone hadn't scrutinized or a food package that didn't list all potential allergens. And every time, Anabelle's reactions got worse. Although she was just a schoolkid, she had to stay alert. "Eating lunch, all my friends would have PB&Js. And I'd be like, I'm going to sit a little bit farther away," she recalls. "And going over to friends' houses after school, we always had to make sure: 'Hey, would you mind making a nut-free meal?'"

Most of that caution is in Anabelle's past now. For the vast majority of patients, peanut allergy is an unpredictable, lifelong affliction. But thanks to a clinical trial that Anabelle entered when she was nine years old, she can now tolerate peanuts and tree nuts well enough to feel safe every day. The drug she received in that trial was approved for treating food allergies by the U.S. Food and Drug Administration in 2024, making it the second food allergy remedy to earn the agency's blessing since 2020. And an array of other clinical trials are tackling peanut allergy in a variety of ways, from new modalities for desensitizing patients to bold new applications of existing drugs. Some have reported striking successes. "It's an amazing time right now," says R. Sharon Chinthrajah, a professor at Stanford Medicine, who led the national trial that Anabelle joined.

In fact, medicine's entire understanding of how to keep children safe from ever developing allergies is being rethought. With peanut reactions, for instance, there are real hopes that children can be protected—definitely from the worst effects and maybe from any at all. "The future looks very bright for our patients to have more choices in different periods in their lifetime," Chinthrajah says. "We're not yet at the cure, but we're definitely moving along on the therapeutic front to be able to deal with this chronic disease."

PEANUT ALLERGIES ARE PERPLEXING, in part because they appeared so recently. Food reactions have occurred throughout recorded history, but widespread peanut problems didn't begin to surface until the 1990s. The effects on everyday life were dramatic: airlines began to deprive passengers of peanuts and announce that certain snacks might threaten someone else onboard. Elementary schools set aside peanut-free tables at lunch, and food manufacturers began to label their baked goods "school-safe" to signal they were free of common allergens. Epinephrine autoinjectors, which can shut down severe allergic shock (and are usually called EpiPens, for the dominant trademarked version), were rare and carried mostly for the occasional beesting. Now they are a ubiquitous, nearly $3-billion product.

Scott Sicherer, a clinician and director of the Jaffe Food Allergy Institute at the Icahn School of Medicine at Mount Sinai in New York City, watched re-

ports of peanut threats rise in real time. In 1997 he and his colleagues conducted the first survey of peanut and tree-nut allergy in the U.S., finding that 1.6 percent of adults and 0.6 percent of children described themselves as allergic based on reactions they had experienced. The group repeated the survey with a similar-size representative sample five years later and learned that the rate of nut allergies reported in children had doubled to 1.2 percent. In a third sampling, conducted 11 years after the first one, the overall rate tripled from that initial measurement to 2.1 percent of children, and peanut allergies were reported in 1.4 percent of kids.

Since then, the prevalence has risen even more. A large national survey of parents conducted between 2015 and 2016 by researchers in Illinois and California found that food allergies affect 7.6 percent of U.S. children, and peanut allergy affects 2.2 percent. An analysis of health-care payment data in 2018 asked how many new diagnoses of peanut allergy there are among children born each year—what statisticians call incidence, as opposed to prevalence—and reported a rate of 5 percent. And what's more common is now also more dire: researchers at the Mayo Clinic have estimated that emergency-department visits for anaphylactic shock caused by foodborne allergies—the kind of reaction that can squeeze shut airways and trigger heart attacks—increased more than threefold between 2005 and 2014. The highest rate was for peanut allergies.

"One out of 10 individuals in the U.S., more than 33 million, has a food allergy," says Sung Poblete, CEO of Food Allergy Research and Education, an advocacy organization. "One out of 13 kids has food allergies. That's two kids out of every classroom."

This increase—which is happening around the world, though not at the same rate in every nation—is a mystery. Food allergy is fundamentally a disease of inflammation. The immune system recognizes certain proteins in a food as unwelcome and launches a cascading reaction that often involves an antibody called IgE. The antibody triggers a whole-body inflammatory response: hives, swelling, vomiting, and, in the worst cases, crashing blood pressure and an inability to breathe. "Inflammatory diseases of many kinds are more common than they used to be," says Brian Vickery, a professor of pediatrics at the Emory University School of Medicine and director of the Food Allergy Program at Children's Healthcare of Atlanta, who has been a principal investigator on multiple clinical trials. "Eczema, type 2 diabetes, atherosclerotic cardiovascular disease, cancer, depression—all these things have inflammatory origins and are more common now."

The reasons seem to be varied. Researchers have proposed that cleaner modern life, early antibiotic exposure, and microbiome damage from detergents and surfactants—all components of what's called the hygiene hypothesis—might influence how often allergies develop. Genetics may predispose people to react to certain foods. There may be a clue as well in which foods provoke reactions. Up to 90 percent of food allergies are caused by just eight things: peanuts, milk, eggs, fish, crustaceans, tree nuts, wheat and soybeans. (These are the foods that, according to a 2004 U.S. law, have to be declared on labels; a separate 2021 law added sesame to the list.) Why these foods are especially allergenic also puzzles researchers. They contain complex proteins, which remain intact during digestion and may trigger the immune system in ways other foods do not; these proteins also may have similarities to common environmental allergens.

Medicine's entire understanding of how to keep children safe from allergies is being rethought.

Regardless of the underlying causes, research is zeroing in on ways to mitigate food allergies. Peanut allergy is the priority because the disruptions it imposes have become so visible in society. But the hope is that some of the new approaches can be applied to other allergies—and to help children such as Anabelle who experience more than one.

THE FIRST PRIORITY IN TACKLING peanut allergy has been children who are at extraordinary risk, the ones whose lives are at stake if they consume something with the smallest cross-contamination from a manufacturing error.

People who suffer from seasonal allergies often receive allergy shots, a program of injections that gradually decreases their sensitivity and keeps their reactions at a level they can tolerate. Allergy shots were briefly tried for peanuts as well, but they were abandoned because of safety concerns, including the 1991 death of a trial participant who received a miscalculated dose. After that, patients' only remaining option was to change their diet, but mistakes and cross-contamination kept putting them at risk. It took more than a decade for immunologists to try a different method of desensitization for peanut allergies that had a century-old history: giving minuscule, escalating doses by mouth, a process called oral immunotherapy. A large international study in 2018 definitively proved that the approach worked, and it became the standard for treating kids whose families weren't willing to trust avoidance. In 2020 it led to the first-ever FDA approval of a therapy for peanut allergy, a powdered form of peanut protein with the trade name Palforzia that is dispensed over months in precisely metered doses.

That was a huge advance—but, for some families, still not a solution. Initially Palforzia was not approved for children younger than four years of age. Dosing needed to be extremely precise and, according to some practitioners, was tricky to manage. Plus, the

drug debuted at the start of the COVID pandemic, when repeat office visits for dose changes became especially challenging. And as the drug's own labeling acknowledges, taking it poses the possibility of reactions. That has left some allergy families searching for alternatives to oral immunotherapy. "Ten to 20 percent of patients can't finish the treatment because of the side effects," says Edwin H. Kim, an associate professor at the University of North Carolina at Chapel Hill School of Medicine and director of the UNC Food Allergy Initiative. "And up to 10 percent of patients experience anaphylaxis at some point while they're on the treatment itself."

Kim has participated in research into two other methods for presenting smaller doses of peanut allergens to the immune system safely: sublingually (under the tongue) and on the skin. The skin method involves a patch containing peanut protein that is applied daily at home for as many as three years; the patch always contains the same dose but is gradually applied for escalating amounts of time. In a phase 3 clinical trial, the results of which were published in 2023, 67 percent of toddlers who were too young to receive Palforzia and who wore the patch were able to raise the amount of peanut protein they could safely consume to the equivalent of three or four peanuts. That was twice as many children as in the placebo group.

The hope for the patch, which has not yet been approved by the FDA, is that it will be easier for kids to tolerate because of its lower dose and easier for parents to manage logistically. Lora Milburn's son, Vance, wore it for a year as a trial participant. He was eight months old when he started showing allergy symptoms—too young to have words for what he was experiencing—and four years old when he entered the trial through Kim's clinic. In the summer of 2025, when Vance was nearing the expected end of his trial participation, his mother thought his sensitivity was already diminished. She did not know whether he received the real treatment or a placebo, but she noticed the way he reacted to the patch. "Some days he doesn't really complain about it; some days he's scratching his back against the wall trying to get the itchies out," she said. "But he knows why we're doing it. If it's nighttime, he's like, 'Mommy, take my patch off, put my new patch on.'"

All these exposure therapies—the patch, the oral doses, the version that goes under the tongue—target reactions to specific peanut allergens. But a separate cadre of researchers has envisioned the struggle to control peanut responses as an entryway to remodeling the way that the immune system reacts to food more broadly.

In 2013 they began testing the efficacy of an existing drug, a monoclonal antibody named omalizumab (marketed as Xolair) that is already approved for severe asthma caused by allergies. "It's an anti-IgE biologic, and IgE antibodies are at the center of the whole allergic inflammatory cascade," Chinthrajah explains. "And the beauty of something like that, where you're targeting allergic inflammation, is that it has the potential to help all allergies."

Investigators launched a trial that admitted children and adults who showed allergies to peanuts and at least two other foods; Anabelle Terry was one of the participants. Using a complex study design with several stages, the scientists tested whether regular doses of the injectable drug worked better to reduce allergic sensitivity than did placebos; whether shorter or longer courses of the drug made a difference; whether it worked best alone or combined with oral immunotherapy; and how often and in what amounts people could consume allergenic food once they stopped the treatment.

In 2024 the researchers (a very large team working in multiple medical centers) published the first results. In children aged one to 17 years, 67 percent of those who received the drug were able to eat the equivalent of four peanuts, enough to keep them safe from any accidental exposure. Based on those results, and anticipating more data, the FDA immediately approved Xolair as a protection against peanut allergy.

Participating in the trial was a significant commitment for families. Jennifer Jennison's son, Jack, was two years old and allergic to eggs, peanuts and cashews—among other foods—when the trial accepted him at its Atlanta site. Every two weeks she or her husband, David, would take time off work to bring their son for an injection. After around seven months, the protocol added tests of small doses of food allergens in applesauce to the office visits; after several hours of observation to make sure the dose was safe, the family carried home boxes of premeasured allergen powder for Jack to eat every day. And in a third phase, Jack progressed to a daily maintenance regimen with actual food: powdered egg white, a cashew and seven Reese's Pieces.

Jack's experience is similar to Anabelle's. She was in the same arm of the trial and progressed to a daily dose of peanuts, walnuts and cashews to keep her protection up. But what happened to the Jennisons afterward shows that no peanut-allergy protection is perfect yet. Convincing a child to eat the same foods every day is no small task. First Jack refused his maintenance dose of cashew. After a while he started to resist the Reese's Pieces, too.

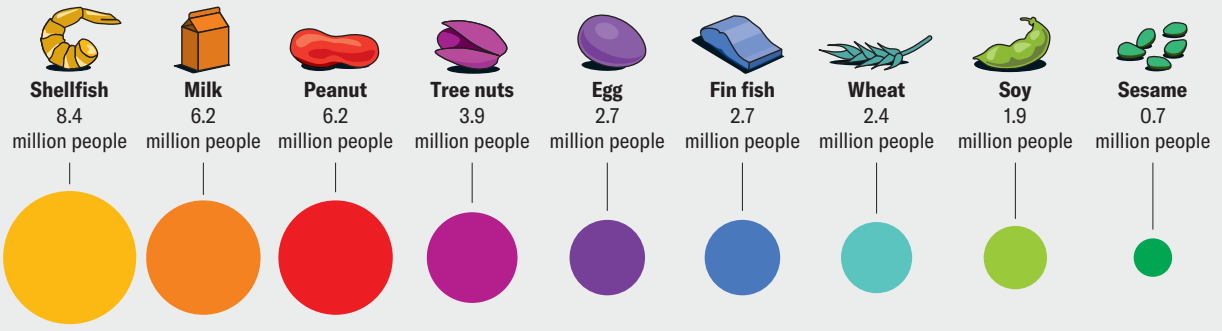
The Jennisons live in Atlanta, the corporate home of Chick-fil-A, and seemingly every kid's birthday party features the restaurant's nuggets as well as a cake—which both contain eggs. "For us, eggs are the most important," Jennifer says. "I still feel more comfortable with the cross-contamination risk of peanut knowing that he had built up a tolerance. But for now we're back to avoidance."

BECAUSE NEW APPROACHES to desensitization have worked so well for severely affected kids, researchers have begun to address the needs of those who are somewhat less allergic. For instance,

A Nation Filled with Food Allergies

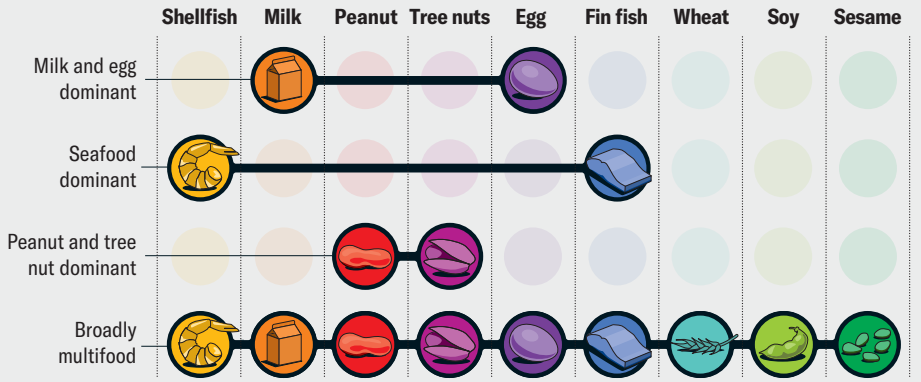
More than 33 million people in the U.S. have at least one food allergy, according to Food Allergy Research and Education, an advocacy group. Among kids, that's two in every classroom. The effects range from digestive upset to a closing, suffocating airway.

Nine major food categories can trigger allergic responses. The most common is shellfish, and the least common is sesame.



In the U.S., approximately **one in 10 adults** (age 18 or older) and approximately **one in 13 children** have at least one food allergy.

People can be allergic to more than one type of food. A 2023 survey of more than 38,000 children reported that 40 percent reacted to foods in different categories. Among 40,000 adults, 48 percent were multisensitive. There were four broadly reactive groups, shown here.



Sources: "Food Allergy Facts and Statistics for the U.S.," published by FARE (Food Allergy Research & Education), July 2024, foodallergy.org (*prevalence data*); "The Epidemiology of Multifood Allergy in the United States: A Population-Based Study," by Christopher M. Warren et al., in *Annals of Allergy, Asthma & Immunology*, Vol. 130; May 2023 (*multiallergy reference*)

some kids can eat half a peanut before suffering a reaction. That's a tiny amount from the perspective of a nonallergic person, but it's a huge, life-threatening dose to a highly allergic one. Such people, whom some immunologists call "high threshold," include possibly 800,000 kids with peanut allergies just in the U.S. But their triggers are so different from those of highly allergic people that they had been excluded from some trials of desensitization strategies. Indeed, immunology didn't have a clear understanding of whether desensitization that started from their baseline would even achieve the same results as in highly allergic kids.

All of that is now changing because after years of diagnosing patients in this class, medical practitioners could perceive that the group was being left behind. "We would have children who maybe would eat half of a serving before they would start to have symptoms," Sicherer says. "And what we would tell those individuals is: 'Your symptoms weren't so bad, so you're not really that much in danger. You still need to avoid it, but if there were a small accident, maybe you would be okay.'"

Jackson Esteves was 10 months old when his parents discovered his allergies. His mother, Holly, who was so thoughtful about her children's diets that she made her own baby food, was starting to introduce him to solids. She made a spinach pancake for her older daughter, slid a few morsels onto Jackson's high-chair tray, and then watched in horror as raised red hives rippled down his body. The pancake contained eggs, and tests showed that Jackson was allergic to them—and to dairy, sesame, tree nuts and peanuts.

This diagnosis a decade ago sent the Esteveses, who live on Long Island in New York State, hurtling into a landscape familiar to other allergy families. "I was suddenly attuned to every food label," Holly says. "I was learning how to modify recipes. I became very insecure in social settings, family parties, birthday

Graphics by Jen Christiansen

parties. I had to bring everything for him." What made it even more complex was that no one else in the family—Jackson's parents, his older sister, or a younger sister who was born soon after the pancake incident—shared Jackson's allergies.

The Esteves family didn't know it at the time, but Jackson's allergies concealed a kernel of promise. Although he was extremely reactive to some foods, medicine considered him just minimally allergic to peanuts—and that made him eligible for a new trial launched by Sicherer and a team of researchers from several institutions, called CAFETERIA. (Allergy researchers seem to be exceptionally fond of complex acronyms. "CAFETERIA" comes from "Challenging to Foods with Escalating Thresholds for Reducing Food Allergy." The Xolair study was known as OUtMATCH, which stood for "Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy in Food Allergic Children and Adults.")

Starting in 2019, children between four and 14 years old consumed escalating doses of peanut butter, first under medical supervision and then at home, beginning with a carefully measured eighth of a teaspoon and increasing every eight weeks until they were consuming one tablespoon daily. Then they were asked to eat two tablespoons of peanut butter—the amount that would go in a sandwich, which an allergic child would never try to consume—every week for 16 weeks but not necessarily in daily doses. Finally, they had to refrain for eight weeks before being tested a final time.

It worked. Among the 32 kids in the peanut-eating arm of the study (as opposed to a control group that avoided peanuts), every child achieved the study's final goal of consuming the equivalent of about three tablespoons of peanut butter without a reaction.

That result was "amazing," says Patricia Fulkerson, chief of the food-allergy section of the National Institute of Allergy and Infectious Diseases, which funded the escalation study. "A 100 percent response rate is hard not to be happy with."

The study's authors say it needs to be repeated in more kids and at different medical centers. Jackson, now about 12 years old, has been able to eat peanuts safely since he completed his participation in CAFETERIA; he'll even eat a PB&J once in a while, although it is not a favorite food. Most of his allergies to other foods remain unaffected, but "he was a success story" all the same, his mother says. "He's over peanut allergy."

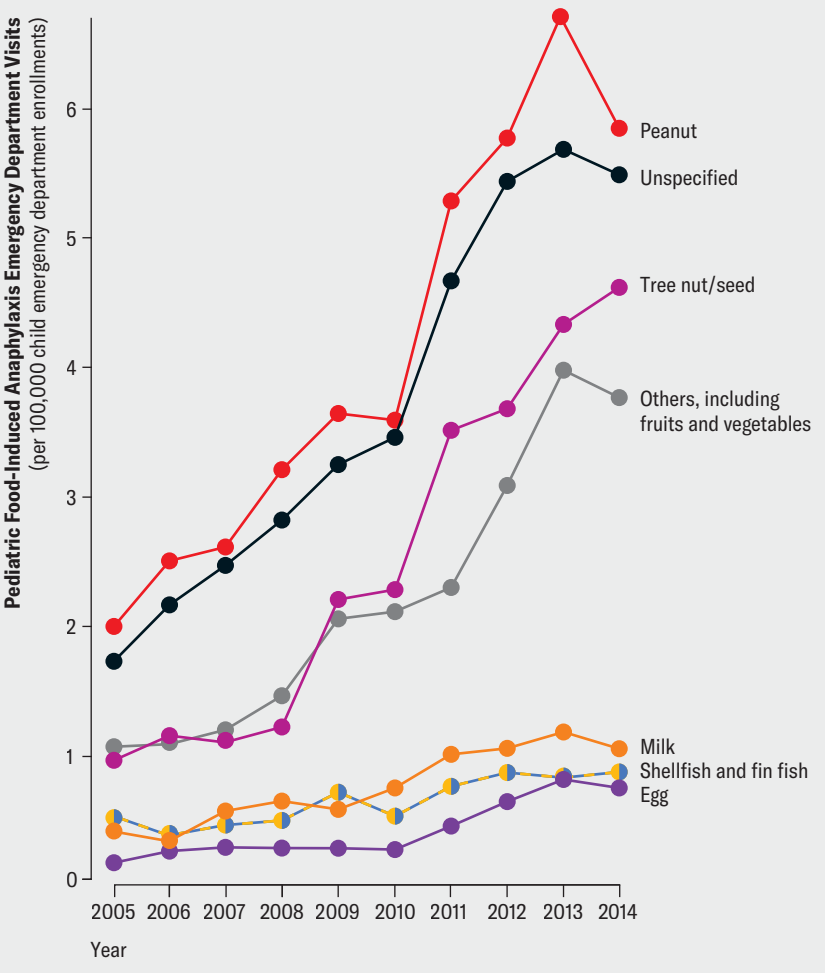
Even though the CAFETERIA study worked at its small scale and the different approach in the OUtMATCH trial resulted in an FDA drug approval, those tests and others share a limiting feature: they are hard for both the children going through them and the parents guiding them. The kids have to push themselves to swallow something that has made them ill in the past and that still, even in tiny doses, might produce an unpleasant reaction. Parents have to endure the stress of watching their children undergo food challenges to test their progress, knowing that life-threatening anaphylaxis might result.

Plus, for highly allergic people, the most that desensitization can offer is to keep them safer, not completely safe. "Ultimately we're not curing the allergy," Vickery says. "We're kind of providing a protective shell around the patient, a way to defend them against an accidental exposure. They're still reading labels, they're still avoiding the food, they are still carrying their epinephrine." What families long for is something that could make peanut allergy just go away.

A NEWLY PROPOSED treatment might manage that by rewriting the immune system's memory of anti-

Allergy Emergencies

Peanut allergies are the third most common food sensitivity, but they send the most children to the hospital with anaphylaxis, a life-threatening reaction. Emergency visits for many food allergies have gone up since 2005.



Source: "National Trends in Emergency Department Visits and Hospitalizations for Food-Induced Anaphylaxis in US Children," by Megan S. Motosue et al., in *Pediatric Allergy and Immunology*, Vol. 29; August 2018 (*emergency department data*)

gens—although research into the approach is in very early stages, and the first small clinical trial began just recently.

The treatment involves successive administration of two drugs, both made by biotechnology company Regeneron. The first drug, dupilumab (marketed as Dupixent), is a monoclonal antibody that is already FDA-approved for treating moderate to severe eczema and asthma and a few other conditions; it works by blocking the action of specific cytokines, signaling proteins that encourage the production of IgE. The second, linvoseltamab, is also an antibody and recently received FDA approval for treating relapsed or refractory multiple myeloma. This cancer affects plasma cells, a category of white blood cell that produces antibodies, including IgE.

Investigators initially thought that dupilumab could be a solo treatment for peanut allergy. But several trials showed that although peanut-specific IgE levels went down under its influence, there was no long-term practical benefit. Even immediately after a course of the drug in one trial, participants were unable to tolerate peanuts. In another test, drug recipients showed improved peanut tolerance right away, but it dropped three months later. IgE availability bounced back.

That led researchers to look at the second drug, which deals a mortal blow to the cells where IgE is manufactured. In mice and monkeys, administering a dose of linvoseltamab during an ongoing course of dupilumab destroyed the cells producing IgE. Continuing the dupilumab while the plasma cells grew back suppressed allergic inflammation and kept the animals' immune systems from restarting the overreactions.

"This is very different than other approaches of trying to build tolerance in patients or trying to just decrease IgE," says Jennifer Maloney, who leads Regeneron's therapeutic work on immune, inflammatory and infectious diseases. "This is something that potentially could remove that allergic antibody from the person."

The company has shared results from a 20-year-old man with multiple severe allergies. Regeneron described his treatment at the J. P. Morgan Healthcare Conference in January 2025, documenting a dramatic drop in his IgE production during the dupilumab course and after the linvoseltamab was given. Since then, the company has started recruiting a small group of patients for an early-phase trial primarily to test safety. Vickery made plans to enroll one patient at Emory, where linvoseltamab was already being used to treat cancer patients.

"We're going to learn something really important," he says. "If we wanted to cure the disease and make it go away, would this be a viable approach to doing so? If it doesn't work, we're going to learn things about why it didn't work and what we might need to do in the next trial."

THERE IS ANOTHER GOAL of peanut-allergy science. It's the ultimate goal: prevention, not desensitization or cure. And that may be possible for children being born now, thanks to a British study that has been running for more than a decade—and to a snack.

In the early 2000s Gideon Lack, an immunologist then at Imperial College London, went to Tel Aviv to give a talk on how food allergies were rising around the world. He asked the audience, all Israeli pediatricians and allergists, how many of them had treated children with peanut allergy. From his own experience in the U.K., he expected every hand to shoot up. Only a few did.

