April–May 2022

SCIENTIFIC AMERICAN

Health & Medicine

Ready for the Next Plague

Building on lessons learned from SARS-CoV-2, pandemic preparedness has taken on renewed urgency

Plus:

Eye Drops Replace Reading Glasses

Cutting-Edge COVID Treatments

What Is the Best Diet for Humans and Earth?

WITH COVERAGE FROM nature

Liz Tormes

Hard-Won Pandemic Gains

The COVID pandemic is by no means over. Despite plunging case numbers in the U.S. as of this writing, many countries in the world are still experiencing peak infection rates. And it is impossible to foresee how the SARS-CoV-2 saga will unfold in the coming months or years. Since 2020 in this country (and others), hard truths about our deficient health-care system, rampant societal inequality and flawed policy-making engine, to name a few, have crystallized—painfully in some cases.

At the same time, vaccine technology, spurred by the successful deployment of mRNA shots, has catapulted progress on treatments for a slew of other infectious diseases from malaria to cancer (as writer Mike May detailed last year). And medicines for COVID itself are under such intense research and development, that several powerful remedies are currently available, with more in the pipeline (see "These Are the Latest COVID Treatments"). Such advancements are only part of a new arsenal of strategies for confronting a future challenged by COVID and any other virus that might arise (see "Preparing for the Next Plague"). It's too flip to call this progress a silver lining in the midst of so much toil and grief. But it is a significant win.

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Health & Medicine

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Chris Gash

On the Cover

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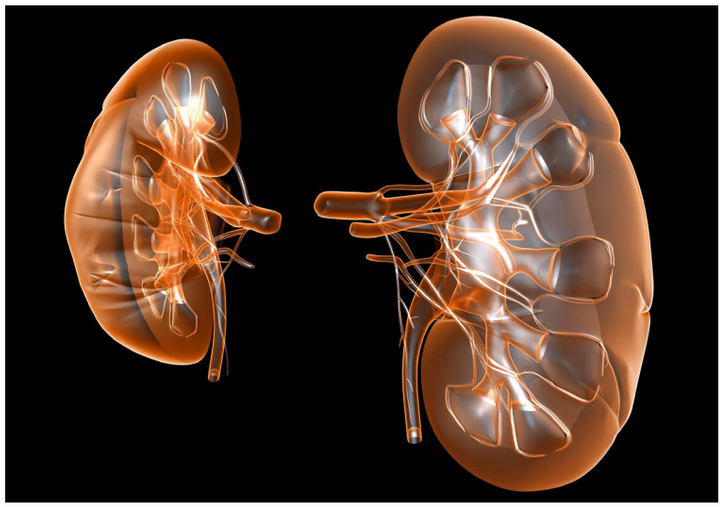

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Chris Gash

FEATURES

OPINION

These Eye Drops Could Replace Your Reading Glasses

Solutions to age-related vision problems now come in a bottle. How well do they work?

Panupong Piewkleng/Getty Images

After I hit middle age, I noticed that printed words on a page didn't look as crisp as they used to. Like many people, I've been wearing reading glasses ever since. But one day recently I squeezed a few drops of a new prescription drug into my eyes instead. A few minutes later the text in front of me was clearer and more sharply focused. But I also noticed the shared kitchen in my office suite was strangely dim, even with the lights on. And I had the faintest whiff of a headache.

After the age of 40, many people start developing presbyopia, a medical term rooted in the Greek phrase for old eyes. It gets harder to read books, food labels and menus. Soon people are reaching for drugstore reading glasses stashed in desk drawers and handbags, but now there is also this bottled solution: prescription eye drops designed to help older people see better up close.

The treatment I used, an Allergan product called Vuity, is the first to reach the market. The drops were approved by the U.S. Food and Drug Administration late last year. Nearly a dozen companies have similar drops in clinical trials, each of them aiming for a "safe, effective, reversible therapy that gives people what they want, which is good near vision," says Eric Donnenfeld, an ophthalmologist at New York University, who consults for Allergan and another drop manufacturer.

All these drops compensate for what happens as the lens within your eye stiffens with age, a normal process. In a healthy younger person, the lens is flexible and automatically focuses light coming from objects near and far. Yet as the lens loses flexibility, nearby images begin to blur.

So how do these drops fix that problem? They do so by shrinking the pupil, the part of the eye that channels light toward the retina, which turns this stimulation into visual signals for the brain. Reducing the pupil opening is similar to reducing the aperture on a camera lens. It blocks extraneous light from more distant objects, bringing the nearby ones into sharper focus. Similarly, a smaller pupil "precludes aberrant light rays from reaching the retina," Donnenfeld says. "That's the key to why the drops work."

Several of the drops, including Vuity, shrink pupils with the same active ingredient: a drug called pilocarpine with a long history as a treatment for glaucoma. Pilocarpine triggers eye muscles to contract. This effect benefits glaucoma patients by opening channels that drain excess fluid from the eye, relieving ocular pressure. The activated muscles also tug on the pupil, which reduces its size. But the muscle tugging can also produce a mild headache centered behind the eyebrows (a condition known as brow ache).

During clinical testing with Vuity, about 30 percent of treated subjects gained the ability to read three added rows of text on a chart positioned at arm's length. The effects wore off gradually over a period of six hours, but other companies are working on longer-acting compounds. Visus Therapeutics in Irvine, Calif., for instance, is developing an eye drop with two active ingredients: one called carbachol that constricts the pupil and another called brimonidine that prevents it from dilating. "We think the effects of treatment can last at least eight hours," says Rhett Schiffman, an ophthalmologist and the company's chief medical officer. Investors have so far poured more than $100 million toward these various products.

But they aren't without controversy. David Guyton, an ophthalmologist at the Johns Hopkins Wilmer Eye Institute in Baltimore, points out that while generic pilocarpine is inexpensive as a glaucoma treatment, a 2.5-milliliter container of Vuity—roughly a month's supply—is not. My bottle cost about $80. (Allergan justifies the high price by saying it has changed the formulation to lessen the sting of the product, making it more comfortable to use.)

Moreover, the drops may create other, less desirable vision changes. "In dim light, the pupils dilate to let more light in, but that will not occur if the pupils are constricted by pilocarpine," Guyton points out. "I should think this effect can be a liability for night driving." Indeed, Vuity's drug label cautions against night driving, but Donnenfeld says that for most people who take the drug as prescribed in the morning, this should not be a problem.

After I tested the drops on my own eyes, a co-worker who also uses reading glasses tried them, too. "I would say it worked—not perfect, but it worked," he says. "The drops reduced—but did not eliminate—the fuzziness of text on my phone." As it did for me, the effect lasted about three hours. For people who hate eyeglasses, the drop route might be worth it. But as I type up the last words on this story, I've got my readers on.

—Charles Schmidt

Pig Kidneys Transplanted to Human in Milestone Experiment

Experts predict that such non-human-to-human "xenotransplants" may become a viable option within the next decade

It's an exciting time to be an organ transplant physician. This past January doctors in Baltimore reported completing the first successful transfer of a pig heart into a living human patient. Now pig kidneys might be just around the corner.

In late September 2021 a team of researchers transplanted a gene-edited pig's two kidneys into the body of a person who had undergone brain death (the irreversible loss of all brain function) in a procedure designed to fully simulate clinical transplantation. Once inserted, the new kidneys sustained blood flow and even produced urine until the study ended 77 hours later. The results were published in the *American Journal of Transplantation.*