This low show of hands was extraordinary, and it immediately presented an opportunity to ask why the U.K. and Israel were so different. After returning home, Lack set up a survey to compare national rates of peanut allergy. To rule out some undetected genetic difference in the Israeli kids, he chose to limit the survey to Jewish children, recruiting roughly 5,000 in each country. The results revealed that the occurrence of peanut allergy in Israeli kids was one-tenth the rate among U.K. ones. A second set of questions posed to a subset of the children, 77 in the U.K. and 99 in Israel, hinted at why the rates were so different. Before their first birthday, Israeli children frequently ate peanuts, often in a ubiquitous snack called Bamba—something like Cheetos but coated in peanut butter instead of cheese. By the time they were 14 months old, almost 80 percent of the Israeli children were eating at least a few grams of peanut protein every month. In contrast, 80 percent of the British children had never tasted peanuts.

It made sense that kids in the U.K. weren't eating peanuts because at the time, medical authorities there and in the U.S. recommended that allergy-causing foods be kept out of the diets of children from allergy-prone families until they were three years old. Lack and his team wondered whether the Israeli experience showed that this well-meaning advice might be wrong. They set up a fresh study, recruiting families with infants who were between four and 10 months old and had severe eczema or showed evidence of egg allergy, signs that their IgE production was already disrupted. The babies were tested for preexisting peanut allergy, and if they were negative, they went into one of two groups. The families of one group were told to keep their children from eating peanuts until they were five years old. The rest of the families were encouraged to introduce their kids to peanut products, preferably Bamba or peanut butter.

When the investigators tested the children five years later, the differences were stark. Among the children told to avoid peanuts, 13.7 percent developed peanut allergies. Among the children who began eating peanuts early, only 1.9 percent did—an 86 percent difference.

Lack published the results in 2015, working with

Early introduction clearly will prevent peanut allergy. "It does work. It's the right thing to do."
—GIDEON LACK *KING'S COLLEGE LONDON*

a team primarily from King's College London, where he had moved to research pediatric allergies. This study, called LEAP (for "Learning Early About Peanut Allergy," in a departure from long acronyms), caused an earthquake in allergy science. Anthony Fauci, at the time the director of NIAID, which helped to fund it, said it had "the potential to transform how we approach food-allergy prevention."

Two more studies cemented the findings. In one, published the following year, children from both arms of the LEAP study were asked to not eat peanut products in their sixth year. Allergy rates rose further among the children who had refrained from peanuts all along, but children who started eating peanut products early maintained their low rates of allergy.

In a third, published in 2024, the team went back to children who had been in the LEAP study and were at least 12 years old to check whether the preventive effect lasted. It had. In the group that refrained from peanuts up to age five, 15.4 percent were allergic to peanuts. In the group that ate peanut products early, only 4.4 percent had bad reactions. Early introduction "overwhelmingly will prevent peanut allergy," Lack says. "It clearly has been shown that it does work. It's the right thing to do."

But there have been persistent challenges to implementing that idea. Health authorities no longer recommend that parents avoid feeding allergy-related foods for three years—but most national and international guidelines still recommend exclusive breastfeeding for six months, and the cultural pressure to maintain that time frame is immense. In 2019 the American Academy of Pediatrics did revise its guidance to allow the introduction of potential allergens at four to six months for children who seem likely to be at high risk, indicated by symptoms of eczema.

Lack worries this approach doesn't provide exposure as early in life as the immune system needs; the children in the LEAP study and in an unrelated 2016 study of early introduction began peanut exposure at four and three months, respectively. "To introduce peanuts effectively in a four-month-old baby, they need to be trained to eat solids already," he says. "If you start the weaning process at four months, then the baby may not get peanut butter in significant quantities until five to six months of age. And if it's a baby with eczema, it's too late."

The challenge of prevention at this point may be not the science of immunology but rather the science of implementation. Scientists have to persuade parents and health-care providers that it's safe to implement new knowledge. Immunologists and allergists are aware that early feeding prevents allergy. Pediatricians, who have to handle many additional issues in young children's lives, might not have caught up. But "an allergist isn't going to see somebody who doesn't have peanut allergy already," NIH's Fulkerson says. "You have to get the pediatricians involved because they're the ones who see the babies first."

As many advances as there have been in the past decade, scientists worry that the fundamentals of peanut allergy still elude them. Why it exists, what triggers it, what keeps the immune system from outgrowing it—these basic questions remain unanswered. But the ability to tackle them is growing. "This field is still relatively early in its development compared with oncology or respiratory medicine, which are targeting very specific biological pathways with very specific precision treatments," Emory's Vickery says. "We're not close to that yet. But can I see that on the horizon? Yes."

Some of the latest approaches may involve new technologies. At the University of California, Los Angeles, a team led by Andre Nel has developed a lipid nanoparticle that uses mRNA—the same technology used in the COVID vaccines that were developed rapidly in 2020—to create fragments of peanut allergens. Those fragments are presented to specific cells. In mice, the treatment damped down the IgE cascade that triggers anaphylaxis.

But this is a difficult time for biomedical research, given political decisions in the White House and its Department of Government Efficiency (DOGE) in 2025 to cancel much of the science emanating from the NIH and the National Science Foundation. Peanut allergy may be due for particular attention from the Trump administration. The president's Secretary of Health and Human Services, Robert F. Kennedy, Jr., has several times endorsed an unsupported contention that peanut allergy is caused by childhood vaccinations. Last year "peanut allergies" appeared on a list of topics that would cause grants to get extra scrutiny within the NIH.

Despite the potential political interference, for now the future seems bright for patients such as Anabelle Terry. As she grows up, the science that has reduced the risks of her allergy is growing along with her. It already has improved her life. It might one day change it for good. "If I go off to summer camp, I have to go away from the other kids for a while and take my nuts to make sure nobody else who has a nut allergy gets sick," she says. "Going on vacations, I always have to bring a giant bag of nuts with me in my backpack. It would feel pretty nice just being able to go in for a little visit and just get a shot. That would let off a big burden."

Maryn McKenna is a journalist specializing in public health, global health and food policy and is a contributing editor at *Scientific American*. She is author of *Big Chicken: The Incredible Story of How Antibiotics Created Modern Agriculture and Changed the Way the World Eats* (National Geographic Books, 2017).

Meat Allergy Alert

The bite of the lone star tick can cause an allergy to red meat, as well as to dairy and some medications

BY TANYA LEWIS

ILLUSTRATION BY SHIDEH GHANDEHARIZADEH

TICKS ARE ANNOYING CREATURES. These nasty, bloodsucking parasites glom on to you when you least expect it. And if they're not removed in time, they can transmit a startling range of pretty horrible diseases.

The bite of the lone star tick, found in the U.S. South, Midwest and mid-Atlantic, can trigger bizarre and sometimes dangerous allergies to red meat (such as beef, pork and venison), dairy, gelatin and some medications. Known as alpha-gal syndrome, the condition is caused by an immune reaction to the sugar alpha-gal (galactose-α-1,3-galactose), which is found in the flesh of most nonprimate mammals. More than 110,000 people in the U.S. tested positive for alpha-gal antibodies from 2010 to 2022, according to a 2023 report from the Centers for Disease Control and Prevention. But researchers think there might be closer to half a million people living with the condition—and the number of cases is increasing.

But not all health-care providers know about alpha-gal syndrome. A 2022 CDC survey found that 42 percent of them had never heard of the condition, and more than a third of those who were aware of it were not confident in diagnosing or managing the allergy. If people with the syndrome consume animals or products containing alpha-gal sugar, they can suffer reactions ranging from diarrhea to hives to anaphylactic shock; at least one person has died from the condition. There is no treatment, and many patients are forced to radically alter their diet for years—or for life.

A Blacksburg, Va.–based company called Revivicor raises pigs that are genetically engineered to lack the alpha-gal gene with the aim of growing organs that can be transplanted into humans. The U.S. Food and Drug Administration approved these "GalSafe" pigs in 2020 for meat as well as medical use (though not specifically for transplants). Revivicor occasionally provides GalSafe pork to people with an alpha-gal allergy, but it does not sell the meat. "We try whenever possible to make GalSafe meat available to alpha-gal patients, but we are not meat producers," says Dewey Steadman, former head of investor relations at Revivicor's parent company United Therapeutics. "We've been unsuccessful in our efforts to find a partner to produce GalSafe meat on a larger scale." The company is focused more on manufacturing organs, he adds.

SCIENTIFIC AMERICAN talked to Gilbert Kersh, one of the authors of the CDC reports and chief of the Rickettsial Zoonoses Branch at the CDC's Division of Vector-Borne Diseases, about what alpha-gal syndrome is and what doctors and the public should know about it.
An edited transcript of the interview follows.

What causes alpha-gal syndrome?

Alpha-gal syndrome is a tick-bite-associated allergic condition. We think people, a few weeks or maybe a couple of months after getting a tick bite, start having allergic reactions when they consume red meat or other products that contain the alpha-gal sugar. Alpha-gal is a sugar that is in most mammalian meat. But it's not present in humans, so humans [with the condition] recognize it as foreign and have a reaction to it. These reactions take place when people are exposed to mammalian meat or other products derived from animals, including dairy products for many patients. These reactions will come two to six hours after they consume the meat or other product.

What are the most common symptoms?

There's a group of patients who report primarily gastrointestinal symptoms, so they'll have diarrhea or vomiting. Often this will come late at night because they've had an evening meal that included red meat. And there are other patients who have more traditional allergic reactions—who will have hives—and some develop anaphylaxis. They may have trouble breathing, swelling of the tongue, those kinds of symptoms—which can be quite serious and often result in visits to the emergency depart-

ment. It's often difficult to tie these reactions to the consumption of meat earlier in the day, and it's also difficult to associate them with tick bites that might have happened weeks or months before any of the symptoms started. All these factors make the syndrome difficult to recognize and diagnose.

And do doctors know how to diagnose the condition?

We did a survey of health-care providers in 2022, and 42 percent of them had not heard of alpha-gal. An additional 35 percent were not too confident in their ability to diagnose or manage a patient who had it. We think there's really a gap in awareness among health-care providers about recognizing these symptoms and the sequence of events that leads to alpha-gal syndrome. One of our objectives is to increase awareness both among the public and among health-care providers so it can be recognized and managed appropriately.

Is there a treatment for the condition?

There's no treatment or cure for alpha-gal syndrome, but patients can manage the condition by avoiding eating things that have the alpha-gal sugar. You can use chicken or fish as a protein source but not pork or venison or beef—all those mammalian meats have the alpha-gal sugar.

Is it a lifelong allergy?

In some patients, the antibodies responsible for the reaction will decline over time. Some patients have reported success in adding back mammalian products over a few years. But for others, it's a lifelong condition.

Is alpha-gal syndrome widespread?

Yes, and it is increasing as well. There is no formal national surveillance for alpha-gal syndrome. In the article on cases of alpha-gal syndrome that we published in 2023 in the CDC's *Morbidity and Mortality Weekly Report,* we used kind of a proxy for formal surveillance. There was a laboratory that did most of the testing for alpha-gal-specific antibodies in the U.S., and it was willing to share its data with us. Looking at those data, we could estimate that over the prior 12 years there were at least 110,000 "suspected" cases of alpha-gal—that means they had a positive lab result, but we didn't have other information about those patients. Given the lack of awareness among health-care providers, however, we suspect that 110,000 is quite a bit of an undercount, and we estimate as many as 450,000 people may be living with the syndrome in the U.S. And the number of positive tests has been going up year by year.

Where are most of the cases occurring?

The majority of cases are in a region starting in Missouri and Arkansas, going east through Tennessee, Kentucky, Virginia and North Carolina, and then stretching up the Eastern Seaboard a little bit. This pattern overlaps what we expect the distribution of the lone star tick to be. We think this tick is the one responsible for most cases in the U.S. In fact, Suffolk County, New York, which is on Long Island, had the most positive test results of any county in the U.S. That's a region that has a large number of lone star ticks, but we also think there's more awareness in that area, so people are getting diagnosed in a more timely manner there.

If you're bitten by this tick, what can you do?

We recommend that anytime you go outdoors, you follow that up with checking for ticks and removing any ticks that you find as soon as possible. We're not certain how long the tick has to be embedded for the alpha-gal antibodies to be introduced, so the safest thing to do is to remove a tick as soon as you find it. But it's better if you don't get bitten by the tick at all. Taking personal protective measures is really important for preventing alpha-gal syndrome: using Environmental Protection Agency–registered repellents, checking yourself for ticks when you return from outdoors, walking in the middle of a trail—those are tick-bite preventions that are applicable to any tickborne disease.

But in this case, that's really the only prevention we have for reducing cases of alpha-gal syndrome. It's also an issue that once you have alpha-gal syndrome, subsequent tick bites can boost the alpha-gal antibodies. So if you want to be one of those people who, over time, improves and can tolerate some mammalian products, you really need to avoid any subsequent tick bites after you have it.

Do people with alpha-gal syndrome react to other things besides red meat and dairy products?

Patients report that it's difficult to completely avoid all the products—the sugar is present in some pharmaceuticals such as gelatin-coated tablets. Marshmallows can contain mammalian products. There's not a comprehensive list of what potentially might have mammalian products. This is the difficulty for patients, especially if they eat out: they don't know exactly how the food's been prepared or what's in there. So it can be quite challenging. But most report that avoiding products with alpha-gal is much better than the symptoms they were having when they were eating meat and having severe reactions.

It's also possible to have a reaction to a vaccine. Those do not seem to be very common, but if you have alpha-gal syndrome, it's important to talk to your health-care provider when you're considering a vaccine. Most vaccines do not cause this problem. Definitely it's not a reason to avoid getting vaccinated.

What should people with alpha-gal syndrome do if they ingest red meat or another product with alpha-gal?

Some patients, after they have these reactions, will carry an EpiPen. But once they get diagnosed and know what to avoid, typically there's less of a risk of a severe reaction.

Tickborne diseases, including Lyme disease, are on the rise in general. Should health-care providers be aware of these illnesses so they can diagnose patients?

Yes, definitely. Over the past 25 or so years we've seen a steady increase in basically all tickborne diseases, and a lot of new tickborne diseases have been identified in the past two decades. So we would encourage awareness about all tickborne conditions—both alpha-gal syndrome and infectious tickborne diseases. That is something to think about when a patient comes in and it's unclear what their diagnosis is. ●

Tanya Lewis is senior desk editor for health and medicine at *Scientific American.* Follow her on Bluesky @tanyalewis.bsky.social

Babies' Gut Bacteria Predict Allergy Risk

Helpful bacteria seem to reduce allergic disease in kids

BY LYDIA DENWORTH | ILLUSTRATION BY JAY BENDT

I STOPPED SENDING PEANUT BUTTER AND JELLY SANDWICHES to school with my kids around 2007. That was roughly the moment when people started talking about a dramatic rise in the number of children with serious nut allergies. Cases of all kinds of allergies in youngsters have increased since then. The prevalence of asthma has doubled since the 1980s, and more than one quarter of children have eczema, food allergies, or hay fever or other seasonal allergies.

A host of studies from around the world strongly suggest that our allergy epidemic is the result of reduced exposure to germs in early life. During this critical window of time, an infant's immune system learns to defend against dangerous microbes and to tolerate good ones that can live in the gut and aid in processes such as digestion. This immune education comes from encountering a wide variety of germs. But as social habits have changed, leading us to spend more time indoors, these encounters have been reduced, and immune overreactions—allergies—have climbed.

This idea, introduced decades ago as the "hygiene hypothesis" and refined over the years, is supported by epidemiological studies showing that having older siblings, attending day care, living on a farm and having pets protect against allergies. But more antiseptic early lives—delivery by cesarean section, not receiving breast milk and getting antibiotic therapy in the first year of life—seem to increase risk.

Now stronger evidence is emerging that clarifies the ways that microbes inside children's guts can trigger allergies. Scientists are working out how the presence or absence of certain bacteria in kids' digestive systems affects allergic risk, thanks to technological advances that let researchers identify more types of gut microbes. Someday it might be possible to replace certain microbes in children and in the population at large and thereby lessen people's susceptibility to allergies.

In infancy, the gut microbiomes of children who later develop allergies or asthma look different from those of children who don't go on to have allergies. "Children who are at the highest risk are missing important health-promoting bacteria in that first year of life," says Stuart Turvey, a pediatric immunologist at the University of British Columbia and British Columbia Children's Hospital.

Among other things, the presence of certain innocuous bacteria early on creates a welcoming environment that allows other, helpful bacteria to follow in predictable waves. If those first "keystone" bacteria are missing, the subsequent waves of colonization are delayed or disrupted. "Microbial exposures in early life can really shape the immune system in ways that they can't much later in life," says Supinda Bunyavanich, a pediatric allergist and immunologist at Mount Sinai in New York City.

In a study of more than 1,100 children published in 2023, Turvey and his colleagues found that children who had these microbiome disruptions at age one were more likely to be diagnosed with eczema, food allergies, allergic rhinitis or asthma at age five. "Not every kid gets all four [diagnoses], but often the kids who had two or more had a more pronounced microbiome imbalance signature," he says.

Work in mice has helped researchers determine which microbes are especially influential and why. Talal Chatila, a physician who directs the food allergy program at Boston Children's Hospital, found that giving allergy-prone mice microbes from the orders Clostridiales and Bacteroidales protected the animals from developing food allergies. "Particular microbes within a healthy gut act to suppress allergic responses," Chatila says. One way they do that is by promoting the formation of regulatory T cells, which help to control immune system responses.

Another type of bacteria that has a positive effect on humans is *Bifidobacterium infantis,* which eats sugars in breast milk and is more abundant in some children who are breastfed. *B. infantis* was once common in people's guts but is much less so now in Western countries. "Only 16 percent of Canadian kids have this, and rates are lower in the U.S.," Turvey says. Among youngsters who had to have antibiotics in infancy, the presence of *B. infantis* protected them against developing asthma by age five, Turvey's studies have shown. Antibiotics reduce microbial diversity in the gut, but these particular bacteria seem to counter those negative effects.

Multiple clinical trials are underway to test allergy treatments with "cocktails" of selected bacteria. Most of these trials involve treating infants who are at high risk for allergies and then following them through childhood to see whether the treatments keep the children allergy-free. For prebiotics and probiotics now on the market, there is no convincing evidence that they can make allergies go away.

The presence of certain innocuous bacteria early on creates a welcoming environment for other, helpful bacteria to follow.

Biotherapeutics are not the only answer. Avoiding unnecessary cesarean sections and antibiotics and enacting policies that support breastfeeding could also help, Bunyavanich says. She is working on a trial comparing children born vaginally, who are exposed to microbes in the birth canal, with children born by C-section who had the mother's vaginal fluids applied at birth. Both will be compared with children born by C-section without any microbial exposure.

The scientists will follow the kids through early childhood to see who has an increased risk of allergies. If this and the other trials do reduce allergies, bringing back the microbes we've lost could turn out to be a key health strategy. ●

Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American.* She is author of *Friendship* (W. W. Norton, 2020).

ALLERGIC TO YOUR PET?

Developing an allergy to your dog or cat can be a nightmare, but hyposensitization could offer permanent relief

BY CHRISTIANE GELITZ

IT'S A NIGHTMARE for any dog or cat owner: suddenly developing an allergy to their pet. Belly rubs and cuddles bring red eyes and a runny nose. Some people can no longer even be in the same room as a pet without their respiratory system sounding the alarm.

Medical professionals' advice in such cases is unanimous: it's best to find the animal a new home because the odds of an allergy disappearing are extremely low. In fact, living with the animal increases the risk that allergic rhinitis, commonly known as hay fever, will turn into more serious allergic asthma.

But saying goodbye to an animal friend is an unbearable thought for many allergy sufferers. And for some, it's not just an emotional problem but also an existential one. This is the case for people who need a guide dog, for example, or have a job in which they can't avoid contact with animals.

The good news: there is a therapy that can significantly alleviate or even cure allergies. The bad news: the treatment is laborious and not entirely risk-free.

An allergy sufferer's immune system acts like an overzealous security guard that keeps mistaking harmless visitors for dangerous intruders. If an innocent visitor fits a certain pattern, the guard automatically detains them and sends messengers to alert the entire security apparatus of an apparent threat.

In this analogy, the classic allergy drugs—antihistamines—take over various security posts, where they prevent the messenger substances, histamines, from raising an alarm. But this only temporarily relieves symptoms. The security guard still thinks harmless visitors are dangerous.

FOR MORE THAN 100 YEARS, however, there has been a procedure that can address an allergy's root cause: specific immunotherapy, also called hyposensitization. As early as 1911, pathologist Leonard Noon used it to successfully relieve hay fever. To this day, it remains the only known treatment that can permanently reeducate the immune system.

Hyposensitization works like this: An allergy sufferer's body is exposed to very small—and then gradually larger—amounts of the harmless visitors (allergens), and the immune system learns over time that they are not really dangerous. But if too much is introduced at once, the guards panic. And the immune system learns slowly: retraining it takes at least three years.

In this process, there are two ways to introduce allergens into the body in a controlled manner: injections under the skin (subcutaneous immunotherapy) and drops or tablets dissolved under the tongue (sublingual immunotherapy). The injections, or allergy shots, require visiting a doctor, say, weekly at the beginning of treatment and later, say, about every four weeks. The tablets or drops are taken under medical supervision the first time, then daily at home. (Allergy shots for animal dander are available in the U.S. Allergy tablets are approved by the Food and Drug Administration only for ragweed, grass pollen and dust mites. Drops are not approved by the FDA. Europe has approved more subcutaneous and sublingual treatments, including injections, drops and tablets.)

Specific immunotherapy has proved effective for tree and grass pollen, and experts assume in principle that it can also work for allergies to animals. "The effect of both methods is about the same, for cats as well as dogs. In 70 to 80 percent of people who finish the therapy correctly, complete success occurs in the sense that they hardly notice any symptoms," says Karl-Christian Bergmann, an allergist at the Institute of Allergology at Charité University Medical Center Berlin.

The first improvements are usually seen after three or four months, Bergmann says, "and then they can take a cat on their lap, and it's very likely that they won't have a cold or watery eyes anymore." Once a three-year treatment is completed, the effect usually lasts for several years. "But that doesn't mean the allergy is cured forever. It's possible that the symptoms will come back after a few years," Bergmann says. No one can say how likely that is.

THE BEST ARGUMENT for hyposensitization is that it reduces the risk of the potentially dangerous spread of allergy symptoms from the upper to the lower respiratory tract—from allergic rhinitis to allergic bronchial asthma, for example. The first signs that such a change has occurred are often chest discomfort and an irritating cough. In severe asthma, the bronchi become chronically inflamed and constricted. There is a risk of shortness of breath or even life-threatening respiratory distress.

In principle, this spread of allergies can be prevented by specific immunotherapy. But the study record for animal

Bondarillia/Getty Images (*preceding pages*)

allergies, unlike for plant pollen allergies, is modest. Reports of success come only from very small studies, and the covered time periods are short. For dog allergy sufferers, there are no large studies at all. The 2022 German guidelines on specific immunotherapy mention "limited evidence" for efficacy in allergies to cats and "insufficient" evidence in dogs. They therefore call for critically weighing the benefits and risks.

This is because there is evidence that serious side effects occur more frequently with treatment involving animal allergens than with other types, warns medical research center Helmholtz Munich's allergy-information service. One example is severe anaphylactic shock, a life-threatening bodily shutdown. The first signs can be harmless, similar to mild side effects that usually pass quickly: after a shot, the skin around the injection site reddens; after the patient takes drops by mouth, the oral mucosa itches. But if the larynx swells up or the circulatory system collapses, the situation quickly becomes dangerous: there is a risk of respiratory distress, unconsciousness and organ failure—an emergency that must be treated immediately.

This risk is the main reason that immunotherapy is often not recommended for pet allergies, says Margitta Worm, an allergist also at Charité. "Compared with immunotherapy against pollen, intolerance reactions occur disproportionately often," she says, adding that deaths are extremely rare and that the danger of a reaction such as anaphylactic shock is probably highest for those who already suffer from asthma or other risk factors. Still, Worm says, "you simply can't rule it out" in anyone. And treatment is especially difficult if patients continue to live with their pets because their exposure to allergens is not controllable.

Adam Chaker, an ear, nose and throat specialist at the Technical University of Munich University Hospital Rechts der Isar, agrees. But he draws a different conclusion. The risk of a life-threatening allergic shock from immunotherapy for a pet allergy is one in a million, Chaker says. It is conceivable but highly improbable that a person could die in such a case if one can exclude risk factors such as cardiovascular diseases. He says specific immunotherapy is "extremely safe" if contact with the animal and its allergens can be minimized—the allergy must be under control.

Chaker is confident that hyposensitization works when it is used correctly. He and his team have investigated the molecular mechanisms behind allergies, with a focus on various biomarkers that indicate at the outset whether a specific immunotherapy will be successful after three years. There is no evidence that treatment is less effective for one respiratory allergen than for another, he says.

The therapy can be more difficult, however, if it requires several different allergens from one species. That's because the extracts used come from the animals themselves—and their compositions can vary. For cat allergy sufferers, the issue is usually negligible because more than 90 percent of them react to the main cat allergen. But for people with dog allergies, the problem tends to be spread across different allergens. Hyposensitization—as well as diagnosis—of dog allergies is therefore often more complicated.

There's also less demand for immunotherapies against dog allergies, compared with those for cat allergies. "Allergies to dogs usually do not cause symptoms as severe as those to cats," Worm explains. "Those affected are more likely to opt for symptomatic therapy with antihistamines and to banish the dog from the bedroom." She advises against permanent treatment of the symptoms with cortisone because of side effects. Allergy sufferers who continue to live with their dog, however, do have a higher risk of developing asthma—albeit lower than they would with a cat. "The therapy of choice, therefore, is always to find the animal a new home," Worm says.

Chaker agrees and says it would be even better not to get into this situation in the first place. He adds that people often tell him, "I want a dog, but I already have other allergies. Is that possible?" or "My child has neurodermatitis. Can we still get a cat?" In such cases, Chaker says, his answer is that it is "not a good idea. Anyone who is already allergic is in a high-risk group for further allergies and allergic asthma."

The situation is different when contact with the animal is difficult to avoid, as with visually impaired people who need guide dogs. In such cases, Chaker recommends specific immunotherapy with the necessary precautions: At the beginning of the treatment, the symptoms must be reduced as much as possible, especially in the case of asthma. This is particularly crucial in the first weeks of therapy, when as few allergens as possible should be allowed in from the outside. In the case of a pollen allergy, the treatment should ideally start in the pollen-free season. This reduces the risks and increases the chances of success. "If you manage to keep the allergen exposure low and control the symptoms well with medication," Chaker says, "you can also treat allergic asthma with immunotherapy."

Additionally, Chaker sees a great need in a different population: people who do not have an animal in the house but suffer from the allergens that pet owners carry into public spaces. "These are the people we could do well to help with specific immunotherapy," he says.

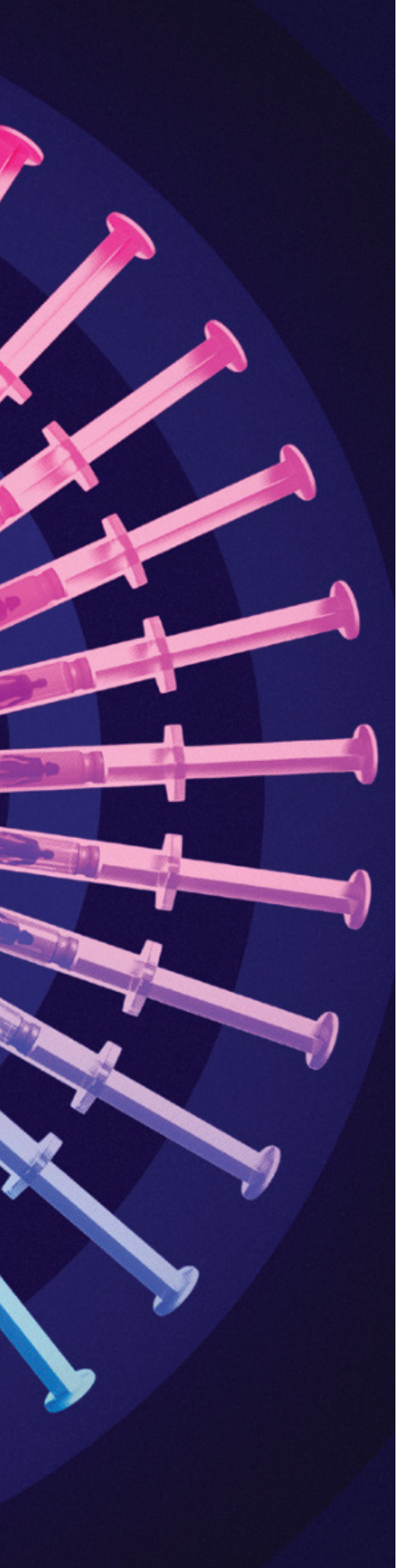
Say, one tablet a day for three years—that certainly seems manageable for those willing to take the risks. But there's no guarantee of success. Symptoms are likely to lessen but not disappear completely, and they may return after a few years. Whether that prospect is enough to try it is something every pet owner must decide for themselves. ●

Tips for Allergies under One Roof

Though not a permanent solution, people can take steps to reduce the amount of allergens in a dog or cat household. Experts recommend:

- Keeping the animal away from as many rooms as possible, especially the bedroom.
- Avoiding carpets and upholstered furniture.
- Reducing blankets and pillows and vacuuming and cleaning regularly.
- Changing and washing clothes frequently.
- Damp mopping and steam cleaning the floor, seating, and other surfaces regularly.
- Bathing the animal once or twice a week.
- Avoiding close contact with the animal.
- Ventilating well on a regular basis or using air purifiers with high-efficiency particulate air (HEPA) filters.

Christiane Gelitz is a psychologist and an editor at *Spektrum der Wissenschaft.*



YOUR PERSONALIZED CANCER VACCINE

Vaccines based on mRNA can be tailored to target a cancer patient's unique tumor mutations. But crumbling support for cancer and mRNA vaccine research has endangered this promising therapy

BY ROWAN MOORE GERETY
ILLUSTRATION BY TAVIS COBURN

AS SOON AS BARBARA BRIGHAM'S CANCEROUS PANCREATIC TUMOR WAS removed from her body in the fall of 2020, the buzz of a pager summoned a researcher to the pathology department in Memorial Sloan Kettering's main hospital in New York City, one floor below. Brigham, then 74, was recovering there until she felt well enough to go home to Shelter Island, near the eastern tip of Long Island. Her tumor and parts of her pancreas, meanwhile, were sent on an elaborate 24-hour course through the laboratory. Hospital staff assigned the organ sample a number and a unique bar code, then extracted a nickel-size piece of tissue to be frozen at –80 degrees Celsius. They soaked it in formalin to prevent degradation, then set it in a machine that gradually replaced the water in each cell with alcohol.

Next, lab staff pinned the pancreas to a foam block, took high-resolution images with a camera fixed overhead and used a scalpel to remove a series of sections of tumor tissue. These sections were embedded in hot paraffin and cut into slices a fraction of the thickness of a human hair, which were prepped, stained and mounted on glass slides to be photographed again. By the time a pathologist looked at Brigham's tumor under a microscope the next day, more than 50 people had helped steer it through the lab. Still, this work was all a prelude.

The real action came some two months later, when Brigham returned to the hospital to receive a vaccine tailored to the mutations that differentiated her tumor from the rest of her pancreas. Made of messenger RNA (mRNA) suspended in tiny fat particles, the vaccine was essentially a set of genetic instructions to help Brigham's immune system go after the mutant proteins unique to her tumor cells. It was, in other words, her very own shot.

Brigham received the last of nine doses of her personalized vaccine in 2021. In the years since then, she's seen one grandchild finish college and get married and another embark on a Ph.D. She has attended dozens of high school basketball and volleyball games for her third and fourth grandchildren and cradled the family's newest arrival, a granddaughter born in 2024. She hosts a weekly mahjongg-and-dessert gathering for a group of friends on Shelter Island and tries to live out her mother's maxim of having "a little adventure" each and every day. "I'm a little crippled here and there with arthritis," Brigham says, but "I never sit still." And she remains free of pancreatic cancer.

Brigham's recovery came as part of a small phase 1 clinical trial conducted by Memorial Sloan

Kettering in partnership with pharmaceutical companies Genentech and BioNTech—the latter, along with Pfizer, helped to produce the first approved mRNA vaccine for COVID-19. Brigham was one of 16 patients in the study who received the vaccine, administered in tandem with standard drugs, and one of eight who experienced a significant immune response. Six of those eight patients are still in remission, along with one of the eight others who did not show much immune response to the vaccine.

Seven of 16 might not sound like much. But that number suggests that the vaccine has tantalizing potential. Pancreatic cancer can be exceptionally fast-growing, and its first signs—weight loss, cramping, a touch of jaundice—are easily missed, so by the time it is diagnosed it is almost always lethal. Only 8 percent of patients with the most common form of the cancer, ductal adenocarcinoma, survive to the five-year mark, and the vast majority of people with the disease show little response to treatment.

The results of Brigham's trial were also an early sign that mRNA vaccines may be effective for a wide variety of cancers: whereas pancreatic cancer is known for its low rate of mutations, the earliest data on personalized mRNA vaccines came from studies of melanoma, which researchers had targeted specifically because it tends to mutate so frequently. An earlier phase 2 trial in patients with advanced melanoma found that for those who received both a personalized mRNA vaccine and so-called immune checkpoint inhibitors, the risk of death or recurrence decreased by almost half compared with those who got only checkpoint inhibitors. Ongoing companion trials are targeting kidney and bladder carcinomas and lung cancer. In each case, the vaccine is additive: administered after surgery and with standard drugs. The shot's job is to prime the immune system to recognize abnormal proteins arising from mutations and attack any lingering malignancy that escaped conventional treatments—or stamp out future recurrence.

Seeing promising results in fundamentally different kinds of tumors has motivated researchers to pursue personalized mRNA vaccines much more broadly. In doing so, they've developed an approach at the nexus of several important trends, pairing insights about our immune system's response to cancer with advances in vaccine production spurred by the COVID pandemic, the rise of algorithms powered by artificial intelligence, and the plummeting cost of genetic sequencing. Today there are at least 50 active clinical trials in the U.S., Europe and Asia targeting more than 20 types of cancer. A melanoma trial led by pharmaceutical companies Moderna and Merck has now reached phase 3, the last step before a medicine can be approved for public consumption. Personalized melanoma vaccines could be available as early as 2028, with mRNA vaccines for other cancers to follow.

But the promise of this novel approach couldn't have come at a more perilous time for the field. In the first weeks of the second Trump administration, U.S. cancer research was thrown into unprecedented turmoil as federal grants were terminated en masse. According to one Senate analysis, funding from the National Cancer Institute was cut by 31 percent in just the first three months of 2025.

By March of that year, cancer researchers worried that mRNA vaccines were facing particular scrutiny. KFF Health News reported that Michael Memoli, acting director of the National Institutes of Health, had asked that any grants, contracts or collaborations involving mRNA be flagged for Health and Human Services Secretary Robert F. Kennedy, Jr., best known prior to assuming that role as one of the nation's most prominent anti-vaccine campaigners. Suddenly, the optimism around personalized mRNA vaccines was overshadowed by a sense that the public investment that sustained cancer research was being dismantled piece by piece.

MUCH OF CANCER'S BIOLOGICAL POWER comes from the fact that to the body, it doesn't always seem like a pathogen. Because cancer arises from mutations in each patient's own DNA, the disease complicates our immune system's central task of differentiating between body and foreign object, host and invader, "self" and "not self."

Physicians long hypothesized that there was a link between cancer and swelling—a critical sign that the immune system "sees" an enemy to ward off. In the 1890s William Coley, now known as the father of immunotherapy, successfully spurred remission in patients with inoperable tumors by injecting them with bacteria like those that cause strep throat. But the mechanisms behind Coley's treatments were poorly understood, and for decades after his discovery, researchers weren't sure our immune systems could detect cancer at all.

Because doctors didn't know exactly how the body perceives and responds to cancer, early treatments were highly invasive and highly toxic: The first tactic was major surgery on the organs where cancer was taking root. That was followed in the 20th century by the development of systemic radiation and chemotherapy to attack cancer cells throughout the body. Over time oncologists narrowed and refined these approaches incrementally, using more precise surgery, more focused radiation and chemo that killed fewer normal cells as collateral. Still, the dream was to harness immunotherapy, which represented a dramatic departure from the usual tactics in seeking to use the human body's own systems to go after cancer in a more targeted way.

The first real proof that immune cells are capable of recognizing tumors didn't come until the 1950s and 1960s. Gradually, researchers came to understand that cancer deploys a host of tricks to suppress

the immune response to growing tumors. Some forms of cancer use fibrous tissue called stroma to construct shields that make it difficult for immune cells to penetrate or attack tumors. Other cancers take advantage of the balancing act our immune systems are always performing when they decide how heavily to invest the body's defenses in warding off a given threat. Some tumors produce proteins that can shut down key immune cells. Tumors may even recruit immune cells to promote the growth of blood vessels that will supply them with oxygen and nutrients.

As scientists learned more about how cancer manipulates the immune system, they started identifying ways to thwart it. Inside our cells, proteins are constantly being chopped up into smaller sequences of amino acids, some of which are then presented on the cell surface as part of what's collectively known as the major histocompatibility complex, or MHC—essentially the immune system's tool for differentiating self and foreign molecules. When the immune system detects a protein from a pathogen, it's supposed to dispatch killer T cells to eliminate the invader. Some cancers can interfere with this process by hijacking the checkpoint proteins that keep our immune system from revving out of control and using them to turn T cells off. Starting in the mid-1990s, several research teams found success by treating mice with checkpoint inhibitors, then a new class of drugs designed to keep tumor cells from concealing their identity and signaling, effectively, "nothing to see here." Thirty years on, checkpoint inhibitors have become a transformative tool in cancer treatment, especially for melanoma.

The research that went into developing checkpoint inhibitors showed conclusively that immune cells detect cancer much in the same way they identify other pathogens: through differences in protein structure determined by DNA—a crucial insight. But as revolutionary as checkpoint inhibitors have been for immunotherapy, they don't work for everyone—far from it. Some 80 percent of patients do not respond to this class of drugs. Researchers are still trying to understand all the mechanisms that play a role in determining who does respond, but one key factor is whether the immune system is able to recognize tumor cells on the basis of their mutations.

This is where mRNA vaccines come in. Jason Luke, a melanoma researcher who now serves as chief medical officer of mRNA-medicine start-up Strand Therapeutics, helped to design several ongoing clinical trials of mRNA vaccines for cancer. He explains that both checkpoint inhibitors and mRNA vaccines build on our deep evolutionary adaptation for fighting pathogens by identifying the proteins they shed in our bodies. But checkpoint inhibitors are effective only if the patient's immune system recognizes the cancer as a threat. In contrast, mRNA vaccines have the potential to work even in patients whose cancers haven't spurred much immune response. The trick, Luke says, is using computational tools to decipher which of a given tumor's mutations are most likely to be found by the immune system.

On a Monday morning in April 2025, I visited surgical oncologist Vinod Balachandran at his lab on the eighth floor of the Memorial Sloan Kettering Cancer Center. Balachandran led the trial Brigham participated in, and he now is director of a center for cancer vaccines that the institution launched in 2024. The entrance to his lab is at the end of a hallway lined with big freezers holding tissue samples.

When I arrived, Balachandran met me just beyond a pair of swinging doors, where postdocs hunched over laptops under rows of high shelves packed with boxes of pipettes and assay plates. He strode to the window and pointed to the brick façade of the main hospital across the street, explaining that tissue samples taken after surgery have only a short distance to travel to the lab, sometimes through a tunnel under East 68th Street. "The proximity of the laboratory tower to where patients are being treated is actually supercritical," he says, because it allows the samples to be processed and put on ice quickly, minimizing the deterioration that begins as soon as tissue is removed from the body.

The work that culminated in Brigham's vaccine grew out of research into a subset of pancreatic cancer survivors known as exceptional responders—the small percentage of people who make it to the five-year mark after a diagnosis. "These patients, you know, they're very rare," Balachandran says. Even at a facility as large as Memorial Sloan Kettering, which sees tens of thousands of cancer patients a year, it was possible to study this group with any precision only because of the hospital's long-standing mandate to save samples of every patient's tissue. When Balachandran joined the faculty in 2015, his research on long-term survivors relied on tissue samples taken more than a decade earlier.

In 2017 Balachandran and his collaborators published a study demonstrating that some patients with pancreatic ductal adenocarcinoma had more cells able to recognize the unique proteins that mutant tumor cells produced and that their immune systems seemed to develop a kind of long-term memory to fight recurrence. In some cases, immune cells with receptors that could bind to these cancer proteins persisted in the blood for more than a decade after the tumors that spawned them were removed. What if, Balachandran wondered, we could equip the 92 percent of patients who are not naturally exceptional responders with the same kinds of biological tools? "If you can teach the immune system to recognize the proteins in, say, pancreatic cancer, perhaps that could provide a blueprint," he says.

As tumors grow and metastasize, they undergo a kind of compressed evolution in which normal

cells with the host's DNA accrue mutations that cause them to divide and multiply abnormally, forming an ever larger group of closely related tumor clones. Many mutations register in the form of abnormal proteins and protein fragments, called neoantigens, some of which accumulate on the surface of the proliferating tumor cells.

Balachandran compared this growing family tree of tumor clones with new variants in a group of viruses, like the Alpha, Delta and Omicron variants of SARS-CoV-2, which emerged as the COVID-19 pandemic wore on. "You'd want a COVID vaccine to be able to target each different virus in that rapidly evolving clade," Balachandran says.

For the development of a cancer vaccine, mapping the evolutionary trajectory of a cancerous tumor is equally important, albeit with a different set of parameters. The goal is not to distinguish between the presentations of two related pathogens but rather to understand at what point a disease derived from one's own body starts to register to the immune system as not self.

"At some point—we don't think immediately—the immune system starts to notice," says Benjamin Greenbaum, Balachandran's colleague at Memorial Sloan Kettering's Olayan Center for Cancer Vaccines, who led the computational work behind the vaccine given to Brigham. In later stages, tumors typically accumulate signs of immune system involvement even if the immune response hasn't been effective—changes in the cell makeup of the microenvironment around the tumor, the display of checkpoint molecules. These signs can be understood as evolutionary adaptations on the part of the tumor in the race to evade detection, Greenbaum explains: "So then the question really became, Can we try to estimate what the immune system is really seeing in cancer?"

TO DEVELOP A WORKABLE MRNA VACCINE, Greenbaum and Balachandran had to both sequence the DNA of the cancerous tumors they were targeting and develop a framework for going after the right neoantigens—those abnormal proteins that offer clues to a tumor's underlying mutations. Neoantigens are made up of short chains of amino acids from proteins with names that look like license plate numbers: PIK3CA, KDM5C. One overarching goal of their collaboration is to discern meaningful patterns in the frequency of the sequences across patients and across cancer types. What neoantigens survive one mutation after another? Which ones show up reliably under certain conditions or look most distinctive to the body's immune defenses?

Some of these sequences, from so-called driver antigens, are present in most clones of a given tumor type. In pancreatic cancer, the driver mutation is often in a gene called *KRAS,* but the resulting antigens don't seem to elicit a reliable immune response in long-term survivors. Instead, when Balachandran and his colleagues sequenced the blood of such survivors, the immune cells present in the highest concentrations were those adapted to antigens resulting from one-off, or "passenger," mutations.

In 2017, at the time that the team published the results of the study, this was a counterintuitive finding. For decades researchers pursuing vaccines and other immune treatments for cancer had focused on melanoma because melanoma tumors have a high rate of genetic mutations. "It looks very different to the immune system than many other types of cancers do," says Michael Postow, a medical oncologist at Memorial Sloan Kettering who is involved in clinical trials of mRNA vaccines for melanoma. "That made it a good target." With all the mutant antigens it produces, melanoma should attract the immune system's attention and trigger it to attack. The conventional wisdom about pancreatic cancer, in contrast, held that it produces so few mutations that it is unlikely to carry passenger antigens that could elicit an immune response.

As demand for COVID vaccines has slackened, there has been a rush to apply mRNA technology to a long list of illnesses.

With the results from the 2017 study of exceptional responders in hand, Balachandran was able to flip that argument on its head. Even if vaccines appear to be well suited for melanoma, there's always a degree of uncertainty in selecting the right antigens to target. For starters, the sequencing of a pancreatic tumor biopsy like Brigham's is really just a snapshot in time. Come back a few months or a few years later or wait for the patient to experience a recurrence, and there's no guarantee the tumor clone that seemed dominant at the time of the initial sequencing will still be a factor in the disease. Each mutation can also have unpredictable effects, with the size, shape or biochemistry of the antigen in question shifting dramatically in response to the change of even a single amino acid.

What is more, not every antigen that corresponds to either self or not self is reliably expressed on the surface of the corresponding cell. A neoantigen that seems characteristic of the tumor might have a profile nearly identical to that of another self-antigen somewhere else in the body. In that case, a vaccine based on that neoantigen might fail to elicit much of an immune response, or it could provoke a response against the wrong target.

The study revealed a potential liability in a strategy for personalized mRNA vaccines that focused on

melanoma: melanoma's high rate of mutations gives rise to a large pool of plausible vaccine targets, but it presents just as many chances to guess wrong. A given tumor could have as many as 10,000 distinct proteins on the surface of its cells; you couldn't possibly target every one. But in pancreatic cancer, Balachandran realized, the smaller number of mutations might improve the odds of picking a suitable antigen to target.

THAT INSIGHT UNDERPINNED the pitch Balachandran brought to Ugur Sahin, co-founder and CEO of German biotech company BioNTech. Their collaboration began before the COVID pandemic, but in 2020 BioNTech was consumed by the effort to bring the world's first mRNA vaccine to market. Together with Moderna, the company demonstrated the vaccine's safety through billions of doses administered worldwide with very few side effects.

Not only was mRNA safe for vaccine delivery, but, as Sahin knew from experience, it is also a flexible platform for genetic information. Whereas traditional vaccines typically require ongoing production of the exact virus they're targeting, most of the genetic information in an mRNA vaccine can stay the same no matter which disease you're fighting.

Another threat to personalized mRNA vaccines for cancer was coming into focus: mounting federal hostility to vaccines.

BioNTech's COVID vaccine built on 30 years of work by Sahin and company co-founder Özlem Türeci that was originally intended for vaccines targeting cancer. As longtime collaborators who are also a married couple, they had tinkered with the nucleotide sequences on the molecule's cap and tail that direct a vaccine to the right part of the cell and tell the immune system what to pay attention to, and they had improved the mRNA's stability so that even a small dose of a vaccine could provoke a full-scale immune response. All that work could be incorporated into vaccines for other diseases; the only thing that needed to change was the genetic information in the middle of the molecule. After obtaining positive results for the mRNA vaccine for melanoma, Sahin agreed to partner with Balachandran to develop an mRNA vaccine for pancreatic cancer.

As global demand for COVID vaccines has slackened, there has been a rush to apply mRNA technology to a long list of illnesses, including malaria, flu, tuberculosis and norovirus. Cancer is a natural target. Despite treatment advances, it remains broadly incurable and is a leading cause of death as life expectancies improve across the world. But because cancer vaccines must be personalized, the biggest change in approach to developing them for an mRNA platform comes not in development but in manufacturing. Both BioNTech and Moderna now confront something like the inverse of the challenge they faced in developing the first COVID shots.

Prior to the pandemic, both companies were upstarts among the giants of the pharmaceutical industry. Neither had brought a product to market. Moderna employed under 1,000 people and had manufactured fewer than 100,000 total doses of its clinical-stage vaccines. Once its Spikevax received emergency use authorization from the U.S. Food and Drug Administration, the company quadrupled its workforce and produced more than a billion doses in just 18 months.

The task facing Scott Nickerson, who oversees Moderna's manufacturing for individualized neoantigen therapies, was to reengineer a process perfected for producing mRNA vaccines for millions of people in batches of thousands of liters. For personalized vaccines, each batch would be a few milliliters at most and would have to be turned around in weeks.

To get there, Moderna is investing heavily in automation, partnering with a robotics firm to prepare sterile kits of raw materials for each batch and thereby minimize operator touch time on the manufacturing floor. The hope is that rather than following a single large batch of vaccine through the entire manufacturing process, workers will eventually be able to move from one small batch to the next after setup.

At both Moderna and BioNTech, the complex logistics of conducting the dozens of different quality-control tests required for each production run falls to algorithms powered by AI. Before being approved for release, doses of Spikevax underwent 40 distinct tests that tracked the chemistry, biochemistry, microbiology and sterility of every vial. With COVID vaccines, the sterility test alone, which ensures that vials are not contaminated with organisms, took two weeks. Refinements have since compressed that test to eight days, Nickerson says. Ultimately the goal is to shrink it to five days and complete the other tests within that same window. "The reason it's hard is we have to design the equipment," he explains. "None of this stuff's off-the-shelf."

At the same time, the background science is, at least in theory, easily adapted from work that's already been done. Lennard Lee, an adviser to the U.K.'s National Health Service overseeing the rollout of clinical trials for cancer vaccines, says the pandemic gave regulators there a running start on trials for mRNA cancer vaccines. In partnership with BioNTech, the NHS launched a program that aims to provide personalized vaccines to up to 10,000 cancer

patients by 2030. And the NHS and Moderna have invested in a facility that could produce up to 250 million vaccines per year.

In that interval, as manufacturers work to reduce production times and costs, clinical trials will evaluate alternative dosage and delivery mechanisms, Lee says. Although current protocol is for vaccines to target micrometastases—small groups of cancer cells that spread to other parts of the body and linger after cancerous tumors are removed surgically—there's no shortage of adjustments that might follow from more data or improved screening. Could one deliver a therapeutic vaccine to tackle a tumor before it is large enough to operate on? Or maybe one could even administer a prophylactic shot that prevents tumor formation in the first place?