"It really demonstrated that we

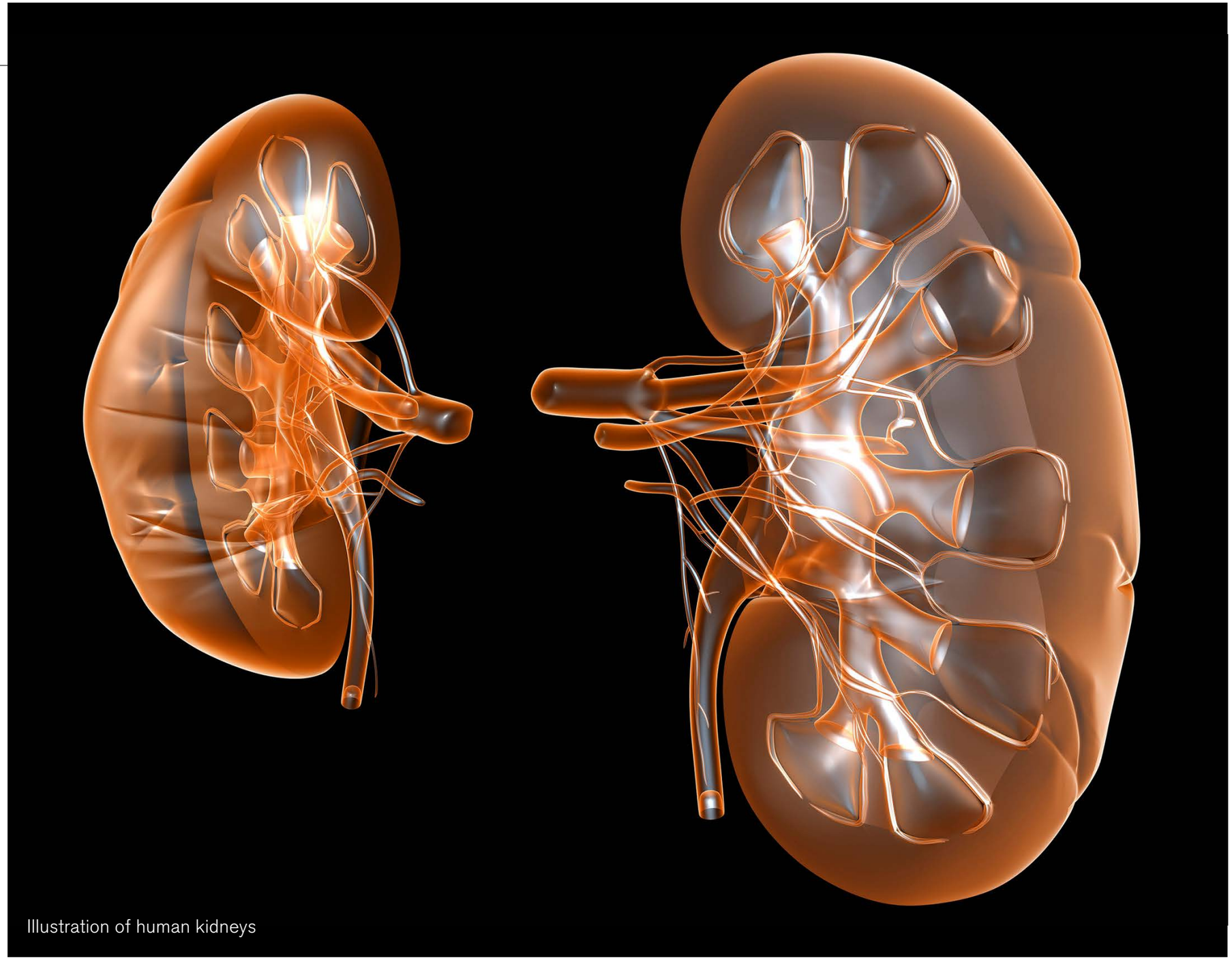


Illustration of human kidneys

Pasieka/Science Photo Library/Getty Images

have the infrastructure to be able to do this," says the new study's lead surgeon Jayme Locke, a transplant surgeon at the University of Alabama at Birmingham (U.A.B.). The investigation's standardized process "is going to be just as important as demonstrating that the pig kidneys are viable in humans."

An organ transplant is full of risks. The human immune system is remarkably good at distinguishing between "self" and "nonself," and when it detects a foreign entity—whether a virus, a strange bacterium or someone else's internal organ—it mounts an attack. This is great for fighting disease. But in the context of transplantation, a strong immune response can eventually cause the body to reject the new organ. To avoid this, doctors prescribe immunosuppressing drugs to the recipient. Unfortunately, these medications also leave the patient susceptible to viruses and bacteria. "The biggest risk is [miscalculating] this balance between rejection and infection," says Dorry Segev, a kidney transplantation specialist at Johns Hopkins University, who was not involved in the research.

For patients receiving a nonhuman organ, a procedure called a xenotransplantation, that risk is multiplied. Xenotransplants (and, in rare cases, poorly matched human organ transplants) can trigger a phenomenon called hyperacute rejection, in which the body begins aggressively attacking the new organ within hours or even minutes of surgery. "It's a different type of rejection. And it's a fundamental barrier," says Paige Porrett, director of vascularized composite allotransplantation and of Clinical and Translational Research at U.A.B.'s Comprehensive Transplant

Institute and lead author of the study.

Porrett's team overcame this obstacle by using kidneys from a designer swine with 10 key genetic tweaks to make its organs a better match for humans. For instance, the donor pig was equipped with genes to help prevent blood clots and regulate blood vessel strength. Another gene, involved in responding to growth hormones, was knocked out to ensure that the transplanted kidneys stayed human-sized inside its recipient. "I certainly wouldn't want a pig-sized kidney," Locke says.

The team's procedure was not the first pig-to-human kidney transplantation: that operation took place on September 25 at N.Y.U. Langone Health, and the recipient was also a person without brain activity. "It was pretty exhilarating," says Robert Montgomery, director of the N.Y.U. Langone Transplant Institute, who performed the surgery with his team. His and his colleagues' research was designed primarily to test the viability of the single kidney. While the organ functioned successfully, removing waste from the blood and disposing of it in the form of urine, it was attached to a blood vessel in the recipient's upper leg rather than implanted in the abdomen, where kidneys normally go.

In contrast, the U.A.B. team executed a full clinical transplant procedure, from assessing organ compatibility to removing the recipient's kidneys and replacing them with the xenotransplants. The researchers also took pains to ensure that the donor pig was raised in a pathogen-free facility, and they had the entire process reviewed by an ethics board. "At times that felt harder than the actual science that we were doing," Porrett says.

The transplantation itself went smoothly: the kidneys showed no signs of hyperacute rejection and even began to function. Within 24 hours, the right kidney produced around 700 milliliters of urine—about as much as an average adult makes in a day. The left kidney only produced a few milliliters on the first day but became more active by the second. This was not unexpected, however, Locke says, because up to a week of delayed function sometimes occurs in human-to-human transplantations.

Keeping a body going for more than a week after brain death is typically difficult. Montgomery notes that the kidneys developed tiny blood clots called fibrin thrombi but that this may be the result of the patient's condition. "There are complications after brain death," he says. "It can be quite stormy." Jim Parsons, the recipient in the U.A.B. study, had been deceased for five days when the operation took place, so the trial was terminated after an additional three days when liver failure and other problems set in. The team hopes to name its protocol the "Parsons model" in honor of him and his family.

There is still a lot of work to do before xenotransplantation becomes routine. Locke and Segev agree that it will take at least another five to 10 years' worth of research before pig kidneys could potentially go mainstream. But they say these advances are incredibly encouraging. We may be fast approaching the day when the nearly 100,000 Americans on the organ transplantation list will no longer have to wait—sometimes for years or in vain—for a human donor.

"For the first time ever, I feel like I will see xenotransplantation in my career," Segev says. "I don't say that lightly."

—Joanna Thompson

COVID Smell Loss and Long COVID Linked to Inflammation

Hamsters eating Cocoa Krispies reveal inflammation pathways from the olfactory system to the brain

An impaired sense of smell affects from about 30 to 75 percent of people infected with the novel coronavirus, according to a recent estimate, suggesting that millions of people worldwide have suffered this condition at some point in the past two years. Called anosmia, the olfactory system dysfunction is typically temporary, but it can take months or longer for a full recovery, making it difficult to enjoy meals and to detect odors such as spoiled food, smoke and others that can signal danger.

Now a February 1 study in *Cell* proposes a detailed biological explanation for COVID-related loss of the sense of smell: The research involved feeding Cocoa Krispies cereal to virus-infected hamsters and then confirming genetic results in

Dmitry Marchenko/EyeEm/Getty Images

human tissue. The team concludes that infection with the coronavirus, or SARS-CoV-2, causes severe inflammation in structural cells in the olfactory system, thereby overwhelming and impairing the function of nerve cells and other smell-related processes deep in the nasal cavity.

A similar cascade of olfactory effects might explain the biological mechanisms behind long COVID, the researchers suggest in a second study that was posted online as a preprint on January 20. To learn more about these related insights into anosmia and long COVID, *Scientific American* spoke with virologist Benjamin tenOever, director of the N.Y.U. Langone Virology Institute and a faculty member at New York University's Grossman School of Medicine. TenOever is part of the team that conducted the anosmia-focused study and is senior author of the long COVID study.

[*An edited transcript of the interview follows.*]

How did you test anosmia and other olfactory effects of SARS-CoV-2 infection?

There has yet to be any biology witnessed in manifestations of COVID-19 in humans that we cannot replicate in hamsters. So we studied three groups of hamsters—a group infected with SARS-CoV-2, a group that received a control substance as a mock infection and an influenza-infected group to provide a benchmark showing the typical immune response to a common respiratory virus. Then we did behavioral tests with the groups, including one that involved withholding food for about 10 hours so the hamsters were good and hungry. And then we took Cocoa Krispies—which the hamsters love—buried the cereal under their bedding and then timed how long it took them to grab it and stuff their face with it.

Among the hamsters infected with the mock or the flu viruses, they all found the Cocoa Krispies within seconds on days zero through day 14 after infection. But the SARS-CoV-2 animals on day one and on day two didn't find the Cocoa Krispies at all. They just left them. So it was very clear that they lost their sense of

smell because, by day 15, they were all back on track, and everybody was very happy and focused on finding and eating the Cocoa Krispies. We then repeated that experiment, but this time we used single-cell sequencing, which lets you see not only all the cells that make up the olfactory system but also where the virus is going and the consequences of that infection in all of those cells.

What did the team learn about the details of the mechanism that underlies anosmia?

What the data show is that the virus is limited to this one type of cell called SUS, or sustentacular—cells in the olfactory tissue in the nasal cavity. This cell type performs an important structural role and ensures that related cells, called olfactory sensory neurons, in that tissue are organized in such a way that you can perceive smells. Following SARS-CoV-2 infection, we find that hamsters have lost more than half of all of their SUS cells in a two-day period. So the structure of the olfactory system has just been totally decayed away because of that significant cell death. And as a result, those SUS cells are now spewing out a great deal of material that triggers inflammation.

On day three, because of the inflammation and damage, janitorlike immune cells called microglia and macrophages come in and engulf all the inflammatory material and clean it up to bring the inflammation invoked by that material back down to baseline.

What happens next to cause the loss of sense of smell?