With a unified health system and world-class research and manufacturing facilities, Lee says, the U.K. is well positioned to advance research that would answer such questions. Fully realizing the potential of personalized mRNA vaccines for cancer, however, will require more trials in the U.S., which has many more cancer research centers than the U.K. But the ability of the U.S. to lead this effort is now in jeopardy.

The federal government has long been the dominant source of funding for cancer research in the U.S. Miriam Merad, a cancer immunologist at the Icahn School of Medicine at Mount Sinai in New York City, says that in a typical year, funding from the NIH accounts for more than half of the research budget at her institution.

In President Donald Trump's first term, threatened cuts to the NIH never quite materialized. Society is not going to let that happen, Merad thought. But just weeks into Trump's second term, the NIH announced plans to limit indirect contributions to research grants to 15 percent, meaning that for every $100 in funding awarded, only $15 extra would be included for overhead—a dramatic departure from historical rates in the range of 50 to 60 percent.

"This is an operation," Merad says, gesturing to the building where she works, which is dotted with six-figure pieces of equipment and has an entire floor dedicated to rearing mice used in research. "We have to pay salaries; we have to buy food for the animals. We have to pay service contracts because we have instruments that need to be serviced all the time." These are not expenses that can be easily paused or restarted based on the fate of a single grant. Within just a few months of the NIH announcement, Merad's department had reduced hires of new postdocs, and Mount Sinai's medical school had to shrink the size of its incoming class.

By May 2025 another threat to personalized mRNA vaccines for cancer was coming into focus: mounting federal hostility to vaccines. Senate Republicans convened a hearing entitled "The Corruption of Science and Federal Health Agencies," featuring the false claim that as many as three out of four deaths from COVID were caused by mRNA vaccines deployed to stop the pandemic. (In fact, COVID vaccinations saved an estimated 2.5 million lives between 2020 and 2024, according to a study published in 2025.) Last June, Kennedy fired all 17 members of the Advisory Committee on Immunization Practices, which makes recommendations on federal vaccine policy. He eventually replaced them with his own advisory committee, which includes several anti-vaccine stalwarts. Kennedy has also slashed research funding for mRNA vaccines. In August he canceled nearly $500 million supporting the development of mRNA vaccines against viruses such as SARS-CoV-2 and influenza. The move intensified the fears of researchers who want to develop mRNA vaccines for other illnesses, among them cancer.

AFTER MY VISIT to Memorial Sloan Kettering, Balachandran's team shared a chart that plotted Brigham's immune response to her personalized mRNA vaccine. Along the bottom, triangles marked the dates of her surgery and each of the nine doses of the vaccine she received over the course of a year. Above them a cluster of brightly colored lines showed the share of her body's T cells targeting the specific mutant proteins in her cancerous tumor. At first, when Brigham's tumor was removed, cells trained to go after each cancer clone were somewhere on the order of one in 500,000 T cells in her blood. A few months after surgery, when she'd had four doses of the vaccine, the lines shot up almost vertically, showing that the most common cancer fighter at that point accounted for around one in 20 to one in 50 T cells—an increase of more than 20,000-fold.

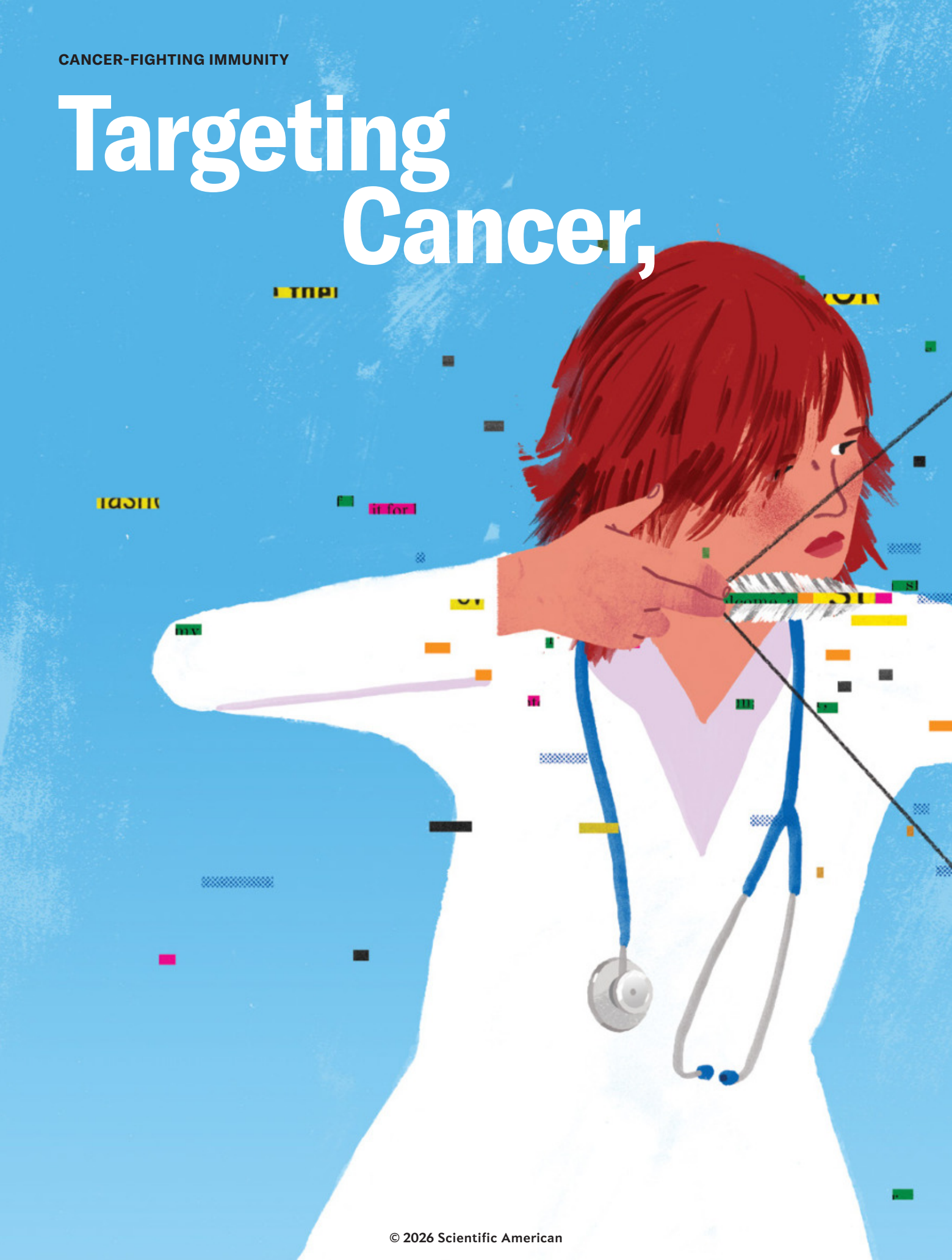
Those T cells dipped a bit in the months before Brigham's last booster shot, given almost a year after her tumor was removed. But they remained in the same range even three years on. A phase 2 clinical trial evaluating the safety and efficacy of the vaccine in a larger patient group is currently underway.

The vaccine for Brigham's cancer was just nine tiny vials of liquid administered through an IV, a private message that only her immune system was meant to decode. But the effort that delivered that coded message was a deeply collective enterprise, one that stretches back through the hundreds of thousands of tissue samples collected, stored and analyzed at Memorial Sloan Kettering, each one taken from the body of a patient who might not have survived their cancer. Also in that vaccine were the contributions of generations of taxpayers who never got to see these results. Perhaps their descendants will be able to beat the disease—if society continues to support this vital work. ●

Rowan Moore Gerety is a reporter and audio producer in Phoenix, Ariz., and author of *Go Tell the Crocodiles: Chasing Prosperity in Mozambique* (The New Press, 2018).

CANCER-FIGHTING IMMUNITY

Targeting Cancer,



Sparing Patients

New drugs, with components that can be repeatedly recombined for the best antitumor effect, are outdoing old-style chemotherapy

BY JYOTI MADHUSOODANAN

ILLUSTRATION BY KEITH NEGLEY

IN THE LONG AND OFTEN DISPIRITING QUEST to cure cancer, the 1998 approval of the drug Herceptin was a tremendously hopeful moment. This drug for breast cancer was the first to use a tumor-specific protein as a homing beacon to find and kill cancer cells. And it worked. Herceptin has benefited millions of people since that time, dramatically increasing the 10-year survival rate—and the cancer-free rate—for what was once one of the worst medical diagnoses. "Honestly, it was sort of earth-shattering," says oncologist Sara M. Tolaney of the Dana-Farber Cancer Institute in Boston.

But the drug has a major limitation. Herceptin's beacon is a protein called HER2, and it works best for people whose tumors are spurred to grow by the HER2 signal—yet that's only about one fifth of breast cancer patients. For the other 80 percent of the more than 250,000 people diagnosed with the disease every year in the U.S., Herceptin offers no benefits.

The hunt for better treatments led researchers to reimagine targeted therapies. By 2022 they had developed one that linked Herceptin to another cancer-killing drug. This therapy, for the first time, could damage tumors that had vanishingly low levels of HER2. The drug, named Enhertu, extended the lives of people with breast cancer by several months, sometimes longer. And it did so with fewer severe side effects than standard chemotherapies. The U.S. Food and Drug Administration approved its use in that year.

The news got even better in 2023. Researchers reported that Enhertu appeared to work even on tumors with seemingly no HER2 at all. (It's possible the cancers did have the protein but at very low levels that escaped standard detection methods.) "Exciting!" says oncologist Shanu Modi of Memorial Sloan Kettering (MSK) Cancer Center in New York City, who helped to run the study that led to Enhertu's approval. "They did this provocative test and saw this almost 30 percent response rate" in tumors apparently lacking the cancer protein, she notes.

Enhertu belongs to an ingenious and growing class of targeted cancer drugs called antibody-drug conjugates, or ADCs. The compounds are built around a particular antibody, an immune system protein that homes in on molecules that are abundant on cancer cells. The antibody is linked to a toxic payload, a drug that kills those cells. An ADC's affinity for cancer means it spares healthy cells, avoiding many of the side effects of traditional chemotherapy. And each antibody can be paired with several different drugs. This Lego-like assembly opens up a world of mix-and-match possibilities. Researchers can use the same drug to treat many cancers by switching up the antibody, or they can attack one type of tumor with many different ADCs that target several cancer biomarkers on the cells. This ability "changes the way we think about drug development," Tolaney says.

The idea for ADCs is not entirely new—the first one was cleared for patient use in 2000—but recently scientists have learned intricate chemical construction techniques that make the compounds much more effective, and they have identified new cancer-specific targets. These advances have driven a wave of new development. At least 19 ADCs have been approved for breast, bladder, ovarian, blood, and other cancers. Approximately 100 others are in the preclinical pipeline. One ADC for breast cancer, known as T-DM1, proved much more effective than Herceptin and has now become the standard of care for early stages of disease. "It is pretty cool to see how things have changed so quickly," Tolaney says.

Buoyed by the successes, researchers and pharmaceutical companies are pouring resources into developing more powerful ADCs—perhaps even ones that can work across a wide range of cancer types. Pharma giants such as Gilead, Roche and BioNTech have invested heavily in their ADC programs; in October 2023, for example, Merck put $4 billion into a partnership with

Daiichi Sankyo, the biotechnology firm that partnered with AstraZeneca to produce Enhertu.

But the new drugs are still beset by some mysterious problems. Some ADCs have side effects similar to those caused by traditional chemotherapies—which shouldn't happen, because the drugs are supposed to target cancer cells alone. On patient forums, people describe needing to reduce their doses because of intolerable nausea or fatigue. These drawbacks limit ADCs' use, so scientists and pharma companies are urgently trying to figure out what is causing them.

IN THE CLINICAL TRIAL that led to Enhertu's approval, patients typically had already received different kinds of chemotherapy drugs, such as medications that stop cells from multiplying. But these drugs—and other forms of chemotherapy—do not distinguish between a cancer cell and a healthy one. Any cell trying to make DNA or multiply is vulnerable, and normal tissue as well as tumors can be attacked. Fully 64 percent of people on standard chemotherapy experience nausea, diarrhea, fatigue, and other negative side effects. For many, these can be as debilitating as cancer itself. Such effects limit the dose people can take and the length of treatment, leaving windows of opportunity for tumors to grow resistant and rebound.

For many years researchers have sought less toxic alternatives, envisioning precision drugs that target cancers and spare healthy cells. The idea of ADCs sprang from the exquisite specificity of antibodies. If highly toxic forms of chemotherapy could be strapped onto antibodies, the toxins would reach only the cancer cells and no others. Although the concept was straightforward, attempts at making ADCs faltered for decades.

Some of the earliest attempts used drugs that just weren't strong enough. In the 1950s, for instance, researchers linked a drug named methotrexate to an antibody that targets carcinoembryonic antigen, a common tumor marker, and tested whether the construct could treat advanced colorectal and ovarian cancers in people. The drug bound to its target but had little therapeutic effect. Researchers then swung too far to the other end of the spectrum and tried using much more toxic drugs instead. But these drugs triggered serious side effects.

Greg Thurber, a chemical engineer at the University of Michigan, looked into this conundrum. He began working on ADCs when studying how antibodies spread through the body to bind to their targets. After ADCs infiltrate a tumor through its network of blood vessels, the compounds slip out of these vessels and into cancer cells to kill them, Thurber says. But the ADCs that existed at the time never got past the cells just outside the blood vessels. They bound too tightly. The key to improved effects, it turned out, was tailoring the antibody parts so they zeroed in on cancer cells but had a loose enough grip for some to slip into the interior of the tumor. "A lot of people in the field had a very simple concept—we put a chemotherapy drug on an antibody, it targets it to the cancer cell, and it will avoid healthy tissue," Thurber says. "That's not at all how they work in reality."

> "Almost every patient who was enrolled on that drug had benefits. It was really so satisfying."
>
> —SHANU MODI *MSK CANCER CENTER*

Tinkering with the drug component of ADCs, as well as the antibody, eventually led to a cancer-killing sweet spot. In 2013 the FDA greenlit T-DM1 for breast cancer. Its antibody is trastuzumab (the "T" in T-DM1), the same antibody used in Herceptin. The drug attached to this antibody is notable because it's too dangerous to be used on its own. Known as emtansine, it was initially discovered in the 1970s but shelved because it was too toxic to too many cells. Tethered together as T-DM1, however, the drug and antibody generally stayed away from healthy cells and proved to be a potent and precise combination.

In the early 2000s Modi helped to conduct a trial of T-DM1—branded Kadcyla by its maker, Genentech—in people who had an especially difficult disease: advanced HER2-positive breast cancer that had spread throughout the body. Only those who had run out of other treatment options were enrolled. "We were taking people who in some cases were really looking to go to hospice," Modi says. Yet "almost every patient who was enrolled on that drug had benefits. It was really so satisfying."

In another trial of about 1,500 people with early breast cancer, an interim data analysis, published in 2019, estimated that 88 percent of those who received T-DM1 would be cancer-free three years later, compared with just 77 percent of those who received Herceptin alone. The drug has proved "more active than most of the therapies we were giving to patients, and it was associated with a better safety profile," Modi says.

Kadcyla's success against difficult-to-treat cancers didn't just transform some patients' lives. It pumped enthusiasm—and, perhaps more important, pharmaceutical industry dollars—into the idea of ADCs. Researchers now knew that when pieced together correctly, it was possible to load an antibody with drugs too toxic to be used otherwise and still produce a medicine that worked better than traditional chemotherapy.

Several similarly designed ADCs have been approved for a range of different cancer types. Many of these carry drugs that inhibit the enzyme topoisomerase 1, which is essential for DNA replication. Like emtansine, the drug used in Kadcyla, newer topoisomerase inhibitors are too toxic to be used as free-standing drugs but are much less harmful when they're largely restricted to tumor cells. And Kadcyla

itself, after being shown to slow or stall late-stage breast cancer, has been tested on patients with very early-stage disease to see whether treatment at that point can not only slow cancer down but actually cure it. Its success "was sort of the catalyst for continued exploration," Modi says. "Can we build on this? Can we do even better?"

DOING BETTER, it turns out, involves designing good linker molecules that tie the antibody to the drug. These tiny structures act like chemical triggers. They must remain perfectly stable until they reach their target, then unclip from the antibody to discharge their payload at the tumor. Some of the earliest attempts at making ADCs failed not because of their antibodies or drugs but as a result of unstable linkers.

Modern ADCs rely on two types of linkers. One kind remains unbroken even when the ADC reaches its target. The other kind, known as cleavable linkers, are chemicals that break in response to very specific cues, such as enzymes that are abundant in tumors, in the spaces between individual cancer cells. Once an ADC is within the tumor's boundaries, these enzymes cleave the linker and release the drug payload.

Cleavable linkers are showing impressive advantages, and the majority of currently approved ADCs now use them. An ADC with a noncleavable linker will kill only the cell it attaches to, but one that splits up could place drug molecules near neighboring tumor cells and destroy them as well. This so-called bystander effect can make the drugs much more effective, Thurber says.

Enhertu, for instance, uses the same antibody as Kadcyla but with a cleavable linker (Kadcyla uses a noncleavable version) and a different drug. Each Enhertu antibody carries approximately eight drug molecules, compared with about three per antibody in Kadcyla. In one study, researchers compared the effects of these two drugs in people with HER2-positive breast cancers. Enhertu was the clear winner. It stopped tumor growth for more than two years on average, whereas Kadcyla did so for just six months. "It was a landslide in terms of how much better it was," Tolaney says. "It's a really nice example of how ADC technology leads to dramatic differences in outcomes."

The bystander effect also explains, in part, why Enhertu is effective against tumors that have barely any HER2: once the ADC enters a tumor and the drug molecules detach, they can kill neighboring tumor cells even if those bystanders don't carry much HER2 on their surface. This action, along with the use of a diagnostic test that can miss extremely low HER2 levels, could explain the results from the trial where the drug seemed to work on tumors with no HER2. That trial employed an assay known as an IHC test. It is generally used to categorize cancers as HER2 positive or negative, not to measure the amount of the protein present. A negative result typically means 10 percent or fewer of the tumor's cells have HER2 on their surfaces. Yet 10 percent may be enough to attract a few Enhertu particles, and the bystander effect might be sufficient to destroy tumor cells, Modi says.

Enhertu is not the only ADC that appears to work this way. In a 2022 study, researchers found that Trodelvy, an ADC that targets a surface protein known as TROP2, seemed to be more effective than standard chemotherapy for people with metastatic triple-negative breast cancer, a particularly hard-to-treat disease. Trodelvy was better irrespective of how much or how little TROP2 was detected on tumors. "That, to me, is wild," Tolaney says. "We're excited about it because these cancers are having benefits [apparently] without the target."

This new generation of ADCs is making a difference in other types of cancers previously thought to be intractable, such as metastatic bladder cancer. In 2021 the FDA approved Trodelvy and another ADC named Padcev to treat this illness. For 30 years the standard of care for this type of bladder cancer was chemotherapy alone, says oncologist David J. Benjamin, who treats genitourinary cancers at Hoag Family Cancer Institute in southern California. "Now we have multiple new treatments, and two of them happen to be antibody-drug conjugates," Benjamin says. In clinical trials for patients with advanced bladder cancer, Padcev combined with a drug that stimulates the immune system shrank tumors or stalled their growth in more than 60 percent of people. In a whopping 30 percent of those who received the two-drug combination, their cancer completely disappeared—an unprecedented success.

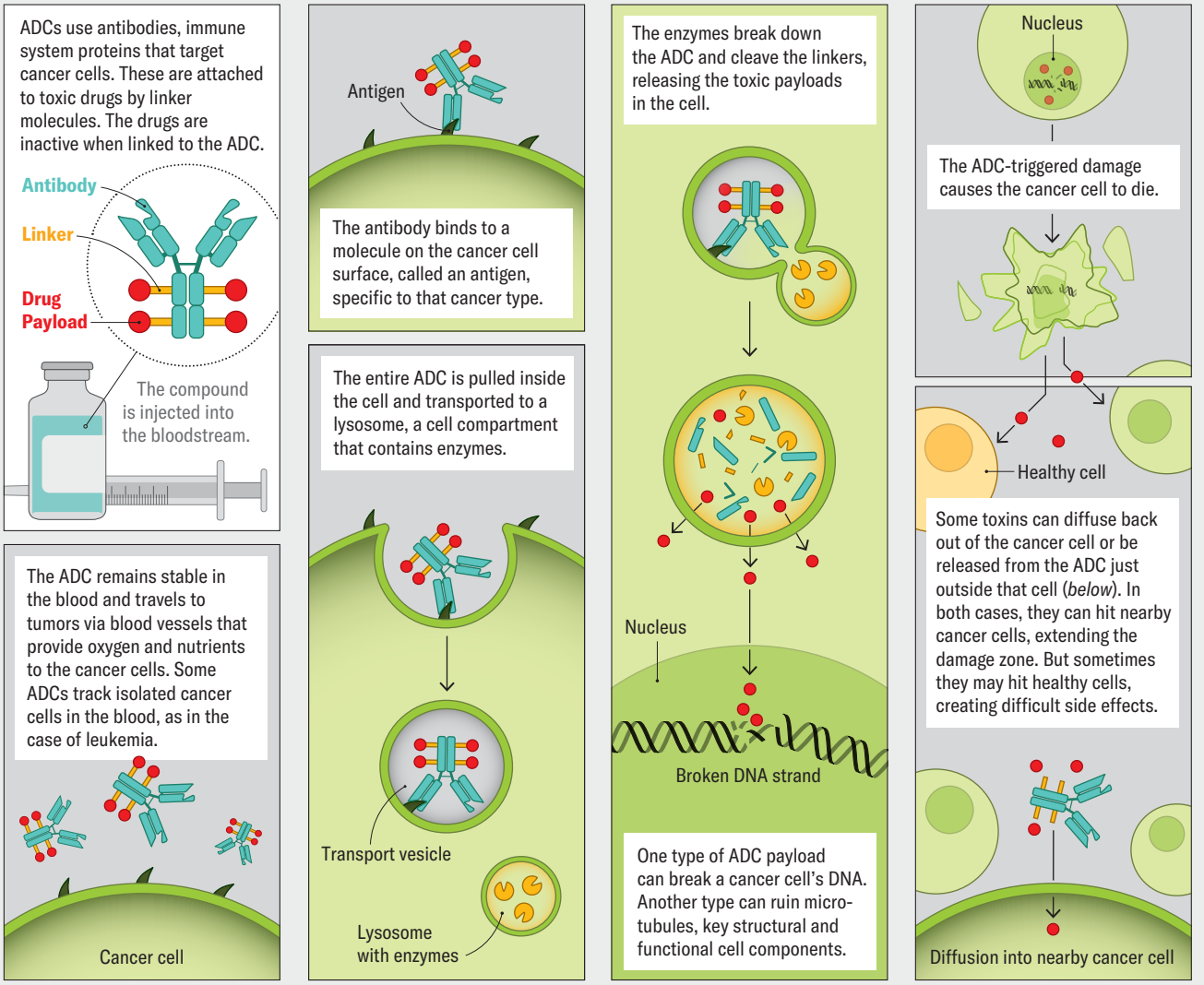
BUT EVEN NEWER ADCS aren't without problems. The bystander effect, which makes them so effective, can spread far enough from the tumor to affect healthy cells, causing hair loss, nausea, diarrhea, fatigue, and other side effects that are disturbingly similar to the fallout of old-school chemo. ADCs also have been linked to a variety of eye problems ranging from conjunctivitis to severe vision loss.

Another explanation for these nasty effects is that there are no protein targets that are exclusive to cancer cells. These proteins, also known as antigens, are more abundant in cancers but may appear in normal cells. That makes some binding of ADCs to healthy cells unavoidable. "I can't think of any examples of true tumor-specific antigens," says Matthew Vander Heiden, a molecular biologist at the Koch Institute at the Massachusetts Institute of Technology. Further, ADCs, like any other medicine or antibody, are eventually ingested and metabolized by noncancerous cells. This process fragments them into smaller pieces, releasing payload drugs from their linkers and triggering reactions.

Still, the ability to take ADCs apart and tweak their components—something that isn't possible with traditional treatments—offers researchers the chance to find versions with fewer side effects and more advantages. Most ADCs have been used at the maximum

Antibody-Drug Conjugates Home in on Cancer

A promising class of drugs combines the ability to hunt cancer cells—and ignore healthy ones—with the power to deliver a tumor-destroying payload. Called antibody-drug conjugates (ADCs), they are made of several parts that can be adapted to numerous cancer types and fine-tuned to achieve different toxic effects.



dose a person can tolerate. That might not be true with future versions. When developing a medication, whether it's a simple painkiller, a chemotherapy or an ADC, researchers begin by figuring out the lowest dose at which the drug is effective. Then they work out the highest dose that people can receive safely. The space between those two doses, known as a therapeutic window, is usually small. But the ability to swap components offers ADC researchers many routes to widening it. Eventually drugmakers might create ADCs so effective that patients never need to take the highest tolerable dose—a much lower one would eliminate tumors without creating unintended consequences such as nausea or hair loss.

Shifting away from toxic chemotherapy-based drugs as payloads could also reduce side effects. Some approved ADCs, for instance, link antibodies to drugs that can activate the body's own immune system to attack cancer cells rather than relying on cell-poisoning chemicals. In addition, scientists are exploring ways to deliver radiation therapy directly to tumors by tethering antibodies to radioisotopes. Joshua Z. Drago, an oncologist at MSK Cancer Center, says that with the right kind of linkers, ADCs "could theoretically deliver any kind of small-molecule medication."

Ultimately, recombined and improved components could lead to the type of swap that cancer patients really care about: exchanging their disease for a cure. ●

Jyoti Madhusoodanan is a health and science journalist based in Portland, Ore. She has a Ph.D. in microbiology.

Graphics consultant: Greg Thurber/University of Michigan

Graphic by Jen Christiansen

Workouts Help to Treat Cancer

Exercise improves survival, limits recurrence, and can be used with surgery and drugs

BY LYDIA DENWORTH | ILLUSTRATION BY JAY BENDT

TO IMPROVE THE QUALITY OF LIFE OF PEOPLE WITH CANCER, oncologists have regularly recommended exercise. Staying fit can make patients feel and function better. But exercise itself was never considered a formal treatment for the disease.

"The thinking in the medical community was that you need biomedical interventions—surgery, radiation therapy, drugs—to treat cancer," says Kerry Courneya, a professor of kinesiology at the University of Alberta who studies physical activity and cancer.

That thinking is changing. Recently strong evidence emerged that exercise lengthens survival times and lowers recurrence risk for several cancer types. Such benefits are usually ascribed to medicine or surgery. But "exercise treats cancer as well as, if not better than, some of the current drugs that we're offering our patients," says Courneya, who led the first large randomized, controlled trial of the effects of workouts on cancer outcomes. It was published in July 2025 in the *New England Journal of Medicine* and involved more than 800 colon cancer patients. Participants with stage 3 and high-risk stage 2 cancer were assigned to a structured exercise program in addition to their oncology care. In a 10-year follow-up period, these people had a 28 percent lower risk of cancer recurrence, new cancers or death than similar patients who received only educational material about physical activity.

These results prompted a standing ovation when presented to the American Society of Clinical Oncology at a meeting last June. They're not the only good news in the field. For 10 different kinds of cancer—breast, prostate, colon, lung, oral, endometrial, respiratory, rectal, bladder and kidney—a 2025 longitudinal study of more than 90,000 cancer survivors in the U.S. found that people survived longer if they engaged in moderate to vigorous physical activity after their diagnosis. Even small amounts of exercise made a difference, but 150 to 300 minutes a week

of moderate-intensity activity, such as brisk walking, was the most effective intervention.

There was a modest additional benefit with higher levels of activity. (Overall, the effect size varied for different cancer types.) Randomized trials of exercise interventions are now underway for breast, ovarian, esophageal and lung cancer, among others.

There had been early hints that exercise provided this kind of help. For instance, a 2011 study showed that men with prostate cancer who did three or more hours of vigorous exercise a week had a reduced risk of death from the disease. Other studies had similar results for breast and colon cancer.

What is it that exercise is doing inside the body that has this therapeutic effect? Exercise triggers so many biological changes at once that it's hard to say for sure. But there are several possibilities, and it's likely they work in combination.

A reduction in overall inflammation is probably a factor, says epidemiologist Stacey Kenfield of the University of California, San Francisco. Another important benefit of exercise is that it makes it easier for the hormone insulin to bind to cells, which brings them fresh energy. When insulin isn't able to bind, the body starts to make more. That's bad because cancer cells may use insulin to grow and divide more quickly.

Myokines, which are proteins released by muscle tissue, could also be important. In the laboratory, serum with high amounts of myokines reduced the growth of prostate cancer cell lines. In studies of men with prostate cancer published in 2022, Kenfield and her colleagues found that participants' levels of myokines were elevated right after a half hour of training with vigorous exercise compared with their levels before the workout. They also found that a supervised exercise program raised levels more than less regimented exercise.

Workouts also seem to mobilize parts of the immune system that keep cancer in check, says immunologist Per thor Straten of the Center for Cancer Immune Therapy in Denmark. In mice, he has shown that voluntary exercise leads to an influx of immune cells into tumors, as well as a more than 60 percent reduction in tumor incidence and growth. During exercise, Straten says, immune system components called natural killer cells and T cells increase significantly in number. "They're really effective killers against cancer cells," he says.

Straten and his colleagues are working on an ongoing randomized trial for lung cancer patients, and they hope it will show that this immune response occurs in people. Supporting findings have appeared in early data from a 2025 study in the U.K. In a small randomized trial of patients with esophageal cancer, half of the participants engaged in structured exercise while undergoing chemotherapy, and half were in a group without a structured program. The tumors of patients who were exercising appear to contain more T cells and natural killer cells.

Recently strong evidence emerged that exercise lengthens survival times and lowers recurrence risk for several cancer types.

Experts say the regularity and intensity of exercise matter. "You need to get the heartbeat up" to stimulate the immune system, Straten says. In the colon cancer study, participants chose their type of exercise but received support such as supervised workout sessions and guidance on behavioral change. That helped them stick with the program, Courneya says. "You can't just advise people to do more exercise and expect them to do it," he explains.

Now many cancer centers are assessing how to provide that kind of support in addition to their medical offerings. If they don't, experts say, the centers won't be delivering on a new standard of care. ●

Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American.* She is author of *Friendship* (W. W. Norton, 2020).

A Double Aging Puzzle

Research suggests that waves of aging-related changes occur at two distinct points in our life

BY SAIMA S. IQBAL | GRAPHIC BY AMANDA MONTAÑEZ

AS A PERSON ENTERS THEIR 60S, THE health effects of aging often start to become strikingly clear. Many people begin to use glasses or hearing aids, or their doctors warn them about a sharply increased risk of diabetes or heart disease. But research suggests that our bodies may undergo a dramatic wave of age-related molecular changes not only in our 60s but also in our mid-40s.

For a study published in 2024 in *Nature Aging,* researchers tracked the levels of more than 135,000 molecules and microbes, all reflective of activity in cells and tissues, in 108 healthy volunteers aged 25 to 75. Each volunteer contributed biological specimens, including blood and stool samples, every three to six months for a median of 1.7 years. Results showed that changes in many molecule and microbe levels clustered around two distinct time points: ages 44 and 60. The findings suggest that aging might accelerate around those periods—and they signal to experts that our 40s and 50s may be a significant time to closely monitor health.

The study supports many people's anecdotal reports of noticing changes in their 40s that range from more muscle injuries to worse hangovers, and the data give clues as to why, says senior study author Michael P. Snyder, a genetics researcher at Stanford Medicine.

Compared with younger participants, people in their 40s and 60s displayed biological differences that appeared to be linked to muscle weakness and loss, declines in heart health, and inefficient caffeine metabolism. Those in their 40s also had reduced activity in cellular pathways responsible for breaking down alcohol and fats—possibly a sign that people start to digest these compounds more slowly around this age. People in their 60s, meanwhile, had lower levels of various immune system molecules, such as inflammatory cytokines, which corresponded to a weakened immune response. They also showed significant differences in levels of certain molecules associated with carbohydrate digestion and heart and kidney function, suggesting that the older participants were more susceptible to type 2 diabetes, cardiovascular disease and kidney issues.

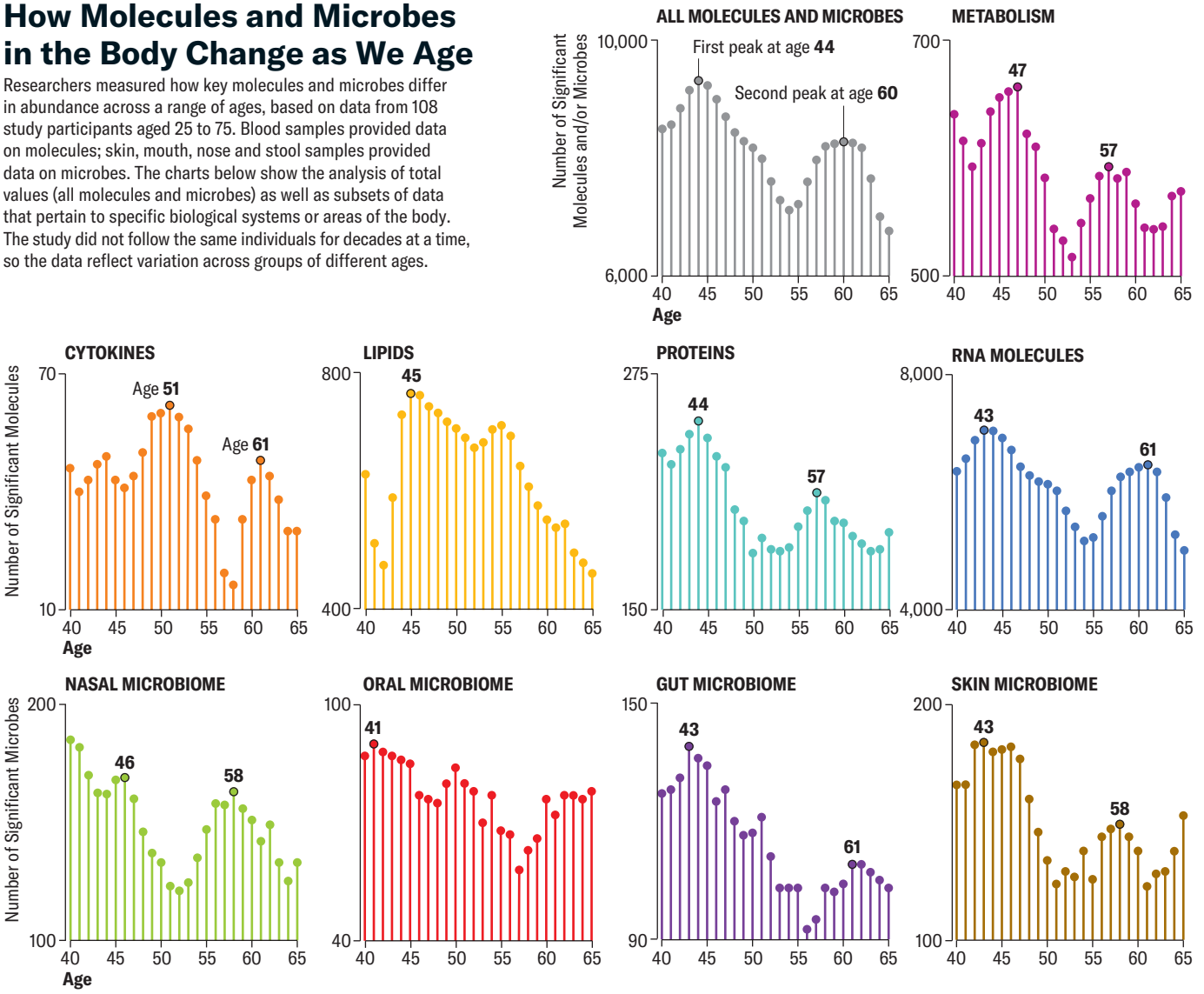
> The data give clues to why people often report experiencing more muscle injuries and worse hangovers in their 40s, the study authors say.

The study's time points are similar to those identified in a 2020 study, in which researchers found that participants' immune systems grew markedly less adept at fighting off pathogens in their late 30s to early 40s and again around age 65. But the newer study's findings are not ironclad; it included a relatively small number of people, all living in California's Palo Alto area. The resulting lack of geographic diversity makes the data less representative of the broader public, notes Aditi Gurkar, who conducts aging-related research at the University of Pittsburgh and was not involved in the *Nature Aging* study. Those sampled likely had some lifestyle factors in common, such as diet, exercise and environmental exposures, which could have swayed the results, she says.

The study also did not follow any individuals for periods longer than about seven years, so scientists cannot be certain that the differences between people in different age groups reflect universal changes. For example, the 40- and 60-year-olds in the study might have aged faster relative to others of the same age in the broader population, Gurkar cautions. She and others say the best way to confirm the results—and to precisely trace age-related biological

How Molecules and Microbes in the Body Change as We Age

Researchers measured how key molecules and microbes differ in abundance across a range of ages, based on data from 108 study participants aged 25 to 75. Blood samples provided data on molecules; skin, mouth, nose and stool samples provided data on microbes. The charts below show the analysis of total values (all molecules and microbes) as well as subsets of data that pertain to specific biological systems or areas of the body. The study did not follow the same individuals for decades at a time, so the data reflect variation across groups of different ages.



shifts—would be through a larger study that tracks the same participants over the course of a lifespan. Collecting data on factors such as disease status, physical function or disability could also help researchers better assess the extent to which age-related shifts affect a person's overall health. (The amount of stress that cells and tissues undergo—referred to as biological aging—varies widely between people of different races and socioeconomic classes, and it even differs between individual organs in a person's body.)

The reasons ages 44 and 60 might be turning points in health are not yet apparent, but the study authors say several hypotheses could be probed in other work. Snyder suspects that for people in their 60s, declines in immune system function might precipitate more widespread organ breakdown. A midlife decline in physical activity, meanwhile, could explain the differences seen among people in their 40s—but so might hormonal changes, including menopause. Menopause alone, however, could not explain the trends in the study, Snyder says: male and female participants appeared to show the same degree of age-related differences at both time points.

Snyder suggests these data can provide actionable health information. People in their 40s might benefit from getting blood tests that track lipid levels, for instance, or from exercising regularly to maintain heart health. He also underscores the importance of early and regular screenings for heart disease for people in this age range who have existing health conditions.

Limitations aside, Gurkar says, the study is a powerful reminder that lifestyle choices such as diet and exercise can accelerate aging—or slow it down. Few studies on aging focus on middle-aged participants or involve biological sampling as comprehensive as that of this paper, she adds. In addition to identifying potential waves of age-related changes, the work provides a crucial first step toward large-scale disease-prediction models based on biological data. ●

Saima S. Iqbal is a science writer who knows many interesting things about the sciences.

Source: "Nonlinear Dynamics of Multi-omics Profiles during Human Aging," by Xiaotao Shen et al.; in *Nature Aging*, Vol. 4; November 2024

WOMEN AT RISK

Nearly four of every five people with autoimmune disorders are female. Sex hormones, genes and even gut bacteria may be reasons why

BY MELINDA WENNER MOYER

ILLUSTRATION BY HAYLEY WALL

MELANIE SEE'S FIRST BOUT of odd symptoms began in 2005. Suddenly she started sweating a lot. She rapidly lost 10 pounds. She got dizzy walking from the bedroom to the couch. She started lactating even though she was not nursing a baby. After a slew of laboratory tests, See, then 45, was diagnosed with Graves' disease, an autoimmune disorder that makes thyroid hormones surge.

Three years later, when See's symptoms from Graves' were under control with medication, her health took another rapid downturn. She lost more weight. She felt extremely tired. Her doctors diagnosed her with celiac disease, another autoimmune disease, which in affected people is set off by eating foods with gluten. Then, in 2015, See began experiencing terrible digestive symptoms and muscle pain. This time her doctors were stumped. "Initial diagnoses were all over the place—vasculitis, lupus, I can't remember what all," See says. "My blood work showed that something was going on, as did the muscle biopsy I had in June 2016, but I didn't fit into any particular box."

After many tests, See was diagnosed with yet a third autoimmune illness: mixed connective tissue disease, a rare ailment that shares some features of lupus.

Women account for an estimated—and astonishing—78 percent of people who have these disorders, which include See's afflictions, as well as lupus, multiple sclerosis, rheumatoid arthritis, and other illnesses in which the body's immune system mistakenly attacks its own cells and tissues. Autoimmune diseases are now among the top 10 causes of death worldwide in women younger than 65.

Why women are so much more likely than men to be plagued by autoimmunity has long been a mystery, but researchers are beginning to narrow down the causes: the different effects of sex hormones, of women's X chromosomes, and even of the community of microbes inside us, which develops differently depending on sex. Evolution may also play a role in the staggering differences observed in autoimmunity, some scientists think. Because autoimmunity is much more common in women, researchers have suggested it might be an evolutionary relic—immune hypervigilance could have given women a reproductive advantage by improving the chances of a successful pregnancy, even if it came at the cost of increased disease risk.

"It is important to understand the underlying biology of these sex differences," says Shannon Dunn, an immunologist at the University of Toronto. "If we can unravel this, we will not only better comprehend how autoimmune diseases get started and find new ways for intervention, but we will also shed light on the sex differences in how humans respond to infection, vaccination, injury and cancer."

THE WILDLY UNEVEN BURDEN of autoimmune diseases is not a new observation. Well over a century ago, when doctors first began diagnosing these conditions, they noticed that women were much more likely to develop such illnesses than men. But back then, doctors tended to think of individual autoimmune diseases as distinct entities with their own unique causes. There was little awareness that they might all be connected in fundamental ways and that they might affect women more often for these shared biological reasons.

Everything changed in the early 1990s, when scientists found that some autoimmune diseases have biological mechanisms in common. Among other things, researchers discovered that immune cells known as $CD4^+$ T helper cells were involved in rheumatoid arthritis, multiple sclerosis and type 1 diabetes. And in 1991 a woman with lupus named Virginia Ladd founded the American Autoimmune Related Diseases Association after discovering that a number of autoimmune diseases plagued various members of her family, suggesting a shared genetic inheritance.

Once researchers began to think of autoimmune diseases as a collection, they started to notice interesting patterns. One was that some of these conditions arise in women after key life transitions. (Almost all of this research has involved cisgender women.) Lupus and multiple sclerosis, for instance, tend to first appear during the childbearing years. Other diseases, such as rheumatoid arthritis, most commonly arise after menopause. Big autoimmune changes can also take place during pregnancy: symptoms in women with rheumatoid arthritis, multiple sclerosis and Graves' disease often wane during pregnancy, whereas in women with lupus symptoms often get worse.

What do all these transitions—puberty, pregnancy

and menopause—have in common? They all involve major changes in the hormones estrogen, progesterone and testosterone. Estrogen levels go up, for instance, during puberty and pregnancy. It is now clear that, although there are exceptions, many autoimmune diseases "are driven by estrogen," says DeLisa Fairweather, a microbiologist and immunologist at the Mayo Clinic in Jacksonville, Fla. Indeed, the use of oral contraceptives and hormone-replacement therapy, both of which add estrogen to the body, has been linked to an increased risk for lupus.

Estrogen, like the other sex hormones, directly influences the expression of a number of genes involved in immunity. For instance, it attaches to and turns on the gene that codes for interferon gamma, a chemical that orchestrates immune responses against pathogens but that can also escalate autoimmune responses. Estrogen also activates B cells, which produce antibodies, proteins that mark and attack foreign substances. But some, known as autoantibodies, can also attack cells made by the body.

Hormones that play key roles in pregnancy, such as progesterone, have dramatic immune effects, too. Many critical immune cells, including T cells and macrophages, feature receptors for progesterone on their surface. When progesterone binds to these receptors, it shifts the body toward a kind of immune response that favors the production of antibodies and autoantibodies. This reaction is known as a Th2 immune response, for type 2 T helper cells. It contrasts with Th1 immune responses, which move the body away from antibody manufacturing and instead activate cells that attack other cells directly.

The rise in progesterone during pregnancy could explain why symptoms of rheumatoid arthritis and multiple sclerosis often wane when women are expecting—these diseases are driven by Th1, not Th2, immune responses, so the progesterone-induced shift eases their immune burden. But "women with multiple sclerosis are at a much higher risk of having a relapse shortly after delivery. And that has to do with the dramatic change and reduction in sex hormones," says Tanuja Chitnis, a neurologist at Brigham and Women's Hospital in Boston.

Testosterone, which women produce but to a lesser degree than men, is another important hormone when it comes to autoimmunity. Receptors for testosterone are found on the surface of B and T cells, and the hormone is largely immunosuppressive. It decreases the responses of immune cells, including neutrophils, natural killer cells and macrophages—which could be one reason that men tend to have lower rates of autoimmune disease. Research has found that men with multiple sclerosis often have lower than normal levels of testosterone and that men with low testosterone because of a condition known as hypogonadism are at increased risk for lupus and rheumatoid arthritis.

All these sex hormones can also affect the expression of key immune genes. In 1997 a consortium of Finnish and German scientists discovered a gene that plays a crucial part in autoimmunity. This gene, which they named *AIRE,* for "autoimmune regulator," is expressed by cells in the thymus, an organ that makes T cells. *AIRE* ensures that key body proteins are shown to developing T cells, and these encounters teach T cells that the proteins are friends, not foes. Also thanks in part to *AIRE,* T cells that start attacking these friendly proteins are destroyed in the thymus before they can be released into the rest of the body, where they could do damage.

Not surprisingly, people in whom *AIRE* is missing or mutated are more likely to develop certain autoimmune diseases. That is because T cells that should be eliminated are not, and "they end up going out into your body and causing autoimmune disease," Dunn says.

As it turns out, *AIRE*'s activity—and that of other, similar genes—is partially controlled by sex hormones. In a 2016 study, researchers at the Sorbonne in Paris showed that in mice, estrogen and progesterone turn down *AIRE* expression, meaning they cause less of the protein it encodes to be made, whereas testosterone ensures that more AIRE protein is made. The researchers also found that after puberty, women tend to make less AIRE than men do, perhaps because of the influence of sex hormones. Less AIRE means that more self-reactive T cells can escape from the thymus and cause autoimmune disease.

Yet despite their influential roles, sex hormones cannot be the whole story. Autoimmune diseases, including lupus and multiple sclerosis, sometimes develop in childhood, before hormones such as estrogen and progesterone ramp up during puberty. This means that other processes must be involved. To find them, some researchers are studying a primary difference between men and women that arises well before birth: the presence or absence of a second X chromosome.

BIOLOGICAL DOGMA holds that women have two X chromosomes, but one copy is turned off in every cell very early in embryonic development in a process known as X inactivation. The extra X chromosome becomes a dark, misshapen mass that persists silently in each cell lineage. This shutdown ensures that the body does not express more X-linked genes than it should. But in recent years scientists have discovered that X inactivation does not happen the way they thought it did. Studies show that at least 15 percent of the genes on the supposedly inactivated X chromosome are still turned on, which means, essentially, that those genes tell women's bodies to make twice the amount of certain proteins compared with levels in men. In women with lupus, for instance, some genes are active on both X copies, and this higher activity correlates with disease severity: sicker lupus patients have more active X-linked genes than women with milder disease.

In fact, many X-linked genes have been directly tied to autoimmune disease. One of them is a gene for toll-

like receptor 7, or TLR-7, a protein that has been implicated in autoimmune disorders such as lupus, polymyositis, scleroderma and Sjogren's syndrome. TLR-7's job is to recognize pathogens and alert other immune cells to their presence; it also increases the production of inflammatory immune chemicals known as interferons, which can ramp up the autoimmune response. Another gene that is often activated on supposedly inactivated X chromosomes in women is *TASL,* and it, too, increases interferon production, to the point where women have at least twice as much of the protein, says Hal Scofield, a physician scientist at the University of Oklahoma Health Sciences Center who studies the role of X inactivation in autoimmune disease.

In the past several years scientists uncovered something bizarre about X inactivation that also supports its role in autoimmunity. Women's inactive X chromosome is maintained in an especially strange way in T and B cells, which are actively involved in immune responses. In 2019 Montserrat Anguera, a biomedical scientist at the University of Pennsylvania, and her colleagues observed that when young immune cells in female mice mature, the cellular mechanisms in place to cover and inactivate their second X chromosome undergo significant, dynamic changes that could make it easier for X-linked genes in these cells to get turned on when they should be off. It was a "crazy discovery," Anguera says.

No one thought that females' immune cells did anything different with regard to X inactivation than other cells did, but it turns out they do—in ways that could directly shape the risk for autoimmunity. In June 2021 Anguera and her team found that B cells in girls and women with lupus evade the normal cellular mechanisms for X inactivation, which likely allows the cells to make more X-linked proteins than they should.

What happens to people with unusual numbers of X chromosomes also points to their important role in autoimmunity. Men with Klinefelter's syndrome, for instance, have two X chromosomes along with a Y chromosome, and they are 14 times more likely than other men to develop lupus. Similarly, women with trisomy X, who have three X chromosomes, are 2.5 and 2.9 times more likely than other women to develop lupus and Sjogren's syndrome, respectively.

Why do women's bodies have these strange mechanisms that increase the risk of disease? Typically, over time evolution eliminates processes that make it harder for species to reproduce and thrive, and X-linked autoimmunity definitely hinders thriving. This paradox suggests to evolutionary biologists that the phenomenon might also provide some significant benefit.

In a 2019 paper in *Trends in Genetics,* Melissa Wilson, a computational and evolutionary biologist at Arizona State University, and her colleagues outlined their pregnancy compensation hypothesis, which is based in part on evolutionary observations. The evolution of the placenta—an organ that provides oxygen and nutrients to fetuses during pregnancy—occurred at the same time mammals evolved sex chromosomes, and it also coincided with the sudden addition of many more genes to the X chromosome. These three developments could all be related.