The adjacent olfactory sensory neurons, which detect odors, typically spend 80 percent of their transcriptional [gene-copying] bandwidth dealing with olfactory-related biology such as processing smells and making different smell-related receptors. Now, suddenly, they are bombarded with all of this other inflammatory information that's demanding, let's say, 50 percent of their transcriptional bandwidth. As a result, the neurons are forced to avert their attention from olfaction, resulting in a dramatic loss of production for the components needed for smell, culminating in anosmia.

The cells are still there, and the cells aren't dying. They are just busy doing something else. And as a result, you will lose your sense of smell because so much bandwidth has been taken away, and your olfactory machinery can no longer comprehend such a complex process. And so, for a brief period of time, about three to five days after infection with SARS-CoV-2, many people lose their sense of smell. But by then, the janitorial cells have cleaned up a lot of that inflammatory material, and progenitor cells replenish the population of SUS cells. And most people get their sense of smell back.

"But if we give steroids that cross the blood-brain barrier to hamsters, and they actually shut this inflammation down, it would suggest that this would also work in human beings."
—Benjamin tenOever

How does this anosmia research relate to the proposed cause of long COVID in your second new study?

This study goes one step further to say, "Yes, all of this olfactory system inflammation can persist for a long time. And the longer it stays there, the longer you respond to it." There are many reasons why the inflammation might last a little bit longer in certain individuals. But what we find is that the inflammatory response in the olfactory system can travel into the brain.

We sequenced all of the organs from SARS-CoV-2-infected hamsters during the first week of infection, when the virus is actively replicating, as well as weeks and months thereafter. In addition to different organs, we also performed this same type of analysis on individual brain compartments, including the prefrontal cortex, striatum, thalamus, cerebellum, trigeminal ganglion and the olfactory bulbs. These analyses demonstrated that the entire body shows signatures of inflammation for weeks following viral clearance.

While this inflammatory response does diminish over time in the body's organs, these transcriptional changes persist much longer in the olfactory bulbs, striatum, thalamus and cere-

bellum. What's more, those transcriptional signatures show loss of a number of metabolic activities as they maintain this heightened inflammatory state. The changes in metabolism scarily look a lot like some of the signatures that come out of, say, Alzheimer's, Parkinson's, ALS [amyotrophic lateral sclerosis] and other neurodegenerative diseases. And in hamsters, we can correlate the ones that have that activity as also doing very poorly on behavioral tests. So the fact that they were behaving differently would suggest that they're also having some kind of cognitive change or behavioral change as a result of this prolonged inflammation that has penetrated many aspects of their neurological circuitry.

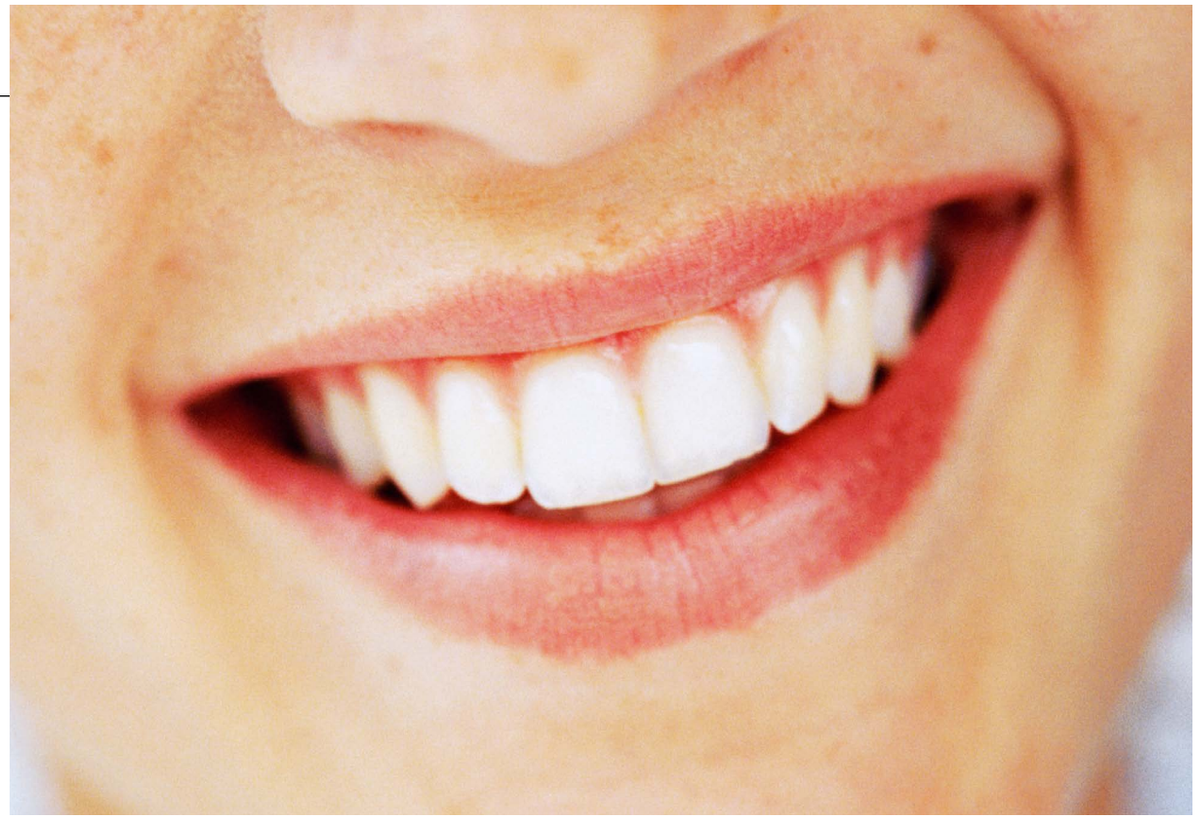
What are the implications of these findings for the treatment of long COVID?

By the time a patient with COVID is in the hospital, the problem usually is no longer replicating virus. It's actually all of that inflammatory material that is still there causing your body to overreact to it. And so we treat with steroids to set everything back down to baseline. This would suggest that the same thing should work in the brain for people with long COVID, but this needs to first be tested in animals to understand dosage, timing and steroid choice.

If researchers found that the coronavirus did infect neurons and that long COVID was actually the by-product of a low-grade infection somewhere in the brain, the last thing you would want to do is give those people steroids. That would actually lower the innate immune defenses in your brain and allow the virus to build up a bigger armament and start replicating anew in the brain, which obviously you don't want. If you give somebody who has SARS-CoV-2 steroids before they have cleared the virus, it's very bad news.

But if we give steroids that cross the blood-brain barrier to hamsters, and they actually shut this inflammation down, it would suggest that this would also work in human beings. Obviously, we need to do more testing before studying this in people. We already have a colony of hamsters with long COVID, and we will soon begin testing steroids and antidepressants to determine possible therapeutic approaches.

—Robin Lloyd



Jerome Tisne/Getty Images

Synthetic Enamel Could Make Teeth Stronger and Smarter

Scientists say that the new material is even more durable than real dental enamel

Enamel, the tough outer covering of a tooth, is the hardest substance in the human body. It is also notoriously difficult to replicate artificially. Throughout history, dentists have repaired damaged and decayed teeth with everything from beeswax to mercury composites to modern ceramic- or resin-based materials. But they might soon have a synthetic option that is much closer to the real thing.

A team of chemical and structural engineers has invented a new material that mimics enamel's fundamental properties: It is strong and—very important—also slightly elastic. This versatile substance could potentially be used to reinforce fractured bones, craft better pacemakers and, beyond serving as a replacement for dental enamel, take fillings to the next level by creating "smart teeth." A study on this work was published in February in *Science*.

Natural enamel has the difficult job of protecting teeth, which are constantly being strained by oral bacteria, acidic foods, chewing and even speaking. Over time the wear and tear adds up. "You carry the same set of teeth for 60 years or maybe even more," says Nicholas Kotov, a chemical engineer at the University of Michigan and co-author of the study. "So it's an enormous chemical and mechanical stress." And unlike bone, enamel cannot be regenerated by the human body.

Enamel's crucial combination of toughness and flexibility is tricky to reproduce. "Soft materials are normally easier to manufacture," Kotov explains. The secret to enamel's uniquely balanced properties lies in its structure. It is composed of millions of closely packed rods of calcium phosphate, which are only visible through an electron microscope.

"Imagine a pack of pencils when you hold them together," says Janet Moradian-Oldak, a biochemist at the University of Southern California who was not involved in the research. This arrangement allows the rods to compress slightly under pressure, rather than shattering, while also keeping the overall structure extremely strong. The artificial enamel mimics this configuration, bundling calcium phosphate rods together with flexible polymer chains.

The researchers fashioned their new material into a tooth shape, then tested whether it would crack under intense heat and pressure. "It's actually very elegant the way that these authors use engineering and harsh laboratory conditions to mimic what cells and nature do," Moradian-Oldak says. Ultimately the team found the artificial enamel could withstand more force than the natural kind.

The material may not be a perfect tooth analogue, however. "I don't see much answered in the paper to mimic the 3-D structure of human enamel," says Thomas Diekwisch, a craniofacial researcher at Texas A&M University, who was not involved in the new study. But, he notes, that doesn't mean it won't be useful. "At least for functional biomimicry, you don't have to exactly reproduce what nature does."

Outside of its obvious potential in dentistry, Kotov envisions the material being used to build better and longer-lasting pacemakers for people with heart conditions or to reinforce crumbling bone in those with severe osteoporosis. He says the material could even be modified to create a "smart tooth," a prosthetic chomper containing sensors that could sync to a smartphone. Such a device could monitor a person's breath and mouth bacteria for anomalies, which would allow doctors to catch conditions such as diabetes before a patient is aware of them.

But before it can debut in the dentist's office, the material has to be affordable, mass-producible, and clinically tested for safety and efficacy. "I'm impressed with the approach that they use," Moradian-Oldak says. "The question is, How practical is it?"

Kotov says his team used strictly biocompatible compounds in the fabrication process, which means the artificial enamel should theoretically be safe for humans. He hopes to see it used in the next few years, but he isn't making any projections. Paraphrasing a quote that's been attributed to such figures as Niels Bohr and Yogi Berra, Kotov says, "It's very difficult to predict anything—especially the future."

—Joanna Thompson

Epstein-Barr Virus Found to Trigger Multiple Sclerosis

The research could mark a turning point in the fight against MS

A connection between the human herpesvirus Epstein-Barr and multiple sclerosis (MS) has long been suspected but has been difficult to prove. Epstein-Barr virus (EBV) is the primary cause of mononucleosis and is so common that 95 percent of adults carry it. Unlike Epstein-Barr, MS, a devastating demyelinating disease of the central nervous system, is relatively rare. It affects 2.8 million people worldwide. But people who contract infectious mononucleosis are at a slightly increased risk of developing MS. In the disease, inflammation damages the myelin sheath that insulates nerve cells, ultimately disrupting signals to and from the brain and causing a variety of symptoms, from numbness and pain to paralysis.

To prove that infection with Epstein-Barr causes MS, however, a research study would have to show

Conceptual image of a neuron affected by multiple sclerosis

Stocktrek Images/Getty Images

that people would not develop the disease if they were not first infected with the virus. A randomized trial to test such a hypothesis by purposely infecting thousands of people would of course be unethical.

Instead researchers at the Harvard T. H. Chan School of Public Health and Harvard Medical School turned to what they call "an experiment of nature." They used two decades of blood samples from more than 10 million young adults on active duty in the U.S. military (the samples were taken for routine HIV testing). About 5 percent of those individuals (several hundred thousand people) were negative for Epstein-Barr when they started military service, and 955 eventually developed MS. The researchers were able to compare the outcomes of those who were subsequently infected and those who were not. The results, published on September 13, 2021, in *Science*, show that the risk of multiple sclerosis increased 32-fold after infection with Epstein-Barr but not after infection with other viruses. "These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS," the researchers wrote.

In an accompanying commentary, immunologists William H. Robinson and Lawrence Steinman, both at Stanford University, wrote, "These findings provide compelling data that implicate EBV as the trigger for the development of MS." Epidemiologist Alberto Ascherio, senior author of the new study, says, "The bottom line is almost: if you're not infected with EBV, you don't get MS. It's rare to get such black-and-white results."

Virologist Jeffrey I. Cohen, who heads the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health and was not involved in the research, is cautious about claiming "cause." He argues that it still must be shown that preventing Epstein-Barr prevents MS but agrees the results are dramatic. "When the original studies were done with cigarette smoking and lung cancer, they found a 25-fold risk factor for people who smoked more than 25

cigarettes a day," Cohen says. "This is even higher."

Much of the world's population, especially in developing countries, is infected with Epstein-Barr very early in life without much ill effect, although the virus can lead to several rare cancers. Everyone else is infected in adolescence and young adulthood, when Epstein-Barr usually leads to infectious mononucleosis, also called "kissing disease" because it is transmitted via saliva. After infection, Epstein-Barr lives on in some B cells of the immune system, and the antibodies developed to fight it remain in the blood.

In the new study, which is a much larger expansion of a 2010 investigation, the researchers analyzed up to three blood samples for each individual with MS: the first taken when most of the military personnel were under the age of 20, the last taken years later, before the onset of the disease, and one in between. The team was looking for seroconversion, or the appearance of antibodies in the blood as evidence of infection.

Each person with MS was also matched with two randomly selected controls without MS, who were of the same age, sex, race or ethnicity, and branch of the military. Out of the 955 cases of MS, they were able to assemble appropriate samples for 801 individuals with the disease and 1,566 controls. Thirty-five of the people who developed MS and 107 controls tested negative for EBV initially. Only one of the 801 people with MS had not been infected with Epstein-Barr before the disease's onset. The risk of developing MS was 32 times greater for those who seroconverted by the third sample, compared with those who did not.

As for the one case of MS in someone who remained negative for Epstein-Barr, it is possible that person was infected after the sample was taken, but it is also true that in diseases that are clinically defined by their symptoms, such as MS, it is highly unlikely that 100 percent of cases derive from the same cause, even if most do, Ascherio says.

"The numbers are just so striking," says Stephen Hauser, director of the University of California, San Francisco, Weill Institute for Neurosciences, who was not involved with the study. "It's really a uniform seroconversion before the onset of MS that is really far more significant than in the control population."

"When the original studies were done with cigarette smoking and lung cancer, they found a 25-fold risk factor for people who smoked more than 25 cigarettes a day. This is even higher."
—Jeffrey I. Cohen

But to be sure Epstein-Barr was the culprit, Ascherio and his colleagues also measured antibodies against cytomegalovirus, another herpesvirus, and found no difference in levels in those who developed MS and those who did not. Using a subset of 30 MS cases and 30 controls, they conducted a scan to detect antibody responses to most of the viruses that infect humans. Again, there was no difference. And to rule out the possibility that infection with Epstein-Barr preceded MS and not the other way around, the team also measured levels of a protein that is elevated in serum when neurons are injured or die and that therefore serves as a marker of the beginning of the pathological process before clinical symptoms appear. The protein levels rose only after Epstein-Barr infection.

One major question remains, however: How does the virus lead to the disease? That is unknown and "elusive," Robinson and Steinman wrote in their commentary. They proposed several possibilities, such as inducing an autoimmune reaction.

Even if Epstein-Barr is the triggering event for MS, infection alone is insufficient for an actual diagnosis. Epstein-Barr, it appears, has to combine with a genetic predisposition and possibly environmental factors, such as smoking and vitamin D deficiency, to increase risk. Understanding the underlying mechanism will be important, the experts say. But meanwhile "this is the best epidemiologic lead we have in terms of the cause of MS," Hauser says.

Historically, we have thought of MS as an autoimmune disease of unknown etiology. "Now we should start thinking of MS as a complication of infection with the Epstein-Barr virus," Ascherio says. "This should open a new chapter in trying to find a way to treat and prevent the disease."

Antivirals that target EBV in infected B cells are one possibility. One of the more exciting developments in MS in recent years was the success of B cell–depletion therapies. In earlier work, Hauser and his colleagues found that the tissue damage in MS is primarily directed by B cells, which attack the myelin sheath protecting nerves. The therapies now approved for use are monoclonal antibodies that kill those B cells, thereby easing inflammation. They are not a cure but are highly effective against MS relapses, reducing the development of new lesions measured by magnetic resonance imaging (MRI) of the brain by an astounding 99 percent. They are also the only therapies shown to be effective against primary progressive MS, a previously untreatable form of the disease.

"One might be able to refine these therapies that are working well and maybe just target the EBV-infected B cells," says immunologist Christian Münz of the University of Zurich, who was also not involved in the new *Science* study.

Others are already working on vaccines that could prevent infection with Epstein-Barr. Moderna, which created an mRNA vaccine against COVID-19, launched a phase 1 trial of an mRNA vaccine for Epstein-Barr in January. And NIAID's Cohen expected to begin a phase 1 trial of another Epstein-Barr vaccine by the end of February. If these researchers succeed, such vaccines might dramatically reduce the incidence of mononucleosis and some cancers. And now it is conceivable that they could do the same for MS.

—Lydia Denworth

Preparing for the Next Plague

SARS-CoV-2 adds impetus to the race for broad-spectrum countermeasures against future global infectious scourges

By Laura DeFrancesco

Chris Gash

Laura DeFrancesco is a senior editor for *Nature Biotechnology*.

LAST SEPTEMBER U.S. PRESIDENT JOE BIDEN ANNOUNCED A PLAN TO PREPARE FOR THE next pandemic, with an initial outlay of $15 billion and a total investment of $65.3 billion over the next 10 years. The first goal is to "design, test, and approve a safe and effective vaccine against any pathogenic human virus within 100 days following the identification of an emergent viral pandemic." A series of steps are laid out to accomplish this, the first being to characterize a so-called prototype pathogen from each of 26 viral families known to infect humans, to help identify potential epitopes that could inform vaccine design.

Pandemic preparedness is hardly a new idea. The most recent of many such efforts was the Obama administration's pandemic playbook in 2016, following outbreaks of Ebola in West Africa and Zika in the Americas. In addition, the U.S. National Institutes for Autoimmunity and Infectious Disease (NIAID) and the U.S. Defense Advanced Research Projects Agency have had their sights on creating countermeasures that could be deployed quickly in the event of any outbreak. The speed with which the COVID-19 mRNA vaccines were developed was not an accident but can be traced back to work funded and directed by both agencies. Yet the success of the present vaccines was also somewhat serendipitous, as coronaviruses have a particularly easy target in their spike (S) protein, not to mention having been the subject of more than a decade of research after the SARS-CoV-1 outbreak in 2002 and Middle Eastern respiratory syndrome (MERS) in 2015. In the next pandemic, the world may not be so lucky.

So with a combination of optimism and fear—optimism that a fast response is possible and fear that the next pathogen might not succumb so easily—pandemic preparedness has taken on a renewed urgency, which, it is hoped, won't dissipate once the current pandemic ends.