During pregnancy, women have to tolerate the growth of the fetus, in which half the DNA is foreign because it comes from the father. This outside origin creates cells that the immune system would normally attack. Women also must tolerate the placenta, which is made by the fetus. Perhaps, Wilson says, X-linked genes and incomplete X inactivation evolved as a way for a woman's body to flexibly respond to the strange new immune requirements of pregnancy. During pregnancy, immunity shifts in dynamic ways: Early in pregnancy, certain healthy immune responses increase, which helps the placenta grow new blood vessels; in the middle of pregnancy, immunity decreases. Then immune responses and inflammation increase again in anticipation of labor.

Other observations align with the predictions of the pregnancy compensation hypothesis. For instance, women today spend a much smaller proportion of their lives pregnant than they did hundreds of years ago, which means that women's immune systems are not suppressed as often as they used to be. This could help explain why autoimmune diseases are increasing among women today, as well as why they were less of a burden in the past. Although validating this hypothesis requires much more research, Wilson says it is possible that "placentation and pregnancy are critical in shaping maternal immune systems, which in turn could suggest why we have these sex differences in disease." Put another way, autoimmunity may be an unfortunate by-product of the complex immune response women need to bear children.

NOT EVERYTHING IN THE BODY is determined by genetics—far from it. One identical twin may develop an autoimmune disease while the other twin, who shares the same genome, does not. The environment is a big piece of the puzzle. It is still unclear which outside exposures might be most important, but research is starting to implicate microbial infections, chemicals such as endocrine disruptors, smoking, diet, stress and the "good" commensal bacteria that live in the intestines.

Some fascinating work in animals points to gut bacteria—collectively referred to as the intestinal microbiome—as a driver of excessive autoimmune disease risk. Jayne Danska, an immunologist and biophysicist at the University of Toronto, has spent much of her career trying to understand the relation between sex and the genetics of autoimmune disease—essentially, whether genes that increase the risk for autoimmunity have varying effects on men versus women. But in 2012 she made a serendipitous discovery that launched her work in a surprising new direction. "It's one of the adages of science that you find the best things that you weren't looking for," she says.

Danska and her team were trying to find risk genes for type 1 diabetes, an autoimmune disease in which the body attacks the insulin-producing beta cells in the pancreas. They were using a lab-bred type of rodent known as nonobese diabetic (NOD) mice. The mice are good models for the human disease, with one striking exception: men and women are equally likely to develop type 1 diabetes—it is one of the few autoimmune diseases that does not predominantly affect women—but in NOD mice, the disease is twice as likely to arise in females.

Danska knew that environmental factors sometimes interact with genes, and she had been looking at gut bacteria as a risk factor. She started to wonder whether, in her mice, gut bacteria differences might be related to the skewed diabetes ratio. To find out, she and her colleagues grew a subset of NOD mice in a germ-free environment, devoid of bacteria and viruses, including the commensal bacteria that normally populate the intestines.

That is when Danska made her first surprising discovery. When she looked at how many of the germ-free animals developed diabetes as adults, "the sex difference went away completely," she recalls. The males were suddenly just as likely to develop diabetes as the females were. "This was a huge finding that we hadn't expected. I just couldn't believe it was true."

But repeating the experiment showed the same effect. Then more work led to more surprises. The researchers took the bacteria from adult male NOD mice and put them into young female NOD mice that had not yet developed diabetes. The female mice then grew into healthy adults without the disease.

Danska's findings, which were published in 2013 in *Science,* provided the first evidence that "the microbes in the gut can influence female-biased autoimmunity," says Martin Kriegel, a rheumatologist and clinical immunologist at the University of Münster in Germany. It is an important finding, he says, that scientists are still working to understand.

No one knows yet why males' gut microbes seem protective. One thing Danska and her team have determined, though, is that testosterone is crucial: When they drew blood from germ-free NOD mice, they found that the diabetes-prone males had lower levels of circulating testosterone than microbe-laden males usually do. And when female mice were colonized with microbes from males and were apparently protected from disease, they had higher circulating levels of testosterone than females with microbes usually do.

All of this suggests that there is something about the microbes in males that increases testosterone and is protective. When Danska and her colleagues took gut microbes out of male mice and put them into the guts of female mice, then blocked testosterone signaling in their bodies, they were again at an increased risk for type 1 diabetes. The findings align with lupus research in men showing that suppressed testosterone appears to raise their risk of that disorder. (The research also lines up with work in a strain of mice in which females are especially prone to lupus. Removing gut bacteria from these female rodents lowers their risk, scientists at the Medical University of South Carolina reported in 2020 in the *Journal of Immunology.*)

It is unclear how microbes might regulate testosterone, or vice versa. Danska's research suggests that the composition of commensal microbes diverges in male and female mice around puberty, so something seems to happen to the bacteria around that time. This may even explain why there is not much of a sex difference in the prevalence of type 1 diabetes in people; the disease typically develops before puberty, before microbes would have a chance to shape risk based on sex. It could be that the microbes are affected by puberty's sudden influx of sex hormones, but it is almost certainly "a two-way road," Kriegel says—the microbes respond to sex hormones, and the sex hormones respond to microbes.

Autoimmunity may be an unfortunate by-product of the complex immune response women need to bear children.

OF COURSE, MICE ARE NOT PEOPLE. But Danska believes that her findings have significant implications for autoimmune diseases that do skew toward women. Perhaps some gut bacteria in women are critical in the development of autoimmunity. If so, tinkering with gut microbes might enable us to thwart disease.

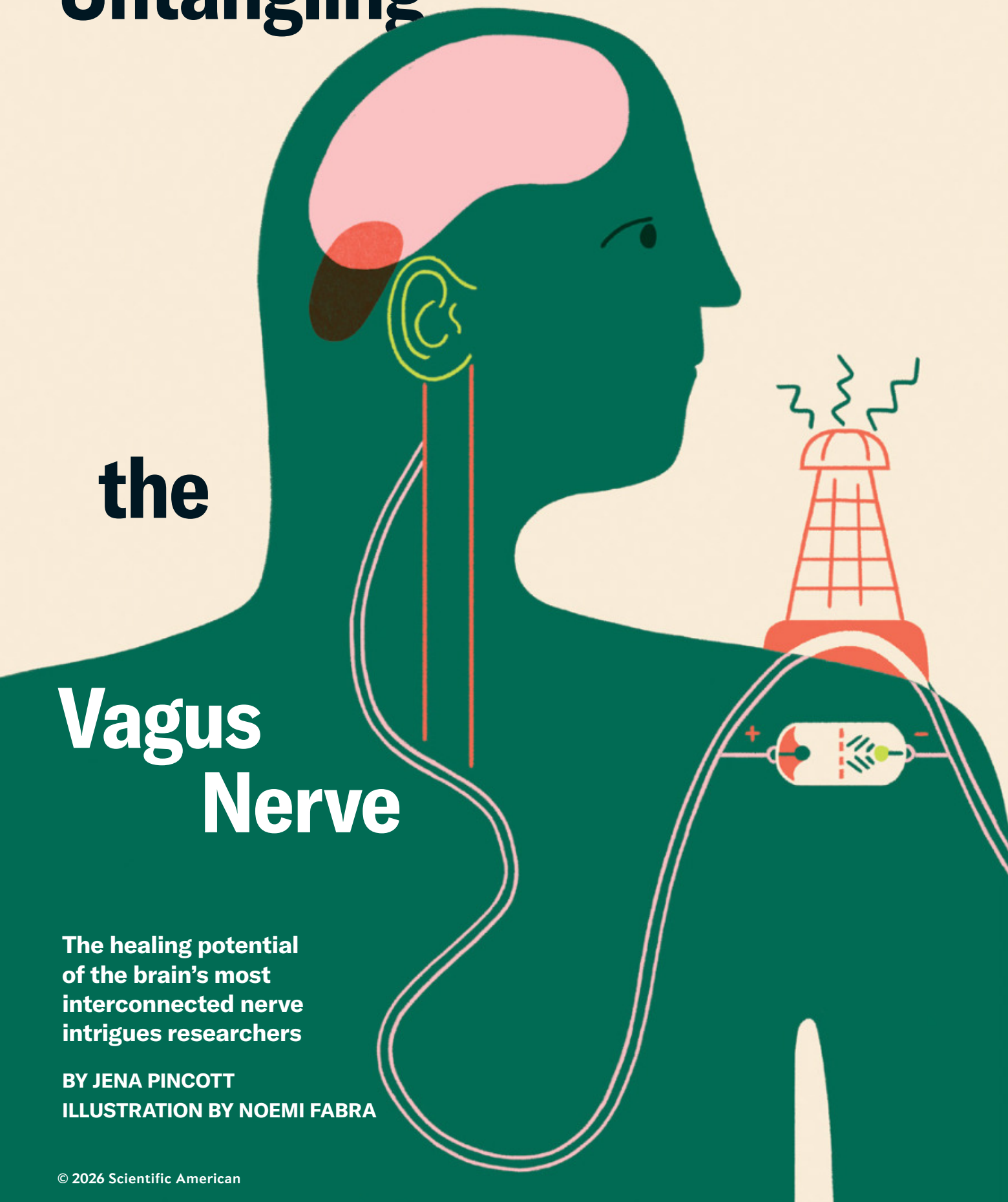
Danska and Kriegel hope it may be possible to develop targeted microbe-based therapies for women at high risk for autoimmune diseases—therapies that can shape the microbiome in protective ways. Other researchers are looking at ways to tweak sex hormone signaling to temper risk. The more scientists learn about why women are vulnerable, the more chances there may be to intervene before diseases develop.

Given that X chromosomes, female sex hormones and female gut bacteria all appear to increase the risk for autoimmunity, it might seem as though biology is somehow conspiring against the female sex. But this autoimmune burden can be seen in another way, too: as a reflection of the importance of women for the survival of our species. "Females have to do all kinds of absolutely remarkable things from an immunological perspective that males just aren't called on to do," Danska says. Autoimmunity may be the cost women's bodies pay for their dynamism—but it is at least a burden that science might eventually be able to eliminate. ●

Melinda Wenner Moyer, a contributing editor at *Scientific American,* is author of, most recently, *Hello, Cruel World! Science-Based Strategies for Raising Terrific Kids in Terrifying Times* (G. P. Putnam & Sons, 2025).

IMMUNE MYSTERIES

Untangling the Vagus Nerve



The healing potential of the brain's most interconnected nerve intrigues researchers

BY JENA PINCOTT

ILLUSTRATION BY NOEMI FABRA

THE VAGUS NERVE IS A VINE of nerve fibers with roots in nearly every organ and shoots in the brain. It helps us detect a racing heart, rising blood pressure, stomachache, discomfort, an overzealous immune system and even alarm calls from microbes in our gut. When it senses trouble, the vagus helps to steady our heart, soothe our stomach, rein in our immune system and calm us down.

Wellness influencers claim we can ice, tone or zap the vagus nerve to fix almost anything—long COVID, headaches, poor memory, extra pounds, the blues. Much of that hype is unfounded. Still, some research on the vagus nerve is intriguing enough—and promising enough—to draw serious scientific attention.

Investigators have long known that activating the vagus with mild electrical pulses can treat some conditions. In 1997 the U.S. Food and Drug Administration approved a vagus nerve stimulation (VNS) device that can be surgically implanted under the collarbone and linked to a wire wrapped around the nerve. It is widely used to treat cases of epilepsy that do not respond to drugs. In 2005 the FDA certified a similar device for treatment-resistant depression, and the agency approved yet another one in 2021 to speed up recovery from stroke. Gadgets that stimulate the vagus nerve from outside the body, such as at the outer ear or neck, have been cleared in many countries, including the U.S., to treat obesity, pain and migraines.

Signaling confidence in the potential of VNS, the National Institutes of Health Common Fund launched a $250-million initiative in 2015 with a second phase in 2022. The program, called SPARC (for Stimulating Peripheral Activity to Relieve Conditions), seeks to map the nerve's individual fibers and circuits and to illuminate their functions. Scientists hope it will enable them to refine existing treatments and find new therapies for other conditions, ranging from inflammatory bowel disease to long COVID. Clinical trials are underway on so-called transcutaneous VNS (tVNS) devices, which are easier to use because they access the vagus from outside the skin, or cutaneous barrier. These tools potentially could be used to treat rheumatoid arthritis, migraine, lupus and chronic fatigue syndrome—and that's just a partial list.

"A truly revolutionary idea can take 20 to 40 years before it's thoroughly adopted," says neurosurgeon Kevin J. Tracey of the Feinstein Institutes for Medical Research in Manhasset, N.Y., "at which point everyone says how we needed that all along." The vagus vine's power may be partly mythical, and the research on it is by no means conclusive or clear. But some scientists say it offers hope for millions suffering from complex, hard-to-treat conditions.

IN 1664 ENGLISH neuroanatomist Thomas Willis named the longest of the brain's nerves the vagus, Latin for "wandering." "We call it the vagus nerve, singular, but there are actually two, one on each side of your body," Tracey says. Each side has up to 100,000 fibers, and each fiber contributes to a specific function: heart rate, breathing, immunity, gut contractions that help to digest food, even speech. About 80 percent of vagal nerve fibers are afferent, reporting to the brain about the state of the body; the rest are efferent, carrying instructions down from the brain. British physiologist Walter Holbrook Gaskell demonstrated in the late 19th century that afferent signals tend to excite, whereas efferent ones quiet.

The first person to zap the vagus with an electric current, using something like a tuning fork pressed against the neck, was American neurologist James Leonard Corning in the 1880s. He was trying to reduce blood flow to the brain to cure epilepsy, but his idea failed. A century later, however, neuroscientist Jacob Zabara of Temple University in Philadelphia found that directly applying an electrical signal to the nerve in a canine could disrupt irregular brain activity, thereby reducing seizures. In 1988 neurologist James Kiffin Penry and neurosurgeon William Bell became the first to implant a VNS device into a human to treat epilepsy.

The VNS device currently used for epilepsy, which delivers a pulse every few minutes, is a direct descendant of Zabara's invention. A pivotal study demonstrated that it cut the frequency of seizures by 45 percent on average after a year. It is believed to work mainly by stimulating the afferent fibers, the ones leading up to the brain.

The treatment had a remarkable side effect: over time it made people happier. Their mood lightened even if they still had frequent seizures. According to Tracey, when doctors told these patients they could remove the implant, many of them replied, "No, leave it in. It makes me feel good." This anecdotal evidence prompted the device maker to begin marketing its vagus nerve stimulator as an innovative treatment for depression.

The accidental discovery excited a wave of research to figure out exactly how the vagus nerve impacts mood—a wave that has yet to crest. Scientists now know that the

vine carries information about heart rate, digestion and, more broadly, the state of the body to many of the brain regions implicated in psychiatric illness. These afferent signals first reach the brain stem's hub, the nucleus tractus solitarius, which sorts them and passes them on. One recipient is the amygdala, which helps us process emotions, especially fear, anxiety and stress. Another is the hypothalamus, involved in the release of stress hormones such as cortisol. A third is the ventral tegmental area, which plays a central role in our experience of pleasure, motivation and reward.

Crucially, the downward signals of the vagus help the body regulate some of its inner activity, such as heart rate, to maintain internal equilibrium. When we encounter a threat, "fight-or-flight" hormones raise our heart rate and blood pressure while curbing activity in the gut and intestines. The vagus nerve detects these changes and reports them to the brain, providing real-time feedback. It also facilitates fine-tuning. When stress signals become excessive, the brain sends messages down the vagus to activate the countervailing "rest-and-digest" system. The vine releases the neurotransmitter acetylcholine at its root tips—in the heart, reducing heart rate and blood pressure, and in the stomach, improving digestion. The system relaxes.

A SECOND SERENDIPITOUS FINDING, in the late 1990s, showed that the vagus nerve can do much more than calm the body. Researchers in Tracey's laboratory were studying a drug to reduce inflammation in the brain. Some inflammation is protective, such as the swelling and redness around a wasp sting that show the immune system is dealing with the venom. But inflammation from an overactive immune system can damage tissues. When the body senses an injury or infection, cells in the spleen release signaling molecules called proinflammatory cytokines into the bloodstream to activate the immune response at the site. If cytokines circulate continuously for months or years—from stress, chronic infection or autoimmune disease—inflammation can cause insidious harm.

To test their anti-inflammatory drug, the researchers injected mice with a toxin that triggered an immune reaction. But there was a mix-up: instead of injecting the toxin into the brain, a member of the lab injected the mice in the abdomen, causing systemic inflammation. Much to Tracey's surprise, the anti-inflammatory drug they subsequently delivered into the brain reduced the inflammation in the body. How did that happen? The blood-brain barrier should have prevented the drug from leaving the brain. "We literally talked about this for months," Tracey recalls. It turned out that the vagus nerve had carried the drug's signal from the brain deep into the body.

Even more astonishing, Tracey found that stimulating the vagus with electricity alone also inhibited inflammation throughout the body—no drugs needed. It was a "life-changing" moment, he recalls. More than half of all deaths from disease are tied to inflammation, including heart ailments, stroke, asthma, diabetes, and autoimmune and neurodegenerative conditions. If exciting the vagus nerve could subdue inflammation without drugs and their side effects, it could mark a breakthrough in treating chronic conditions safely.

Depression seemed like a good place to start. People with depression experience a variety of symptoms, but they share some commonalities: sadness, loss of motivation and social withdrawal. Almost a third of people with major depression also have inflammation. "Cytokines cause depression," Tracey says. "If I inject you with these inflammatory molecules, you will get fatigued and lose interest in things that normally bring you happiness." When people who have cancer receive immunotherapy that includes cytokines, he adds, doctors often will prescribe prophylactic antidepressants. People who suffer from anxiety and post-traumatic stress disorder also often have inflammation.

Efforts to use vagus nerve treatment to help people with depression took off—and then stalled. The fda approved VNS in 2005 after several trials found that using it for a year alleviated depression in at least 30 percent of patients. Two years later, however, the Centers for Medicare and Medicaid Services (cms) announced that it would not pay for the treatment, citing insufficient evidence of efficacy. The treatment can cost $30,000 or more in the U.S. for implanted devices, which puts it out of reach for most patients. A 2017 study of 800 people with treatment-resistant depression found that five years of VNS fully cured 43.3 percent of them and halved symptoms for 67.6 percent. Following the success of this study, the cms agreed to reimburse patients participating in a large new clinical trial the device maker launched in 2019.

Optimistically named RECOVER, the trial could establish VNS eligibility for Medicare coverage. Over several years clinicians have been recruiting thousands of participants with major depressive disorder who have failed to improve with at least four other treatments—people who might be excluded from drug clinical trials. "This study is for the sickest of the sick, a population that VNS studies have never shied away from," says Charles Conway, director of the Center for the Advancement of Research in Resistant Mood and Affective Disorders at Washington University in St. Louis, who is leading the trial. The study aims to track each patient for five years.

EVERY FIVE AND A HALF minutes Gina Bolton feels a soft tingle near her throat. For a few seconds her voice enters a higher register. It makes her sound choked and upset, but it means a stimulator the size of a quarter, implanted near her collarbone, is working, she says. The device sends tiny, regular bursts of current—around two milliamps—every few minutes through a wire coiled around a vagus nerve near her vocal cords.

Bolton has had her stimulator since the summer of 2021, when she enrolled in the RECOVER trial. For 30 years she had tried every conventional treatment—psychotherapy, "tons of meds," transcranial magnetic stimulation (which applies magnetic fields to excite neurons), and even electroconvulsive or "shock" therapy, in which electrodes on her scalp delivered electric current directly to her brain. The effects never lasted. When her son and daughter were young, she'd drop them off at school, forcing a smile and a hello, then retreat to bed. More than once she tried to take her own life.

Several months in, Bolton says, she started to notice a change in her behavior: "I was having emotions." She realized she could laugh again, and if something sad was happening,

IF YOU NEED HELP:
If you or someone you know is struggling or having thoughts of suicide, help is available.

Call the **988 Suicide & Crisis Lifeline at 988**

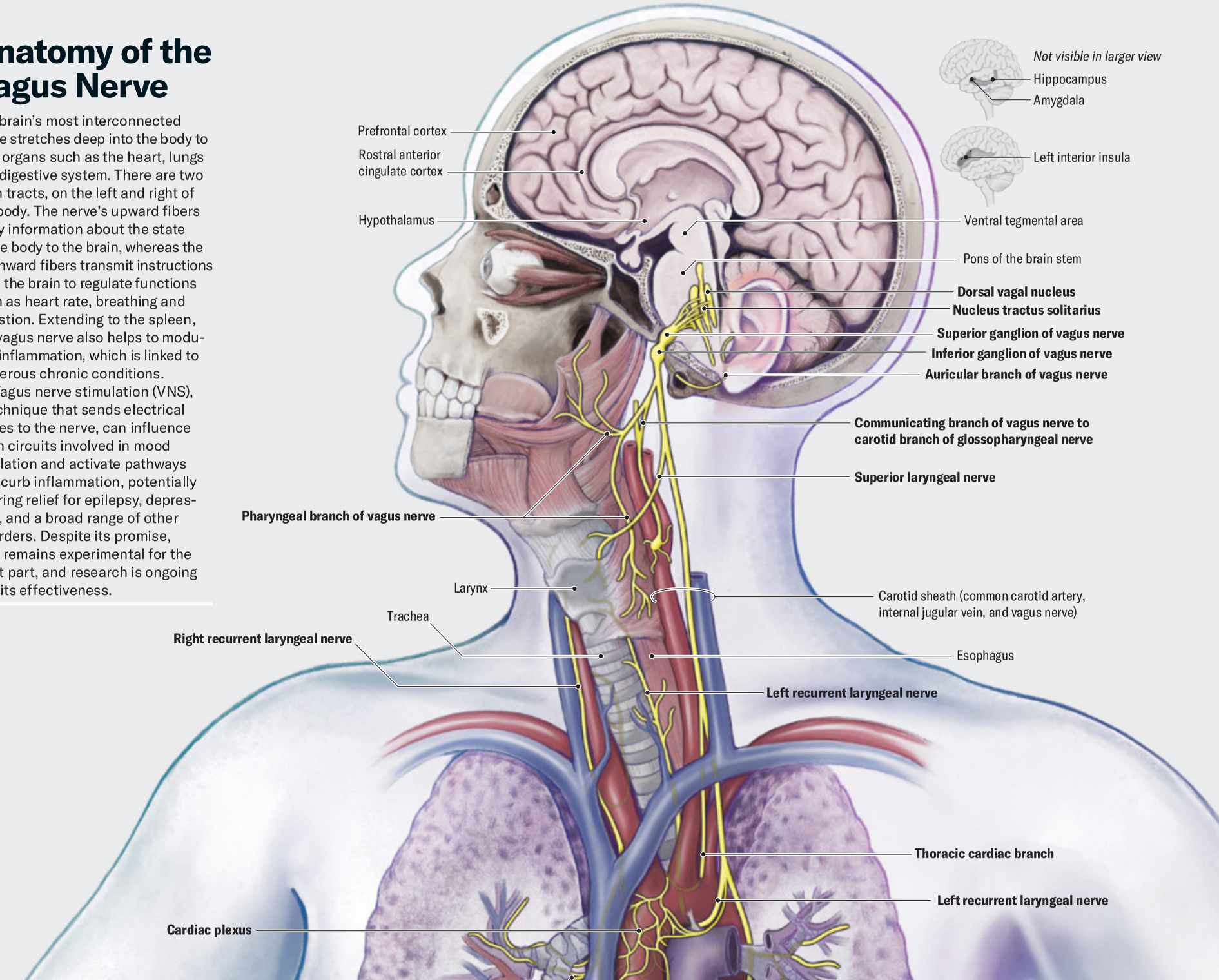
Use the online **Lifeline Chat at 988lifeline.org/chat**

Or contact the **Crisis Text Line by texting TALK to 741741**

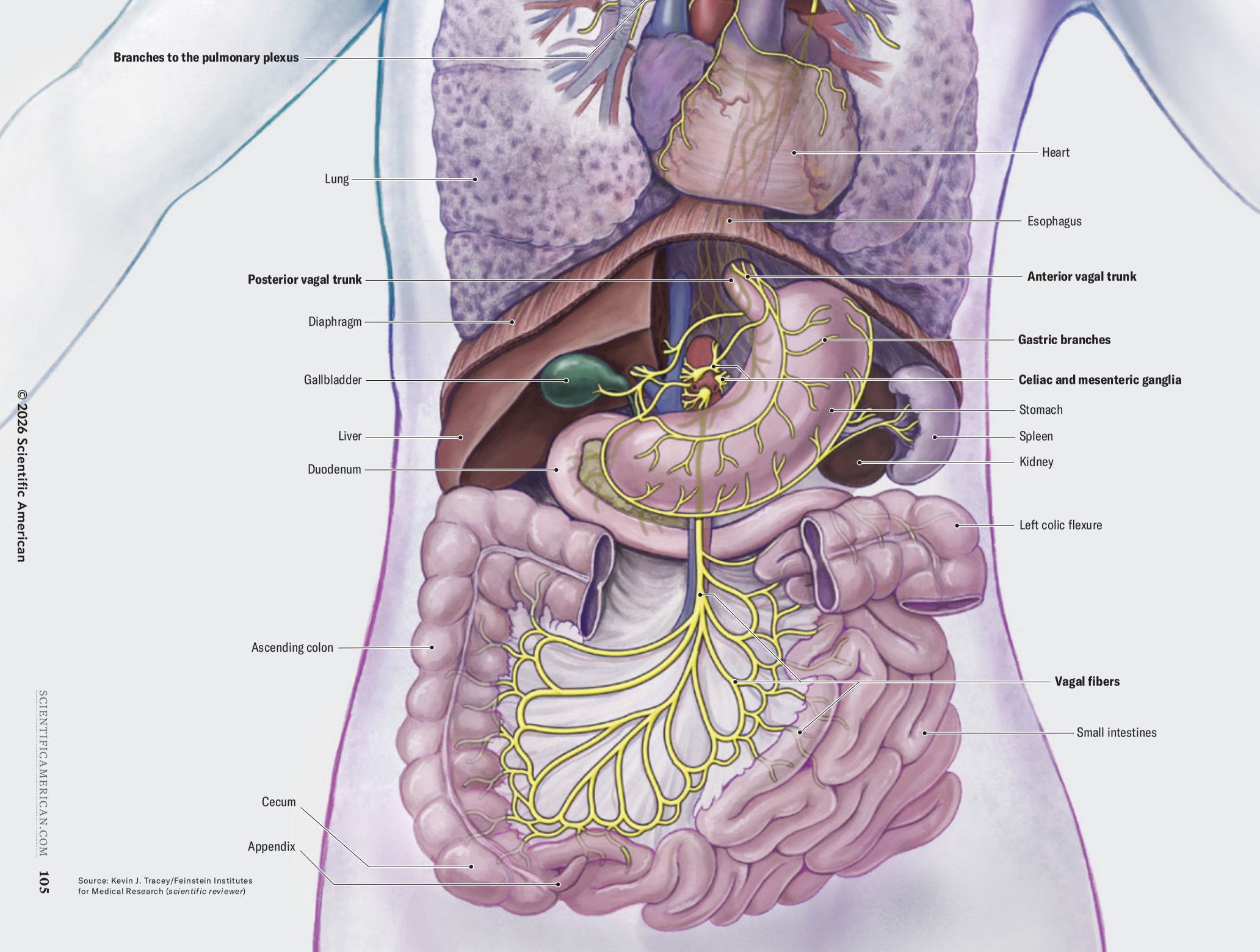
Anatomy of the Vagus Nerve

The brain's most interconnected nerve stretches deep into the body to vital organs such as the heart, lungs and digestive system. There are two main tracts, on the left and right of the body. The nerve's upward fibers carry information about the state of the body to the brain, whereas the downward fibers transmit instructions from the brain to regulate functions such as heart rate, breathing and digestion. Extending to the spleen, the vagus nerve also helps to modulate inflammation, which is linked to numerous chronic conditions.