VACCINES 2.0

The teams working on mRNA vaccines for SARS-CoV-2 are already turning their attention to the next pandemic. They are trying to leverage the knowledge gained from the successes of first-generation SARS-CoV-2 vaccines for the next set of pandemic vaccines.

One advantage of the mRNA vaccine platform, according to Moderna's CSO Andrea Carfi, is that different mRNAs can be combined to target more than one pathogen or, in the case of SARS-CoV-2, more than one variant. Moderna has already announced that it has preclinical data on a combination flu and COVID-19 vaccine, which will be going into clinical trials in 2022, and it has plans for multivalent vaccines against SARS-CoV-2 variants Beta and Delta. There is no limit to the number of RNAs that can be combined, Carfi says. Moderna also has a cytomegalovirus (CMV) vaccine about to enter phase 3 trials that has six mRNAs and has preclinical data on another comprising 10 mRNAs. Understanding how these mRNA cocktails give rise to an immune response is something the company is still working on. What its researchers can say is that they have tested multivalent vaccines encoding different proteins, and they can detect antibodies against the individual proteins. When it comes to timing, Carfi thinks they can go even faster with their SARS-CoV-2 mRNA vaccine (which took 63 days from sequence selection to trial) by optimizing manufacturing and clinical readiness.

Given that the SARS-CoV-2 vaccine constituted the first experience of putting this type of vaccine in people's arms on a global scale, safety had to be prioritized. But now, with hundreds of millions of people vaccinated, Carfi speculates that the U.S. Food and Drug Administration may have more confidence and familiarity with the platform, which could shave some time off the regulatory review process in the future as well.

Ralph Baric's group at the University of North Carolina has been collaborating with the leading mRNA research groups from University of Pennsylvania, NIAID and Duke University. Their next-generation vaccine is a chimeric mRNA vaccine that builds on the modular nature of the coronavirus S protein. According to David Martinez, a postdoc in Baric's group since 2018, "The idea is to design a spike that instead of being monomorphic and eliciting immunity to one virus, you could increase the immunogenicity by having coverage for three viruses within one spike." This is possible because there are

three sites that are the targets of protective antibodies—the N-terminal domain, the receptor-binding domain (RBD) and the S2 domain. In a study published in *Science*, the Baric group report on a set of four different chimeric mRNA vaccines with different combinations of N-terminal domain, RBD and S-protein mRNAs and show they can raise high levels of neutralizing antibodies against multiple sarbecoviruses (the subgenus of coronaviruses encompassing SARS-1 and SARS-2). A vaccine with only the SARS-CoV-2 S protein vaccine did not show the same breadth. One chimeric vaccine, however, raised antibodies against SARS-CoV, SARS-CoV-2, the SARS-CoV-2 Beta variant and two bat coronaviruses (CoVRsShC014 and Cov1-WIV-1) that are thought to be poised for human emergence because they can replicate well in human primary airway cells. Although the level of antibodies was lower than with a monovalent vaccine, the breadth of coverage was greater.

Another way of going for breadth is to vaccinate with viruslike particles (VLP). According to Adam Simpson, CEO of Icosavax, a spinout from the University of Washington's Institute of Protein Design, "a VLP will inherently have a breadth of response that's different [from] a soluble protein whether it's made from a mRNA or not." Not all viruses can be made into VLPs, however, and Icosavax's magic has been in using a computationally designed two-component system developed at the university, where any antigen can be displayed in an immunogenic array. The two components comprise proteins that are made separately and, when combined, self-assemble into a 128-subunit particle (VLP) with multifaceted icosahedral symmetry (imagine a soccer ball). The antigen (in the case of SARS-CoV-2, the RBD) is linked to one of the proteins via a linker comprising eight, 12 or 16 glycine and serine residues. "The reason it's so important," says Simpson, "is that it is a platform where we can put any antigen we want onto the VLP, and as components are proteins, they can be made by anyone with the technology for manufacturing proteins." In their case, the antigen is made in a mammalian cell line (CHO cells) so that it's properly glycosylated and the second component in *Escherichia coli* because it's inexpensive. "If you can make a protein, you can make our vaccine," Simpson says.

"If you can make a protein, you can make our vaccine."
—Adam Simpson

Although other mRNA and protein nanoparticle vaccines are multiplexing to get breadth of protection, Simpson thinks that won't be necessary with their VLPs. "If they look and smell like viruses, the body will react," he says. In 2020 preclinical work with a SARS-CoV-2 VLP displaying 60 RBDs, conducted at the University of Washington, Neil King's group found the VLPs not only produced 10-fold higher titers than the S protein (a version engineered to stabilize the protein in the form it has before fusing with a cell it infects, employed in COVID vaccines) but also targeted multiple epitopes, suggesting that it would be hard for the virus to mutate around the VLP vaccine, which protects against related strains not in the vaccine. With a $10-million grant from the Gates Foundation and a partnership with Amgen, which is providing one of the protein components of the SARS-CoV-2 VLP, Icosavax has advanced VLP IVX-3441 into a phase 1/2 clinical trial in Australia. A different VLP provided by University of Washington researchers is being tested in clinical trials by SK Bioscience.

Also at the University of Washington, David Veesler's group, which participated in the discovery work behind some anti-SARS-CoV-2 monoclonal antibodies being developed by Vir Biotechnology as well as Icosavax's VLP, continues to investigate how understanding of the basis of immunity to infectious agents can be used to guide vaccine design. In recently published work from his group, multivalent, mosaic VLPs and cocktails of different RBD VLPs raised neutralizing antibodies against a range of coronavirus variants and protected mice in challenge experiments with SARS-CoV-1, even when the combination did not include its RBD. Veesler calls this an example of a second-generation vaccine, vaccine 2.0, which would be broadly neutralizing for multiple variants of SARS-CoV-2 and other sarbecoviruses. Vaccine 3.0 would be for betacoronaviruses, which encompasses multiple lineages of which sarbecoviruses are only one. This is a long way off, however, because of the large diversity in the family, Veesler says.

"I'm careful not to use the term 'pan-sarbecovirus.' There are reasons for that: there's a lot of diversity among known sarbecoviruses, and we know that we might have only scratched the surface. There are so many that we have not yet discovered."

ACCELERATED ASPIRATIONS

The Coalition for Epidemic Preparedness Innovations (CEPI) aims to accelerate the development of vaccines against emerging infectious diseases. Part of its rationale is to counter the boom-and-bust cycle of commercial development programs, which receive an influx of funding at the outset of an outbreak but historically run out of funding when the epidemic threat recedes. The CEPI was launched at Davos in 2017 after the Ebola epidemic in West Africa had killed more than 11,000 people; here again, vaccine development came too late to save any lives. Since its founding, the CEPI has supported a number of innovative vaccine programs, as well as some conventional ones.

In response to the current epidemic, the group has put $200 million on the table to start the race toward broadly protective vaccines both against SARS-CoV-2—this call ended last September, and applications are under review—and one for betacoronaviruses (the family that encompasses MERS as well as SARS viruses) more generally, which closed on October 1, 2021. "There's an awful lot of room for improvement, not just stability, which has been well covered in the media, but also the productivity, driving down the costs, improving the safety profile and potentially improving the longevity of the response," says Nick Jackson, the CEPI's head of programs and innovations.

In the U.S., DARPA recognized that traditional vaccine development time lines prevent vaccines from being an effective countermeasure in a sudden outbreak. In 2012 it launched a five-year program, ADEPT-PROTECT (Autonomous Diagnostics to Enable Prevention and Therapeutics), to develop alternative technologies. Initially this set out to explore nucleic-acid-based therapies rather than the more traditional types based on inactivated viruses or recombinant protein subunits. In fact, the first clinical trial using a systemically administered mRNA-based therapeutic encoding a secreted protein, Moderna's monoclonal antibody (mAb) to chikungunya virus, was developed with DARPA backing (the company funded its phase 1 trial).

The research behind that therapy came from another DARPA-supported group, Vanderbilt's Vaccine Center, which is directed by James Crowe. Crowe's group isolated potent neutralizing antibodies from a previously infected person, from which they determined the genetic sequence, which was used as the template for the mRNA-encoded antibody. Using the same approach, Crowe's group has produced other protective antibodies, among them a cocktail of antibodies that inactivates Ebola virus and an antibody against Zika virus. In September 2019, Moderna reported phase 1 clinical trial results of its chikungunya therapy. A few months later they, along with the rest of the world, turned their attention to SARS-CoV-2.

"We screened around six million B cells to identify around 500 unique antibodies that bound to the spike protein within a week."
—Carl Hansen

In March 2020, a mere 63 days after the company received the sequence of SARS-CoV-2, a Moderna mRNA vaccine, mRNA 1273, developed in partnership with the Vaccine Research Center at NIAID, became the first COVID-19 vaccine to enter clinical trials. This effort came about because of support from DARPA—a $25-million grant in 2003 to develop mRNA vaccines, followed by $56 million in 2020 to support manufacturing of the SARS-CoV-2 mRNA vaccine. DNA vaccine company Inovia was the second company to trial a nucleic-acid-based COVID-19 vaccine, in April 2020, with backing from the Bill and Melinda Gates Foundation and DARPA. After some fits and starts (the FDA imposed a clinical hold because of problems with the device used to deliver the DNA), this vaccine (INO-4800) received authorization to conduct phase 3 trials in Mexico and the U.S.

ANTIBODIES AS FIRST RESPONDERS

In 2017, as the ADEPT program was winding down, a follow-on program was spawned, the Pandemic Prevention Platform, or P3. This program set up a challenge: to produce a protective antibody against a virus within 60 days of receiving a sample. According to P3's program manager Amy Jenkins, "We envisioned that the likely approach would be a nucleic-acid-based antibody that would be similar to vaccines. It would deploy as an RNA-based antibody, which would turn the body into a bioreactor." Four teams took up the challenge: AbCellera Biologics, MedImmune/AstraZeneca, Duke University and Crowe's group at Vanderbilt University.

The groups practiced on various viruses, but then in 2019, halfway through the program, they were confronted with the real-life challenge of SARS-CoV-2. Crowe says that he and Jenkins contemplated whether they were ready to tackle this, especially as, early on, patient samples were unavailable. But as soon as a U.S. patient was identified in January 2020, they decided to go for it. The first step—identifying an antibody—was achieved in roughly a week by AbCellera, followed by Vanderbilt. As AbCellera's CEO Carl Hansen described it, "We screened around six million B cells to identify around 500 unique antibodies that bound to the spike protein within a week."

As part of the P3 program, AbCellera had participated in a couple of capability demonstrations—pressure testing—that were critical leading up to the pandemic. "It allowed us build relationships and to figure out all the weak spots in handoffs and communication," Hansen says. Similarly, Vanderbilt's group had done a full Zika sprint in 78 days and was partway through sprints for an H3N2 and an H1N1 antibody when they pivoted to SARS-CoV-2. With lessons learned from these first two sprints, they went from receipt of convalescent patient blood sample in March 2020 (from individuals who had been infected in Wuhan, China, in December 2019) to the transfer of antibody sequences for validated potently neutralizing antibodies to AstraZeneca in 25 days.

At that point, Jenkins felt that technology for using nucleic acid vectors to deliver the mAbs was not far

enough along in development to make an mRNA-encoded mAb at the scale required for an already out-of-control pandemic. "The more sure bet in the spring of 2020 was to take the antibodies into more traditional platforms. So that's what we did." AbCellera Biologics teamed up with Eli Lilly (which was not receiving P3 funding); and in May 2020, just 91 days after receiving the patient sample, they dosed their first patient. "They didn't hit 60 days, but we were only half way through the program," Jenkins says. Lilly received an emergency use authorization (EUA) for bamlanivimab (a humanized IgG1 with modified Fc regions) for treating patients with mild to moderate COVID-19 in November 2020. "The encouraging thing was that they were quickly discovered, and among the first interventions along with remdesivir and some steroids—encouraging that we could deploy so rapidly, being honest, and surprised that protein-based manufacturing was quick," she says.

Hansen gives credit to their partner, Lilly, for stepping up. "Lilly deserves tremendous credit for recognizing the opportunity. They haven't traditionally been in infectious disease, and they wanted to be a positive force in responding to COVID," he says. Although the EUA for bamlanivimab as a monotherapy was revoked by the FDA in April 2021, it is still in use along with a second antibody, etesevimab, that Lilly licensed from Shanghai Junshi Biosciences. Collectively these antibodies have been used to treat approximately 600,000 patients, according to Hansen. "The results have shown, if you look at the stats, [this] has probably saved tens of thousands of lives and tens of thousands of hospitalizations," he says.

From their COVID-19 sprints, Vanderbilt isolated hundreds of SARS-CoV-2 antibodies and licensed two to AstraZeneca, which engineered them to extend the half-life and to eliminate potentially harmful effector functions. AstraZeneca took AZD7442, a combination of two long-acting antibodies, tixagevimab and cilgavimab, that block the SARS-CoV-2 S protein from binding to its host receptor angiotensin-converting enzyme 2 (ACE2) into clinical trials for prevention of COVID-19. Tixagevimab and cilgavimab are both human IgG1 mAbs engineered with five amino acid substitutions (at positions T240, M241, Y308, T310 and E312). Last September the company reported phase 3 clinical trial results on more than 3,000 at-risk (uninfected) people: the antibodies were 77 percent effective in preventing infection, making this the first mAb combination to demonstrate prevention of COVID-19—an important first in demonstrating a new way to enlist antibodies during a pandemic.

"The more sure bet in the spring of 2020 was to take the antibodies into more traditional platforms. So that's what we did."
—Amy Jenkins

PAIN POINTS

The P3 groups collectively demonstrated that antibodies can be isolated and deployed quickly, not just for treatment but also for prevention, and that this can be done even from scratch in a few months, faster than for typical vaccines. And although the RNA vaccines were also put into arms in amazingly short order, a vaccine-induced immune response can take weeks to months to develop. Furthermore, RNA vaccines may not work for all viruses nor for all people, such as those who are immunocompromised (by some estimates, as many as 15 million in the U.S. alone). For tamping down an emerging potential pandemic, antibodies potentially provide a better solution to contain an outbreak in its early days, while vaccine development and production proceed.

Historically, however, only a few anti-infective antibodies have ever been developed and approved for use. Two decades separated the approvals of the first two marketed anti-infective mAbs: palivizumab in 1999 and bezlotoxumab in 2017. The former is a humanized IgG1k mAb targeting an epitope in the A antigenic site of the respiratory syncytial virus (RSV) F protein; the latter is a human IgG1 mAb that binds *Clostridium difficile* toxin B.

There are several reasons why such mAbs have not taken the world by storm. Much as for antibiotics, the commercial market for anti-infective antibodies has essentially failed. Most biotech companies working on mAb development have focused instead on more lucrative conditions in oncology, inflammatory disease or rare conditions.

Any manufacturing base for an anti-infective mAb indicated for use in a pandemic must have the capacity to make antibodies for millions, or even billions, of people. Yet antibody manufacturing capacity, which typically uses mammalian (CHO) cells, is expensive and is finite worldwide. Even though the market is gargantuan, the high cost of goods for bulk manufacture of CHO cells means that anti-infective mAbs are not an attractive business proposition, as they have low product price points and low returns on investment. And the problems don't stop there: antibodies also pose problems for distribution in limited-resource public health settings because they must be administered by intravenous infusion, which requires hospitals or infusion centers and trained personnel, which very often are absent in resource-poor countries.

Several antibody engineering biotechs have been chipping away at these issues and have already started clinical testing (or will soon) of mAbs as prophylactics. Cen-

tivax, through a combination of dry- and wet-lab techniques, has increased the mAb's half-life, broadened its delivery modes, increased its potency and removed potential unwanted effector functions—enabling, among other things, intramuscular injections of small amounts of their antibodies, which simplifies their administration and potentially drives down cost. Centivax founder Jacob Glanville applied his decades-long study of antibody structure-function relationships to understanding the properties of populations of complementarity-determining region mutations that are found on naturally occurring antibodies after surviving selection. The Centivax team combined that bioinformatics information with phage display, where they can apply multifactor selection for features such as high-affinity mAb binders and the lack of self-protein–protein interactions to avoid viscosity problems, among other properties. Centivax plans to take its first product, CENT-B9 for SARS-CoV-2, into clinical trials soon, with funding from the U.S. Naval Medical Research Center, which has an interest in prophylactic antibodies to stop infections from spreading throughout a ship.

Adagio Therapeutics, which was spun out of the antibody engineering company Adimab in 2020 to fight the pandemic, has an engineered fully human mAb that reacts with all known SARS-CoV-2 variants now in phase 2/3 trials for both disease treatment and prophylaxis. (Adagio is doing research and clinical development all on its own, having raised more than $450 million in venture capital and $356 million in an initial public offering in 2021.) Tillman Gerngross, Adagio's founder and CEO, took a gamble that the pandemic was not going to go away quickly and embarked on a program of antibody design that would capture all the known and potentially unknown variants of SARS-CoV-2. "We knew we weren't going to win the race because it takes time to do all this engineering work. So from the beginning, we needed the best molecule with the expectation that it is going to be a longer haul and not just a pandemic that goes away, which is exactly how it played out," he says. Adagio's lead antibody, ADG20, was among a group isolated from a convalescent SARS-1 donor and targets a conserved epitope on the S protein present on all SARS-1, SARS-2 and many potential emergent bat viruses. Using its antibody engineering platform, the company was able to retain breadth while improving binding affinity 500-fold and neutralizing capacity 70-fold. ADG20 is the only small-molecule-like intramuscular injectable mAb that has this breadth, covering all SARS-CoV-2 variants, at such high affinity, according to Gerngross.

"There is no biological system in which neutralization is the only correlate of the efficacy of an antibody against viruses."
—Herbert "Skip" Virgin

Crowe, although he directs Vanderbilt's vaccine center and is a believer in vaccines, thinks that intramuscular delivery will be a game changer for the use of mAbs in prophylaxis. The question is how long they will protect against illness. The AstraZeneca trial went for three months and stopped when people started getting vaccinated. Crowe notes that he has been saying for years that for flu, an antibody—specifically one with a half-life extension to around 90 days days, enabling protection potentially for up to a year—would be a better alternative, as flu vaccines lose potency after a few months. "I get why people don't like saying this out loud. But this type of antibody could work better and longer," he says.

For pandemic preparedness, Herbert "Skip" Virgin, executive vice president of research and CSO at the infectious disease company Vir Biotechnology, says: "What you want is an antibody that binds to as many of the viruses of a group as possible, that is insensitive to variation that's occurring in a pandemic or historically, and that is potent at a low dose as you can only manufacture so much, as you want to save as many lives as you can. These are the properties that are going to make the difference between a truly exceptional pandemic preparedness antibody and everything else. That's our philosophy, that's what we do, and we think we have the antibodies that do this."