Vagus nerve stimulation (VNS), a technique that sends electrical pulses to the nerve, can influence brain circuits involved in mood regulation and activate pathways that curb inflammation, potentially offering relief for epilepsy, depression, and a broad range of other disorders. Despite its promise, VNS remains experimental for the most part, and research is ongoing into its effectiveness.



Graphic by Mesa Schumacher



Source: Kevin J. Tracey/Feinstein Institutes for Medical Research (*scientific reviewer*)

When the vagus nerve brings news of dangerous inflammation in the body, the brain sends down signals to soothe it.

she could cry. "Before, I was just numb." In the summer of 2023, two years after she started VNS, Bolton went off the antidepressants she'd taken for most of her adult life. The device had replaced the drugs.

But in June 2024, after a year of observing about 500 patients, the RECOVER trial posted mixed results. Many of the patients with depression who were getting pulses to their vagus nerve showed meaningful improvement—but so did those whose devices were not activated. (Participants were not told for the first year whether their device was sending pulses, but Bolton says she could sense them.) Another mysterious ability of the brain and body—the placebo effect—had evidently kicked in.

The result was disappointing but not entirely unexpected, says Sarah Lisanby, founding dean of the Arizona State University John Shufeldt School of Medicine and Medical Engineering. The placebo response gets in the way of all studies of psychiatric devices, she notes. Further, she adds, research on VNS is scant compared with the decades' worth of evidence supporting electroconvulsive therapy, which alleviates depression in up to three quarters of patients but impairs memory (among other side effects that Bolton found intolerable).

Meanwhile the RECOVER study continues. Conway and other researchers hope its data can be used to predict who is most likely to benefit from future VNS work. The study does not track inflammation, but it could turn out to be a key marker. In February 2024 researchers at the University of Montreal published a pilot study on people with depression who had elevated inflammatory markers. After four years of VNS, almost all of them improved significantly as their inflammation decreased. Patients who have known inflammatory disease may be prime candidates for trials in the future.

Scientists, including Charles Raison of the University of Wisconsin–Madison and Andrew Miller of Emory University, have meanwhile identified mechanisms by which inflammation can cause depression. Inflammatory cytokines circulating in the blood can weaken or even breach the protective barrier between blood vessels and the brain. Once inside the brain, they trigger its immune cells, called microglia, to produce further inflammatory agents.

Inflammation in the brain can interfere with the production of neurotransmitters, including serotonin and dopamine, thereby diminishing feelings of well-being, motivation and pleasure. It also reduces the production of brain-derived neurotrophic factor (BDNF), a molecule that helps neurons grow and form connections. When BDNF levels drop, links between neurons weaken. That makes it harder for the prefrontal cortex, the brain region that helps us manage our emotions, to curb alarm calls from the amygdala and for the hippocampus, involved in learning and memory, to recover from a stressful event.

Could the vagus nerve soothe inflammation in the body to break this dismal cycle? Tracey and other researchers have mapped out its anti-inflammatory channels and how they work. When the nerve's afferent fibers bring news of dangerous inflammation in the body, the brain sends signals back down the efferent pathways. These orders prompt the release of acetylcholine in the spleen, where immune cells reside. Acetylcholine prompts white blood cells called macrophages to reduce their production of proinflammatory cytokines. It may also cue macrophages in the spleen to transform so that instead of destroying infected or damaged tissues as they normally do, they go to the sources of inflammation, including the gut, and help tissues regenerate. In their healing incarnations, macrophages may even repair damage that inflammation causes in the brain and prompt the formation of new neurons and circuits, Tracey says.

With inflammatory disorders—including, Tracey suspects, depression—a disruption in the signals traveling down the vagus can prevent the nerve's anti-inflammatory function from kicking in. The pathway may be impaired or the signal too weak, allowing inflammation to become chronic and harmful.

All this knowledge has, however, been hard to convert into treatments. A meta-analysis led by Sharmili Edwin Thanarajah of the University Hospital Frankfurt in Germany showed that VNS does not consistently resolve inflammation. And even for the third of people with depression who have proinflammatory cytokines in their blood, VNS might reduce their depression but not their inflammation. Something else is going on.

DEPRESSION IS A COMPLEX and variable condition. "Depressed people may look similar, but they don't all have the same disease," Tracey says. This heterogeneity could mean different types of vagus nerve signals might be effective for different people. Some might benefit from signals going down from the brain that curb inflammation and soothe the body, whereas others may benefit more from signals going up.

Neuroimaging offers some clues. Although findings vary with the type of VNS and the regimen used, stimulation of the vagus generally strengthens connections between the prefrontal cortex and the amygdala—which may lead to better control over emotions. It also boosts activity in the left anterior insula, which is associated with emotion processing. Further, a team led by Jian Kong of Massachusetts General Hospital and Harvard Medical School found that when VNS is used to treat depression, it appears to enhance connectivity between the medial hypothalamus, involved in regulating stress responses, and the rostral anterior cingulate cortex, associated with self-referential thinking. This shift may indicate increased integration of emotional and cognitive processes.

Some of these improvements could come from a VNS-induced increase in the neurotransmitters norepinephrine and serotonin, which, in studies of rodents, are associated with enhanced energy and alertness. Animal studies also indicate that VNS boosts BDNF, which helps to restore neural connections lost to stress and depression. Moreover, the treatment appears to replenish other signaling molecules that are frequently imbalanced in depression, such as gamma-aminobutyric acid and glutamate.

But to Conway, VNS's effect on dopamine pathways is one of the most compelling mechanisms. Dopamine is a crucial transmitter involved in motivation and pleasure, and its level in people with de-

pression is low. More than a decade ago Conway and his colleagues used imaging to study how a year of VNS would change the brains of participants with major depression. They found that patients who responded to treatment showed increased activation in the ventral tegmental area, where dopamine is made.

Some surprising recent research also indicates that VNS can boost dopamine circuits in the brains of people with major depression. In a 2024 study, Nils B. Kroemer, a neuroscientist at both the University of Bonn and the University of Tübingen in Germany, gave tVNS to patients with depression while they repeatedly pressed a button to elevate a ball, for which they received small rewards. The tVNS significantly invigorated them and increased their drive to get food and cash.

An hour-long session of tVNS paired with a game treats only a symptom of major depression—a lack of desire and motivation. But with a condition that can be so debilitating, any improvement is welcome.

Kroemer believes that for at least some depressed people the lack of motivation may come from reduced sensory input to the brain. Internal signals from the gut and other organs, transmitted up the vagus nerve, give us a sense of drive: a hunger, literally and figuratively. "If the stomach is empty, there seems to be a strong hardwired motivational signal that gets us to explore new options," Kroemer says. But that happens only if the signals transmit—which requires a healthy vagus nerve.

Kroemer and others have investigated the gut microbiome's contribution to motivation and its interactions with tVNS. Gut bacteria and their metabolites send signals up the vagus nerve to the nucleus tractus solitarius and the brain. These pathways modulate the release of neurotransmitters, including dopamine and serotonin, which regulate mental states. The brain also sends signals down the vagus nerve to the gut, influencing aspects of the gut environment such as inflammation and digestion, which in turn affect the composition of resident bacteria. There's some evidence that beneficial bacteria can reduce depression, anxiety, panic attacks and stress, whereas pathogenic microbes may worsen these states. Future interventions may combine tVNS with approaches aimed at optimizing the gut microbiome, such as a fiber-rich diet or specific probiotic combinations.

FEW PEOPLE with depression or other psychiatric disorders have access to VNS outside of a clinical trial (more than 135,000 patients have received an implant). Instead an increasing number of researchers and clinicians have turned to tVNS, which is cheaper and more convenient.

A surgically implanted device is presumed to be more effective, Conway says, "because it's attached to the nerve and sends a signal 24/7 for certain." Imaging studies also find that implants activate more brain areas than tVNS does. Externally applied VNS has other limitations as well: devices that clip to the ear stimulate primarily afferent fibers, and ones applied at the neck may not efficiently reach the vagus nerve, which is buried deep within.

Most studies with tVNS have been small and limited. A randomized trial led by Kong found that eight weeks of tVNS administered through the ear was as effective as the antidepressant citalopram (Celexa) for major depression. For PTSD, a 2021 pilot study led by Omer T. Inan of the Georgia Institute of Technology and J. Douglas Bremner of Emory University found that three months of twice-daily tVNS self-administered to the neck blocked participants' inflammatory response to memories of traumatic events and reduced stress symptoms by 31 percent compared with people in the control group—prompting the FDA to grant the treatment a "breakthrough device" designation, which accelerates the development and review process. For anxiety, another pilot study, at Leiden University in the Netherlands, showed that "high worriers" had fewer intrusive thoughts after using ear-clip tVNS compared with people who received sham stimulation.

Increasingly, clinicians are combining tVNS with conventional treatments such as antidepressants and cognitive-behavioral therapy. These devices also enable individuals to self-treat many different conditions, including anxiety, stress and even general malaise. There is, however, no consensus on protocol for any given condition; worse, the inability to target specific fibers can lead to unwanted outcomes. Contrary to popular belief, VNS does not have only calming effects. Some pathways trigger arousal, increasing alertness and vigor—or, if overstimulated, jitteriness and anxiety.

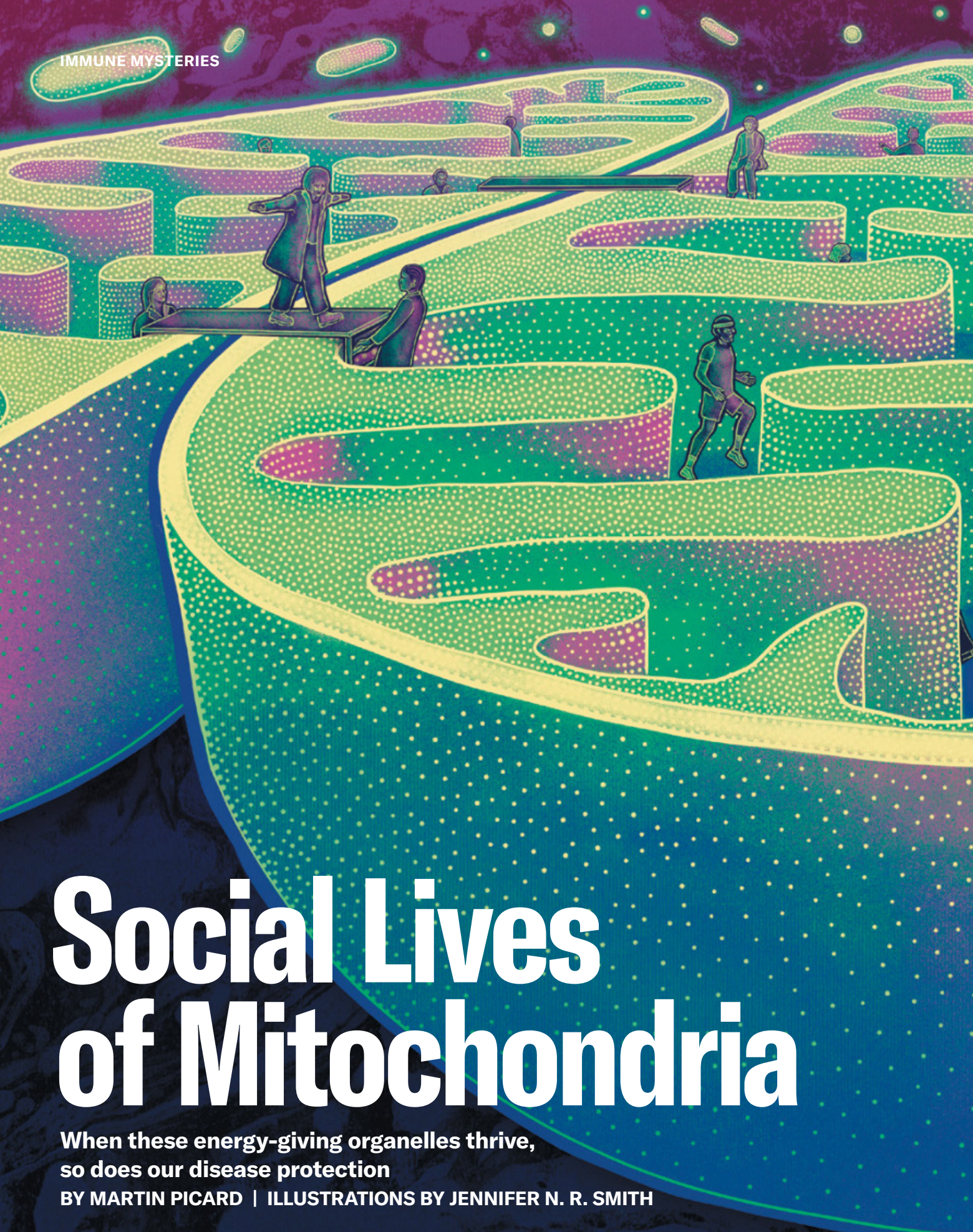
Meanwhile SPARC researchers have compiled a massive data-sharing platform that includes detailed maps and models of the vagus nerve, along with other tools, with new submissions being continuously integrated. By leveraging artificial intelligence and other technologies, SPARC teams aim to isolate single fibers and circuits, along with their pathways, and track what they do. The goal is to develop strategies for targeting specific nerve fibers involved in a variety of conditions. The ambitious list includes Crohn's disease, Parkinson's disease, traumatic brain injury and pain management.

In the near future, these technologies could become more personalized. Ongoing developments in VNS involve stimulating multiple contacts along the vagus nerve to activate fibers connected to specific organs while avoiding those that have adverse effects. Emerging "closed-loop" systems could let scientists adjust stimulation parameters based on real-time feedback from the body—responding to signals such as food cravings, heart rate or inflammation.

Some proponents see VNS assuming entirely new forms. Once a neural circuit is identified, it can be targeted in any number of ways: focused ultrasound or tiny implants in various parts of the body, even the brain stem. In 2024 researchers at Columbia University's Zuckerman Institute identified the precise circuit in the nucleus tractus solitarius and vagus nerve that informs the brain of emerging inflammation in the body and determines the response—essentially, the dial for inflammation, which they proposed controlling with drugs.

As for Bolton, she plans to continue VNS, or its future incarnation, for the rest of her life. She still remembers the exact moment she realized the treatment was working. It was several months into the trial, and she was driving to a check-in appointment. Bolton could feel the device's intermittent pulse, as well as something else: the beat of the song playing on the car radio. She found herself tapping her fingers on the steering wheel in time with the music. "I had not wanted to be alive for so long," she says, "and now, suddenly, I realized I did." The beat went on, and for the first time in years, she found herself singing. ●

Jena Pincott is a freelance science writer and author of several books, including *Do Chocolate Lovers Have Sweeter Babies?: The Surprising Science of Pregnancy* (Simon & Schuster, 2011).



Social Lives of Mitochondria

When these energy-giving organelles thrive, so does our disease protection

BY MARTIN PICARD | ILLUSTRATIONS BY JENNIFER N. R. SMITH

ALWAYS WANTED TO UNDERSTAND LIFE. What moves us? What allows us to heal and thrive? And what goes wrong when we get sick or when we eventually stop breathing and die? My search for answers to these stupendously ambitious questions led me, it now seems inexorably, to mitochondria.

In biology classes from high school through university, I learned that mitochondria are little objects that reside within each cell and serve as "powerhouses," combining oxygen and food to yield energy for the body. This idea of mitochondria being little batteries with a built-in charger, about as interesting as the one in my phone, left me unprepared for the vital reality of these organelles when I first saw them under a microscope in 2011. They were luminous because of a glowing dye I had put in them, and they were dynamic—constantly moving, stretching, morphing, touching one another. They were beautiful. That night, a graduate student alone in a dark laboratory in Newcastle upon Tyne in England, I became a mitochondriac: hooked on mitochondria.

A profound insight by biologist Lynn Margulis helped me make sense of what I was seeing. She postulated in 1967 that mitochondria descend from a bacterium that was engulfed by a larger ancestral cell about 1.5 billion years ago. Instead of consuming this tidbit, the larger cell let it continue living within. Margulis called this event endosymbiosis, which means, roughly, "living or working together from the inside." The host cell had no energy source that used oxygen—which, thanks to cyanobacteria, was already abundant in the atmosphere; mitochondria filled this gap. The unlikely union allowed cells to communicate and cooperate and let their awareness expand beyond their own boundaries, enabling a more complex future in the form of multicellular animals. Mitochondria made cells social, binding them in a contract whereby the survival of each cell depends on every other one, and thus made us possible.

Amazingly, my co-workers and I have discovered that mitochondria are themselves social beings. At least, they foreshadow sociality. Like the bacterium they descended from, they have a life cycle: old ones die out, and new ones are born out of existing ones. Communities of these organelles live within each cell, usually clustered around the nucleus. Mitochondria communicate, both within their own cells and among other cells, reaching out to support one another in times of need and generally helping the community flourish. They produce the heat that keeps our bodies warm. They receive signals about aspects of the environment in which we live, such as air pollution levels and stress triggers, and then integrate this information and emit signals such as molecules that regulate processes within the cell and, indeed, throughout the body.

When our mitochondria thrive, so do we. When they malfunction—when, for instance, their ability to change energy into forms required for biochemical reactions is impaired—we may experience conditions as diverse as diabetes, cancer, autism and neurodegenerative disorders. And as mitochondria accumulate defects over a lifetime of stress and other insults, they contribute to aging and, ultimately, death. To understand these processes—to see how to sustain physical and mental health—it helps to understand how energy moves through our bodies and minds. That requires a deeper look into mitochondria and their social lives.

LONG BEFORE I GOT MY FIRST glimpse of mitochondria, I had boned up on the basics of their structure and biology. We inherit our mitochondria from our mother—from the egg cell, to be precise. Mitochondria have their own DNA, which consists of only 37 genes, compared with the thousands of genes in the spiraling chromosomes inside the cell nucleus. This ring of mi-

tochondrial DNA, or mtDNA, is sheltered within two membranes. The outer shell, shaped like the skin of a sausage, encases the mitochondrion and selectively allows molecules to enter or exit. The inner membrane is made of densely packed proteins and has many folds, called cristae, which serve as a site for chemical reactions, much like the plates suspended inside a battery.

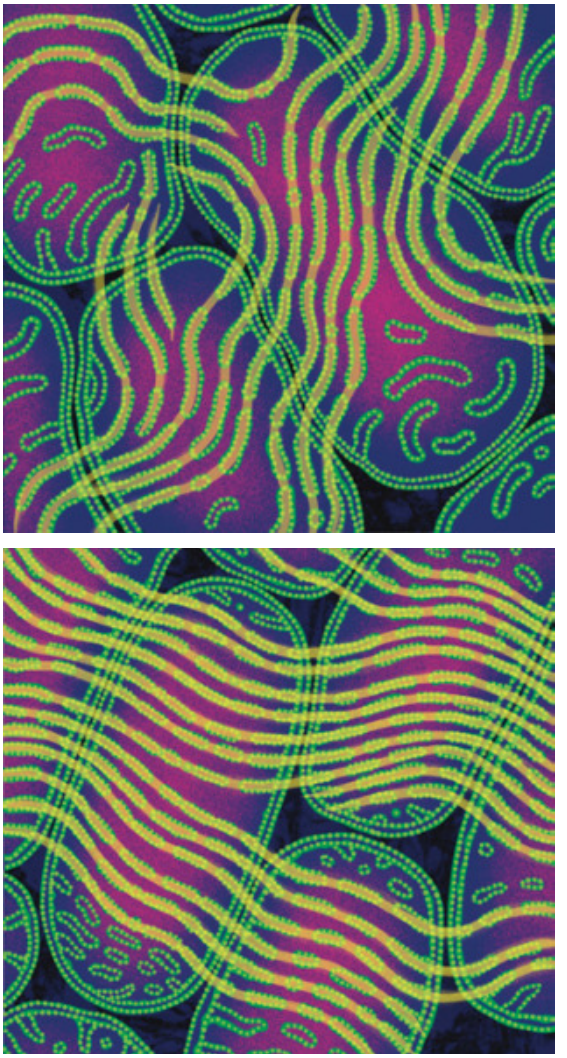
In the 1960s British biochemists Peter Mitchell and Jennifer Moyle discovered how electrons derived from carbon in food combine with oxygen in the cristae, releasing a spark of energy that is captured as a gradient in electrical voltage across the membrane. This voltage provides the driving force for all processes in the body and brain, from warming to manufacturing molecules to thinking. Mitochondria also produce a molecule called adenosine triphosphate, which serves as a portable unit of energy that powers hundreds of biochemical reactions within each cell.

Returning from the U.K., I started a postdoctoral fellowship with geneticist and evolutionary biologist Douglas Wallace at the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia. In 1988 Wallace had discovered the first-ever link between a mutation in mtDNA and a human disease. He had gone on to map some of mitochondrial biology's fundamental connections to various diseases and the aging process, laying the foundation of the field of mitochondrial medicine. In Philadelphia, I began working with a fellow postdoc, Meagan McManus, who wanted to understand how defective mitochondria could cause cardiovascular and neurological diseases. McManus asked me to photograph with an electron microscope the mitochondria in the hearts of mice with a specific mtDNA mutation that led to heart failure.

Our team was also experimenting with three-dimensional imaging using electron tomography, the same technology that allows a radiologist to see a patient's internal organs in 3D. Weeks later, the director of this project, Dewight Williams of the University of Pennsylvania, brought me to a room where the million-dollar tomography microscope stood, as high as the ceiling, to show me reconstructed movies of mitochondria.

The tomography gave us a 3D view of the cristae. Some mitochondria in the hearts of the sick mice had jagged, highly irregular cristae—the unhealthy look I had been seeing in the 2D pictures. But one thing showed up in 3D that we had never seen in the flat images: even when mitochondria looked unhealthy, their cristae looked healthy at places where the mitochondria touched one another. They were interacting, helping one another's internal organization. These mito-mito junctions also had more cristae than any other part of the same mitochondrion. "Meagan has to see this!" I thought, rushing to the lab across campus.