Vir's first commercial product, sotrovimab—a human IgG1k mAb engineered with an Fc domain of increased FcRn binding affinity that targets a conserved epitope on the SARS-CoV-2 S protein RBD—was granted full approval in Australia in August 2021, as well as EUAs in multiple countries. This mAb, derived from B cells of a patient who recovered from SARS-1 in 2003, targets an epitope on the S protein that is conserved in the sarbecovirus family.

The antibody was engineered to extend its half-life, which, according to Virgin, providentially enhances distribution to the lung. Vir has a second mAb under development (VIR-7832) that in addition contains a mutation (with an Fc engineered to create M428L and N434S amino acid substitutions for increased human FcRn affinity) that has been shown in vitro to recruit effector functions. Virgin says that his team believes this offers the potential for the antibody to function as a T cell vaccine, creating what they are calling dual-action antibodies. "This might not be the most popular way to word this—neutralization as a concept is easy to tell and easy to sell, but it's not accurate. There is no biological system in which neutralization is the only correlate of the efficacy of an antibody against viruses," he says. Sotrovimab is in trials now for intramuscular administration, according to Bolyn Hub-

by, Vir's chief corporate affairs officer, which she says will be a "huge milestone in transitioning away from intravenous." More recently, Vir researchers and collaborators have identified a number of antibodies with unique properties, among them broadly neutralizing activity targeting a cryptic epitope in the RBD and a narrow escape profile (mutation scanning showed that only one substitution leads to escape).

DOWN THE ROAD

There are two approaches to pandemic preparedness: create platforms that can quickly be deployed or have a stock of broadly effective products on the shelf—antivirals, antibodies and vaccines. Several consortia are gearing up to do the latter.

Crowe's group at Vanderbilt came up with the idea they call Ahead 100, with the goal of making best-in-class antibodies for each of 100 targets from among the 25 families of viruses that are pathogenic to humans, to take them through a phase 1 safety trial with good manufacturing practice material and stockpile 10,000 doses. He calculates that getting to that point will take $25 million, so going beyond that for 100 antibodies is impractical for any single group. Instead Crowe helped organize a consortium, the Global Pandemic Prevention and Biodefense Center—potentially a $2.5-billion project—which launched on August 11, 2021, to take this idea forward. The organization is housed in what is called the Connected DMV—Washington, D.C., Maryland and Virginia—where there is a concentration of federal agencies (NIH, FDA and Fort Detrick) and pharmaceutical company headquarters (AstraZeneca, GlaxoSmithkline and Emergent BioSolutions). Crowe raised $2.5 million for the planning phase from the Gates Foundation, the CEPI, the U.S. government, and two commercial partners (Regeneron and Moderna). The consortium is looking for partners to put in $25 million per target in the first project: Advanced Human Epidemic Antibody Defenses 100 (AHEAD 100), which will be led by Crowe.

"You can tune the immune response by adjusting one pair of vectors, which one you give first and the interval between the shots."
—Nancy Sullivan

The CEPI is thinking along the same lines. It is launching what Jackson described as "a world-class effort to rank all the families according to their threat level, in the most sophisticated way possible, by tapping into crowd-sourcing virologists, experts who understand zoonotic spillovers capable of using models and computational elements to derive a definitive list for what are the greatest threats across the families we know." Additionally, the coalition is working with a network of manufacturers to support the expansion of vaccine manufacturing capability around the world. "We want the regions to have equitable access and avoid the nationalisms and bilateral deals that have been problematic in this outbreak."

And the alphabet soup of U.S. agencies are seemingly keeping their focus on the threat. DARPA has a new program called Nucleic Acids on Demand Worldwide (NOW), which is looking to develop mobile manufacturing capacities that can be located where the need is greatest, thereby potentially shortening the time to distribute vaccines and therapies. In October 2021 the NIAID announced a $36-plus-million program to develop pancoronavirus vaccines, with funding going to three academic programs, located at the University of Wisconsin–Madison, Brigham and Women's Hospital in Boston and Duke University in North Carolina. Recognizing the need for a comprehensive strategy, the funding is going to multidisciplinary groups with expertise in virology and immunology, immunogen design, and innovative vaccine and adjuvant platforms and technologies.

But preparing for the next coronavirus is not going to be enough. Nancy Sullivan, chief of the Biodefense Research Section at the NIAID, points out that even within a virus family, a single approach may not be a true prototype for the entire family. Her experience with filoviruses demonstrated this: "DNA vaccines protect against Marburg, but they don't protect against Ebola." What's needed, she points out, is "building a knowledge base, in a rational way, and trying to incorporate some flexibility, not focusing on the hundreds of viruses that exist but instead focusing on the immunological principles that underpin protection and building that toolbox to cover those different immunological pathways." Something simple, such as the order in which you give prime and boost doses and the interval between them, can shape the immune response. "You can tune the immune response by adjusting one pair of vectors, which one you give first and the interval between the shots," she says.

Jeffry Ulmer, a retired vaccine expert with experience at Chiron, Merck, Novartis and GlaxoSmithKline, worries the SARS-CoV-2 vaccine success may be the exception, rather than the rule, for future pandemics. "We saw a spectacular success with [mRNA vaccines for] COVID-19, but pretty much everything else that was tried also worked, including DNA. It ought to give us pause that this particular antigen is relatively easy and that the next application of the technology could face a much more difficult task." SA

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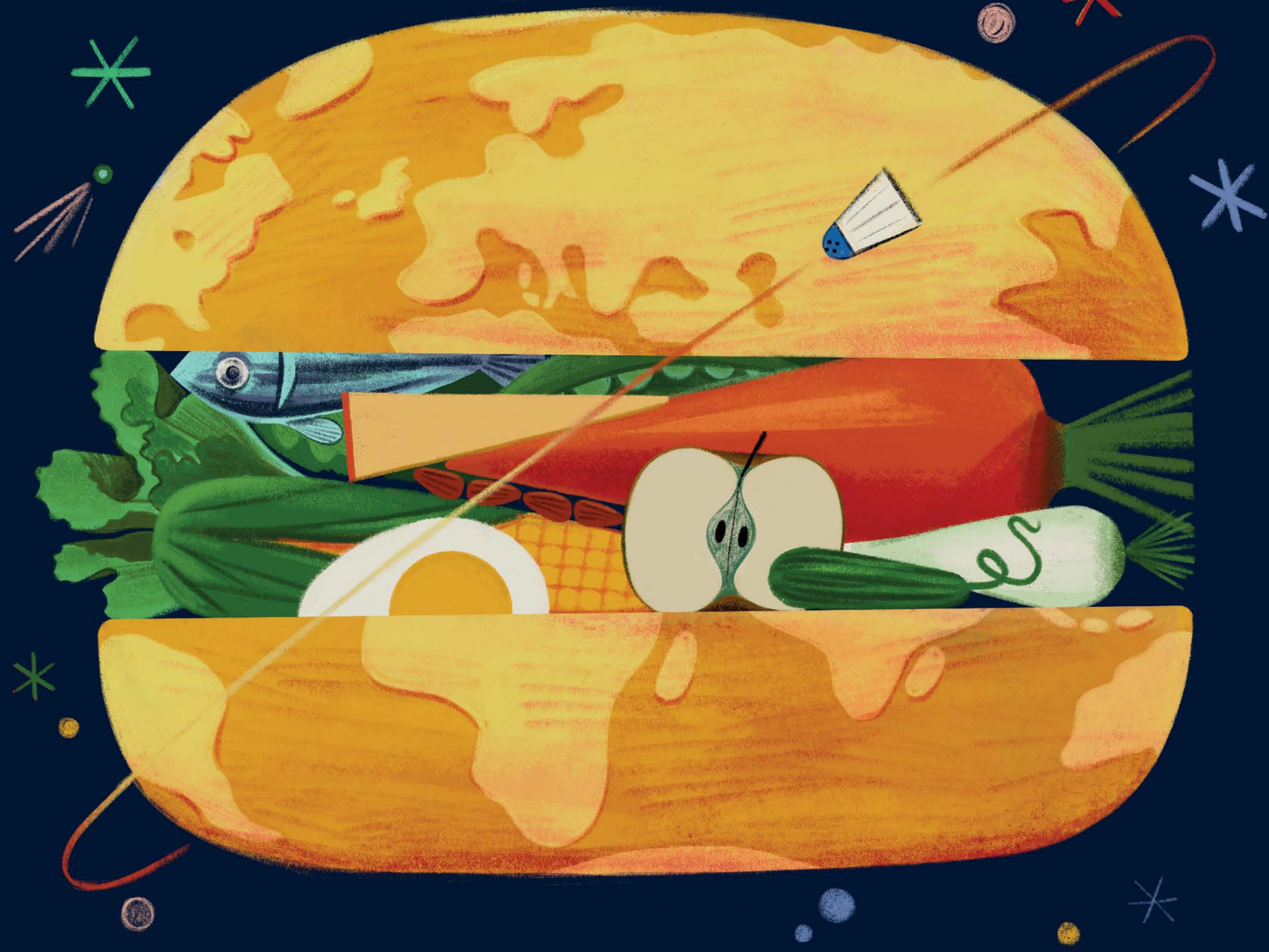

What Humanity Should Eat to Stay Healthy and Save the Planet

What we eat needs to be nutritious and sustainable. Researchers are trying to figure out what that looks like around the world

By Gayathri Vaidyanathan

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A clutch of fishing villages dot the coast near Kilifi, north of Mombasa in Kenya. These waters are home to parrot fish, octopus and other edible species. But despite living on the shores, the children in the villages rarely eat seafood. Their staple meal is ugali, maize (corn) flour mixed with water, and most of their nutrition comes from plants. Almost half the kids here have stunted growth—twice the national rate.