As I restarted the movie for McManus, I narrated what I had seen a few minutes earlier: "Mitochondria are influencing one another!" We watched the looping video a few times. Then McManus said, her voice pitched high with excitement, "And the cristae line up! The cristae line up between mitochondria!" She drew a line with her extended finger across a junction between mitochondria.

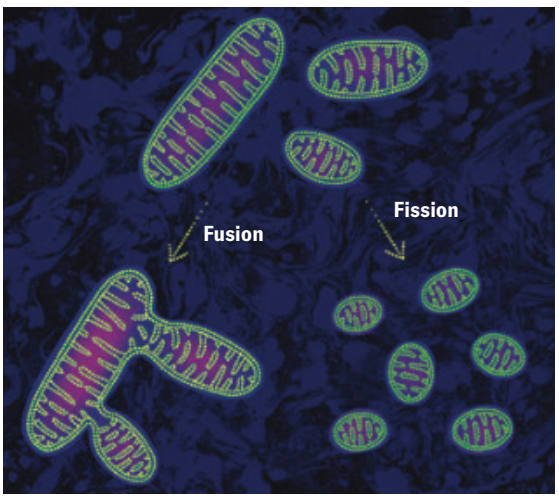


I had pored over thousands of electron microscopy images from the best microscopists. Never had I heard about cristae in one mitochondrion aligning with the cristae of another mitochondrion. While in Newcastle, I had seen a 1983 paper by Russian scientists Lora E. Bakeeva and Vladimir P. Skulachev describing "intermitochondrial contacts," and I had demonstrated that these contacts increased after exercise—perhaps increasing energy efficiency. How had we all missed the alignment? Yet instead of lying there as parallel plates, like textbooks often portrayed them, the cristae formed parallel ribbons undulating across mitochondria. It almost looked like the cristae were helping their neighbors organize to achieve the typical, healthy, regular array.

At the next lab meeting, I suggested that these patterns looked like iron filings aligned around a magnet. Cristae are full of iron-sulfur clusters that may be paramagnetic. If they are, maybe there were electromagnetic fields induced by the flow of electrical charge across the cristae? Could they induce the cris-

tae to line up? So far this hypothesis appears to be the best one for how cristae align across mitochondria. For me, it also opened the door to thinking about how the forces of physics might have contributed to the evolution of multicellular life—all the way to us.

THIS DISCOVERY and the thoughts it spurred changed my view of mitochondria forever. Hundreds of hours in the dark dungeon where I studied mitochondria and numerous collaborations later, I had learned one important lesson: mitochondria exchange information. The fingerprint of that exchange lay right there in the patterns of their cristae. Further studies at the University of Tsukuba in Japan and elsewhere, using cells with varying levels of mitochondrial dysfunction caused by mtDNA mutations, showed that healthy mitochondria can donate intact mtDNA to mutant mitochondria. In conditions of scarce energy supply, mitochondria fuse with one another into long strands to share mtDNA. Isolated mitochondria without mtDNA or with mutated mtDNA can similarly fuse with healthy mitochondria, restoring their normal function.

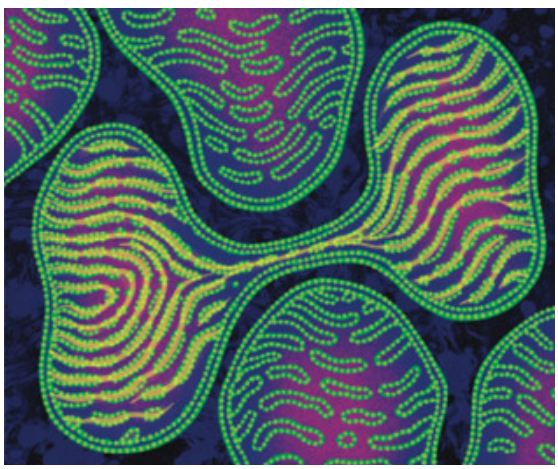


Fusion enhances the resilience not only of mitochondria but also of cells; interfering with these interactions leads to isolated mitochondria that accumulate mtDNA defects and ultimately die, along with the cells they live in. In people, decreased levels of mitofusin 2, a protein located in the outer mitochondrial membrane that helps with fusion, are correlated with neurodegeneration. And mice with mitochondria that have been engineered to impede fusion in the nucleus accumbens, a brain region involved in regulating reward, are more anxious.

Could there be yet other ways in which mitochondria communicate? Could they act like their bacterial ancestors, which build biofilms and use membrane protrusions, electrical fields and secreted molecules to cooperate and conquer the living world with their versatile collective behaviors? Could mitochondrial communication reveal a broader internal universe of energy and information exchange? Could mitochondrial junctions and aligned cristae operate like neuronal synapses, with the resulting mitochondrial collective behaving essentially like an intracellular brain?

IN 2016, SHORTLY AFTER STARTING my own lab at Columbia University, I was back in Newcastle on a visit to Doug Turnbull's Wellcome Center for Mitochondrial Research. I was again sitting at the electron microscope, this time with a stellar British graduate student, Amy Vincent. We were imaging muscle from the calf of a woman with an mtDNA mutation that caused a rare mitochondrial disease. By coincidence, her mutation was similar to the one McManus's mice had had.

What Vincent and I found that afternoon opened another avenue of inquiry. In front of our eyes lay mitochondrial nanotunnels: thin membrane protrusions—the same kind that bacteria use to share their circular DNA! For the first time in humans, Vincent and I saw that mitochondria send thin tubular structures out toward one another, like feelers that some solitary cells use to search for a more hospitable environment or a healthy fellow cell. By imaging dozens of other muscle samples, we found that people whose mitochondria don't work well have more nanotunnels. It was as if unhealthy mitochondria with mtDNA mutations were reaching out for help.



Perhaps the most remarkable aspect of the mitochondrial collective, however, is that mitochondria from different parts of the body talk to one another, using hormones as their language. Mitochondria catalyze the first step in making steroid hormones we use for sustaining and reproducing life. Cortisol, the hormone that increases blood glucose levels to fuel the stress response, is made in the mitochondria of the adrenal glands, which sit on top of the kidneys. Testosterone, estrogen and progesterone are synthesized mainly by mitochondria in the reproductive organs. Interestingly, brain mitochondria have receptors to sense both stress and sex hormones. So we have a population of mitochondria in the adrenal glands that signal directly, via the blood, to mitochondria in the brain.

Further, mitochondria are not all created equal. In the same way that humans develop specialties in different social and economic roles and organs specialize

in executing complementary functions (the liver feeds other organs, the heart pumps, the brain integrates information and issues directives), mitochondria also specialize. Across organs and cell types, mitochondria look different. Their protein contents are different. They move differently. And their ability to sense, integrate and signal specific information varies according to the cell they inhabit. Mitochondrial specialization most likely affords gains in efficiency, allowing an organism to survive at a lower overall energy cost.

My co-workers and I recently built the first map of mitochondria in the human brain. Even within this single organ there are different types of mitochondria in different parts of the cortex and in deeper, subcortical brain regions. The brain uses 20 percent of the body's energy, despite constituting only 2 percent of the body's mass, so an efficient source of power is critical to its functioning. My colleagues, notably Michel Thiebaut de Schotten of the French National Center for Scientific Research and Eugene V. Mosharov of Columbia, and I found that the more recently evolved brain areas, which have the highest energy expenditure, have mitochondria that are more strongly specialized for energy transformation.

Mitochondria within a cell may also look very different from one another. For example, in neurons, "dendritic" mitochondria are found in the fibers, or dendrites, through which neurons receive signals from other cells. These mitochondria are stable filaments that stretch over 10 to 30 microns—a stupendously long distance for this type of structure—and have several mtDNA copies. "Axonal" mitochondria move along the linear axons, which conduct signals to other neurons, as if they were cellular highways. They are generally short and stubby (up to a micron in length), and many lack mtDNA. "Cytoplasmic" mitochondria cluster around the nucleus and look like something between the dendritic and axonal types. Similar grouping and specialization of mitochondria exists in muscle and fat cells.

These findings, taken together, led behavioral neuroscientist Carmen Sandi of the Swiss Federal Institute of Technology and me to propose in 2021 that mitochondria are social organelles. If you are like me and your eyebrow rises when you hear the term "social" applied to a subcellular organelle, you are having a normal reflex. Nevertheless, Sandi and I argue that mitochondria show all the features of social beings—a shared environment inside the cell or body, communication, formation of groups or types, synchronization of behavior, interdependence, and specialization in the tasks they perform.

In a subsequent paper, which required a painfully long review of more than 400 studies, Orian S. Shirihai of the University of California, Los Angeles, and I established that the mitochondrial collective operates as a mitochondrial information-processing system, or MIPS. Like the animals they exist within and support, which must respond flexibly to the environment, the mitochondria sense signals, integrate this information in the membrane potential of their cristae, and produce signals that regulate the genes of the cell and shape cell behavior.

Your eyes transform light into electrical impulses that coalesce into an image in your visual field, and your ears transform air-pressure waves into electrical pulses that you eventually perceive as sounds. Likewise, mitochondria transform dozens of hormonal, metabolic, chemical, and other information streams into their electrical membrane potential. This "bioenergetic" state then leads to the production of secondary messenger molecules that are intelligible to the nucleus. So in the same way you read messages on your phone, which receives signals, transforms them and projects decipherable information onto its screen, the nucleus of your cells can "read" the environment through the MIPS that surrounds it.

Rather than having supplementary roles like those of battery chargers, mitochondria are more like the motherboard of the cell. Genes sit inert in the nucleus until energy and the right message come along to turn some of them on and some others off. Mitochondria provide these messages, speaking the language of the epigenome—the malleable layer of regulation that sits on top of the genome to regulate its expression.

My colleague Timothy Shutt of the University of Calgary likes to call mitochondria the "CEO of the cell": the chief executive organelle. This metaphor captures how mitochondria not only are involved in integrating information but also give orders. They dictate whether the cell divides, differentiates or dies. Indeed, mitochondria have a veto on cell life or death. If the MIPS deems it necessary, it triggers programmed cell death, or apoptosis—a form of self-sacrifice for the greater good of the organism.

So vital are mitochondria that in difficult times cells may donate entire mitochondria to other cells. "In cellular emergencies, newly arrived mitochondria might kick-start tissue repair, fire up the immune system or rescue distressed cells from death," journalist Gemma Conroy noted in a *Nature* news story in April 2025. Inside tumors, cancer cells and immune cells appear to compete for mitochondria, using them as a kind of bioweapon. An international effort I participated in, led by Jonathan R. Brestoff of the Washington University School of Medicine in St. Louis, has created an entirely new lexicon to guide the emerging field of mitochondria transfer and transplantation.

ALL WELL AND GOOD, you may think. What does all this mean for my health or how long I'm going to live?

The short answer is that it may have everything to do with human health. Diabetes, neurodegenerative conditions, cancer and even mental health illnesses are all emerging as metabolic disorders involving malfunctioning mitochondria. And these findings are indicating new routes for intervention.

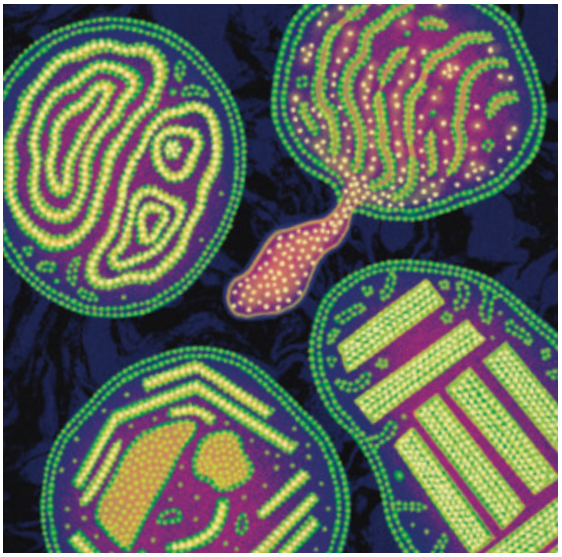
Mitochondria drive health—or disease—in several

ways. One route derives from their role as energy processors. In an electrical circuit, if we crank up the input voltage too much, we can blow it out. Similarly, if our cells are exposed to too much glucose or fat—or, worse, both together, causing what doctors refer to as glucolipotoxicity—the mitochondria undergo fission and fragment into little bits, accumulate mtDNA defects, and produce signals that end up prematurely aging or killing the cell. Experiments in cells and in mice have shown that pharmacologically or genetically preventing mitochondrial fission induced by excessive glucose and fats may protect against insulin resistance.

Cancer, too, may be a disorder of cellular metabolism. Cancer cells can burn glucose without oxygen, which suggests either that something is wrong with their mitochondria or that they prefer to reserve mitochondria for use in cell division—and proliferation.

A second pathway is through mitochondria's influence on gene expression. Mitochondrial signals alter the expression of more than 66 percent of genes in the nuclear chromosomes. By changing which genes are expressed and to what extent, mutations in mtDNA may completely alter the nature, behavior and stress resilience of cells and ultimately of the whole organism.

Mitochondria can look terribly odd when sick. In people with mtDNA defects that cause rare mitochondrial diseases, such as the person in whose mitochondria we first saw nanotunnels, the cristae in particular can look somewhat alien—like crop circles with regular angles, paracrystalline inclusions, and other weird shapes.



Notably, abnormal mitochondrial shape and function are emerging as biomarkers and potential causes of cognitive and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and others. Clinically, a neurobiological subtype of autism spectrum disorder involves defects in mitochondrial biology.

A third pathway is inflammation. When cells are injured or stressed, they may leak mtDNA into the cell's interior, the cytoplasm, or even into the blood. Along with Caroline Trumpff of Columbia, Anna Marsland and Brett Kaufman of the University of Pittsburgh, and other co-workers, I found that mental stress induced by having to speak in public for five minutes increased the amount of free-floating mtDNA in the blood. People in ICUs who are grievously ill tend to have very high levels of mtDNA in their blood. Because mtDNA rings resemble bacterial DNA, immune cells see them as pathogens and mount an attack that can develop into inflammation. And inflammation, clinicians know well, is linked to the onset and progression of a host of chronic health conditions.

Just how defective mitochondria lead to illness in the body and mind is a question that has yet to be answered. But there are simple ways to ensure our mitochondria stay healthy. One is exercise. When you move vigorously, your cells consume energy rapidly, powering up the membrane potential of your mitochondria. If your exercise leaves you feeling out of breath, it is a sign that your mitochondria are working hard. Because the brain-body entity is expert at anticipating and preparing for the future, if you move in a way that activates your mitochondria, your body thinks, "Next time this happens, I'll be ready!" To get ready, it makes more mitochondria and keeps them working at their best.

Surprisingly, social connections, too, may promote the health of our brain mitochondria. In a major study led by David A. Bennett of Rush Medical College in Chicago, researchers asked hundreds of individuals aged 65 and older in the Chicago area to fill out surveys, take cognitive tests and give blood every year until they died. After death their brains were collected to enable analysis of their mitochondria. My colleague Trumpff used those data to ask whether positive mental states such as feeling purpose in life, optimism and a sense of connectedness—or, in contrast, negative mental states such as perceived stress, depression and social isolation—could be related to the mitochondria's ability to transform energy.

What Trumpff learned was remarkable: the amount of energy-transforming proteins in mitochondria in the prefrontal cortex was significantly correlated with how many positive and negative experiences people reported in the year before they died. This finding aligned with previous studies relating early-life adversity or daily mood markers such as feelings of love, closeness or trust to mitochondria in blood immune cells. Our states of mind might affect the biology of our mitochondria, modulating how well they transform energy.

Another intervention that can be remarkably effective is diet. Medical ketogenic therapy or "nutritional ketosis," which involves cutting out all refined sugars, limiting intake of carbohydrates, and making up the calorie difference with more proteins and fats, has been shown to sustainably reverse insulin resistance and type 2 diabetes. The ketogenic diet has been used for decades to ward off seizures and thereby "stabilize" the brain in children and adults with intractable and otherwise incurable epilepsy. A ketogenic diet can even ameliorate the mental state and cognitive function of

people with Alzheimer's. It enhances brain-network stability, a marker of brain aging—and this function may explain why some people on the diet sleep better.

The ketogenic diet can have astonishing effects in other diseases as well, as evinced by the story of Lauren Kennedy West, a Canadian woman diagnosed with schizophrenia and bipolar disease at the age of 25. Her life progressively felt too difficult to navigate, "like there was no space for me in the world," she explained in a moving account of her journey posted on YouTube in 2024. In December 2023 West began nutritional ketogenic therapy. A couple of weeks later she noticed she had more energy. Many of her symptoms lessened. After about nine months she was symptom-free, had tapered her medication in collaboration with her care team, and continued to feel better. Late in 2024 she took her last dose of antipsychotic medication.

West's experience parallels initial positive results from a pilot trial of 21 people with bipolar disease and schizophrenia. Numerous other clinical trials of the ketogenic diet for people with severe mental illnesses such as schizophrenia, depression, anxiety and obsessive compulsive disorder have been undertaken around the world. (Many of these trials have been by funded by the Baszucki Group, a philanthropic foundation formed after Matt Baszucki, the son of the group's founders, successfully treated his bipolar disease with the ketogenic diet. In 2024 I received the Baszucki Prize in Science, which I used to help fund my lab at Columbia.)

A recent study of 28,995 people in the U.S., 4,484 of whom had significant depression symptoms, also supports the protective effects of low-sugar diets on mental health. People whose diet was "more ketogenic"—low in carbohydrates and sugars relative to lipids and proteins—were less than half as likely to develop depression compared with people whose diet was fairly rich in sugars.

How does it work? From a mitocentric perspective, the ketogenic diet does three things. First, it leads to the supply of an efficient fuel source by the liver, which feeds other organs in the body. If you fast or eat a ketogenic diet, your liver takes the fats from your love handles or your food and breaks them down into smaller bits called ketone bodies. This process happens inside the liver's mitochondria. Second, after entering the blood, ketone bodies reach the organs, some of which, including the brain, prefer ketone bodies over other fuels such as glucose, proteins and fats. So in the presence of various fuel sources, the brain will preferentially burn ketones.

The third thing may have to do with efficiency—and might explain why ketone bodies are the preferred fuel for the brain. Glucose has to traverse a number of hurdles before getting to neuron mitochondria—it detours through astrocytes, crosses several membranes and goes through several enzymatic reactions. In contrast, ketone bodies are taken up directly by the mitochondria in neurons, where they are burned. It's a far less convoluted path.

So ketosis, or the burning of ketone bodies, may exert its effects on the brain by enabling energy to directly flow between mitochondria. Ketones in your blood open a stream of communication between producer and consumer mitochondria, fostering their sociality throughout your body.

ONCE WE REGARD MITOCHONDRIA as dynamic energy and information processors, an entirely new perspective of life emerges. Think of yourself as a waterfall. The waterfall exists only insofar as the water molecules keep flowing down. You learn as much about the waterfall when you scoop up a few inert H_2O molecules as you learn about how healthy a person is by sequencing their genome: close to nothing.

The waterfall cannot be understood from its parts, only from its movement. And once the flow stops, there is no more waterfall. The waterfall is not a thing that appears and disappears. It is a *process*—a process that flows and stops flowing. Like a waterfall, you are not a thing. You are a process—an energetic process, to be precise.

Your fundamentally energetic nature has two main implications. The first is that as a dynamic process, you are bound to change. Your body continually sheds, kills and makes cells. Your mind also changes. Some parts of your mind, such as your personality, are relatively stable. But then again, that can change, too—when you are "hangry," for instance, and become less than your best self. That's an energy deficit changing your mind.

Some drugs can dramatically change your mind. Psychedelics, for example, act on the serotonin system to desynchronize the human brain. They also dissolve the sense of self, or "ego." Change brain-energy patterns, change the mind. The mind, then, may essentially be an energy pattern. Further, energy flowing through your brain somehow *feels* like something. As Nirosha Murugan of Wilfrid Laurier University in Ontario and I postulated in a paper, humans may be wired to experience excessive resistance to energy flow as aversive. In contrast, smoothly flowing energy, as occurs after an enjoyable exercise session or when you are working on a stimulating project, feels good. When energy ceases flowing to your brain—if your heart stops, for example—your conscious awareness quickly fades, and you no longer are.

Does all this say anything useful about my original questions? I suspect we now have answers. The key to life and health may lie in how easily energy flows through your mitochondria with each breath you take. So next time you skip that appealing sugary treat, go outside for a stroll, hit the gym or decide to spend time with someone you care about, know that you are supporting your mitochondria. Keeping energy flowing through your mitochondrial collective may be the key to good health and a meaningful life. ●

Martin Picard is an associate professor of behavioral medicine in Columbia University's departments of psychiatry and neurology and at the Robert N. Butler Columbia Aging Center. He directs the school's Mitochondrial PsychoBiology Group.

Greenery Improves Health

More contact with nature helps both body and mind

BY LYDIA DENWORTH | ILLUSTRATION BY JAY BENDT

LIKE SO MANY PEOPLE, I took refuge in the outdoors during the worst of the COVID pandemic. Being outside reduced the chance of infection, but it also helped in other ways. "I think everybody got that nature seemed to be the solution for a lot of the stress people were dealing with," says Jay Maddock, an experimental psychologist and director of the Center for Health & Nature at Texas A&M University.

More time in the green is associated with lower blood pressure, strengthened immune systems, lower risk of cardiovascular disease and improved sleep. A 2024 study found it might slow the shortening of the telomeres that cap our chromosomes, a sign of biological aging. And there is convincing evidence that time in nature reduces depressive symptoms, alleviates stress and improves cognitive function. A 2019 study of more than 19,000 people in the U.K. found that those who reported spending at least 120 minutes in nature every week had better health or higher well-being than those who spent less time. It didn't matter whether people reached the total time in many small increments or one long block.

The research is also highlighting health inequality created by disparities in access to green space—something else the pandemic shone a spotlight on. Jennifer D. Roberts, a health equity scholar at the University of Maryland, says the lowest-income communities are "less likely to have trees; they're less likely to have parks of ample acreage and high quality." According to one study, neighborhoods that were once redlined (a now outlawed practice that deemed certain areas "hazardous" for investment) have less green space today than areas with similar demographics that were not redlined.

Access to parks and other greenery is linked to health disparities that can't be explained by factors such as race, ethnicity and socioeconomic status alone, says epidemiologist Marcia P. Jimenez of the Boston University School of Public Health. "There are higher-level determinants of health, which are our access to food, our exposure to air pollution, noise, green space and the socioeconomic status of our neighborhood." More access to green space tends to give a bigger relative health boost to disadvantaged groups than to more privileged ones, research shows. "If we were to increase greenness among these vulnerable populations, we could essentially tackle health inequalities," Jimenez says.

To get a more precise measure of local greenery, scientists can use Google Street View data and something called the normalized difference vegetation index, which uses satellite imagery to quantify plant density and health in an area of land. NatureQuant, a company based in Bend, Ore., used machine learning to develop NatureScore, which combines multiple datasets on parks, tree canopies, and air, noise and light pollution to develop a score between 0 and 100 as a proxy for greenness for every address in the U.S. (a heavily urban environment would generally score below 30 and a forest above 70).

In a 2024 study, Maddock and his colleagues were the first to use NatureScore to analyze health outcomes, specifically for mental health. They looked at outpatient mental health service utilization, mostly for depression, anxiety or stress, across 1,169 zip codes in Texas. After adjusting for demographic and socioeconomic factors, they found that rates of mental health service use were about 50 percent lower in neighborhoods with NatureScores higher than 60. In 2022 Jimenez and her colleagues published a paper in *JAMA Open Network* using data from the long-running Nurses' Health Study II to show that living in areas with more green space was associated with higher scores for overall cognition and for psychomotor speed and attention. This difference could be partly explained by fewer depressive symptoms.

There are several possible explanations for these findings. Nature may provide a respite from the mental fatigue of modern life and the built environment, restoring attentional resources. Supporting this idea, a 2024 experiment showed that a 40-minute walk in nature enhanced people's ability to coordinate higher-level cognitive functions more than a 40-minute walk in an urban environment.

A second theory suggests that time spent in nature activates the parasympathetic nervous system, which reduces the body's stress responses. Studies have shown reductions in cortisol levels—part of those responses—after exposure to greenery. In addition, time outdoors encourages physical activity and offers chances for social connection, both of which improve mental and physical well-being.

Studies such as Jimenez's and Maddock's are aimed at policymakers more than individuals, but they remind us all of the importance of seeking out greenery wherever we live. I have downloaded the NatureDose app, another NatureQuant product, which allows me to track time outside the way I count steps. And we should heed the advice Jimenez gives her students: "I see how stressed they are, especially during exams," she says. "I tell them, 'Go out for a walk.'" ●

Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American*. She is author of *Friendship* (W. W. Norton, 2020).