In 2020 Lora Iannotti, a public health researcher at Washington University in St. Louis, and her Kenyan colleagues asked people in the villages why the children weren't eating seafood, even though all the parents fish for a living; studies show that fish and other animal-source foods can improve growth. The parents said it made more financial sense for them to sell their catch than to eat it.

So, Iannotti and her team are running a controlled experiment. They have given fishers modified traps that have small openings that allow young fish to escape. This should improve spawning and the health of the overfished ocean and reef areas over time and eventually increase incomes, Iannotti says. Then, for half the families, community health workers are using home visits, cooking demonstrations and messaging to encourage parents to feed their children more fish, especially plentiful and fast-growing local species such as "tafi," or white spotted rabbitfish (*Siganus canaliculatus*) and octopus. The scientists will track whether children from these families eat better and are growing taller than ones who don't receive the messaging.

The aim of the experiment, Iannotti says, is to understand "which seafoods can we choose that are healthy for the ecosystem as well as healthy in the diet." The proposed diet should also be culturally acceptable and affordable, she says.

Iannotti is wrestling with questions that are a major focus of researchers, the United Nations, international funders and many nations looking for diets that are good for both people and the planet. More than two billion people are overweight or obese, mostly in the Western world. At the same time, 811 million people are not getting enough calories or nutrition, mostly in low- and middle-income nations. Unhealthy diets contributed to more deaths globally in 2017 than any other factor, including smoking. As the world's population continues to rise and more people start to eat like Westerners do, the production of meat, dairy and eggs will need to rise by about 44 percent by 2050, according to the U.N. Food and Agriculture Organization (FAO).

That poses an environmental problem alongside the health concerns. Our current industrialized food system already emits about one quarter of the world's greenhouse gas emissions. It also accounts for 70 percent of freshwater use and 40 percent of land coverage and relies on fertilizers that disrupt the cycling of nitrogen and phosphorus and are responsible for much of the pollution in rivers and coasts.

In 2019 a consortium of 37 nutritionists, ecologists and other experts from 16 countries—the EAT-*Lancet* Commission on Food, Planet, Health—released a report that called for a broad dietary change that would take into account both nutrition and the environment. A person following the EAT-*Lancet* reference diet would be "flexitarian," eating plants on most days and occasionally a small amount of meat or fish.

The report provoked a flurry of attention toward sustainable diets and some criticism about whether it was practical for everyone. Some scientists are now trying to test environmentally sustainable diets in local contexts, without compromising nutrition or damaging livelihoods.

"We need to make progress toward eating diets that have dramatically lower ecological footprints, or it'll be a matter of a few decades before we start to see global collapses of biodiversity, land use and all of it," says Sam Myers, director of the Planetary Health Alliance, a global consortium in Boston that studies the health impacts of environmental change.

EMISSIONS ON THE MENU

Producing food generates so much greenhouse gas pollution that at the current rate, even if nations cut all nonfood emissions to zero, they still wouldn't be able to limit temperature rise to 1.5 degrees Celsius—the climate target in the Paris agreement. A large proportion

of emissions from the food system—30 to 50 percent, according to some estimates—comes from the livestock supply chain because animals are inefficient at converting feed to food.

In 2014 David Tilman, an ecologist at the University of Minnesota, and Michael Clark, a food-systems scientist at the University of Oxford, estimated that changes in urbanization and population growth globally between 2010 and 2050 would cause an 80 percent increase in food-related emissions.

But if everyone, on average, ate a more plant-based diet and emissions from all other sectors were halted, the world would have a 50 percent chance of meeting the climate change target of 1.5 degrees C. And if diets improved alongside broader changes in the food system, such as cutting down waste, the chance of hitting the target would rise to 67 percent.

Such findings are not popular with the meat industry. For example, when in 2015 the U.S. Department of Agriculture was revising its dietary guidelines, which happens every five years, it briefly considered factoring in the environment after researchers lobbied the advisory committee. But the idea was overruled, allegedly in response to industry pressure, says Timothy Griffin, a food-systems scientist at Tufts University, who was involved in the lobbying effort. Nevertheless, people took notice of the attempt. “The biggest accomplishment is that it brought a lot of attention to the issue of sustainability,” he says.

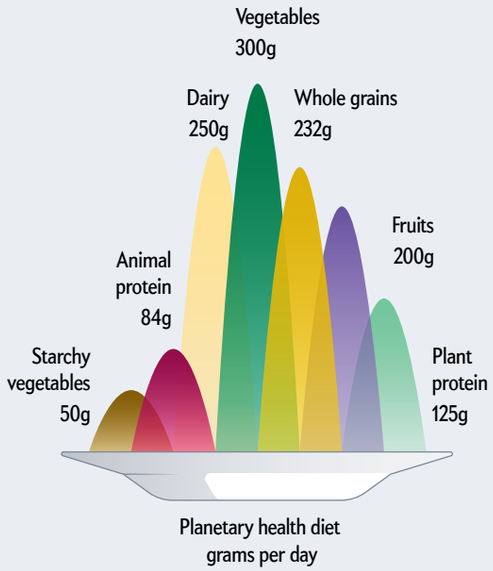
The EAT-*Lancet* commission, which was funded by Wellcome, a U.K.-based charity, helped to build a stronger case. Nutritionists reviewed the literature to craft a basic healthy diet composed of whole foods. Then the team set environmental limits for the diet,

A child is weighed as part of a study into sustainable fishing and child nutrition in a village near Kilifi Creek, Kenya.

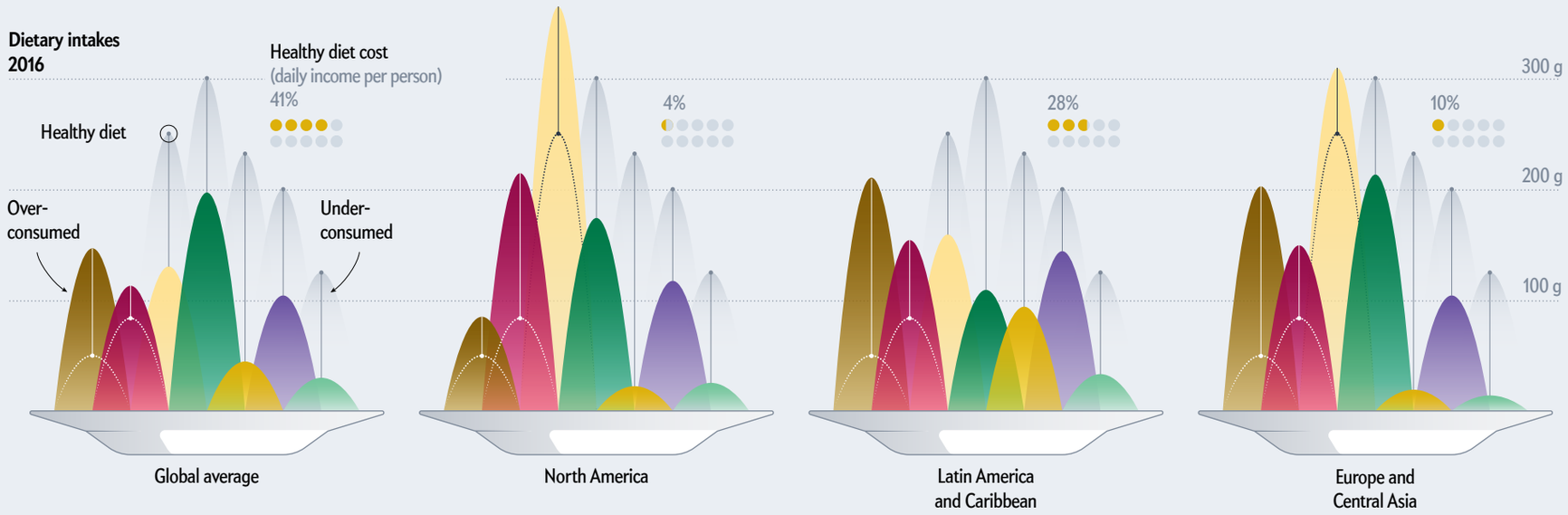
Lora Iannotti

Healthy Eating

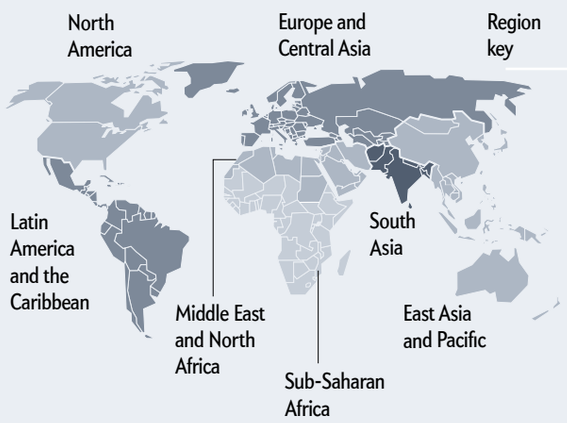
A commission of food researchers devised a "planetary health" diet—meant to be nutritious and sustainable—and compared its composition with the average diets in different regions. Further studies showed that, in many regions, following the proposed diet would be prohibitively expensive.

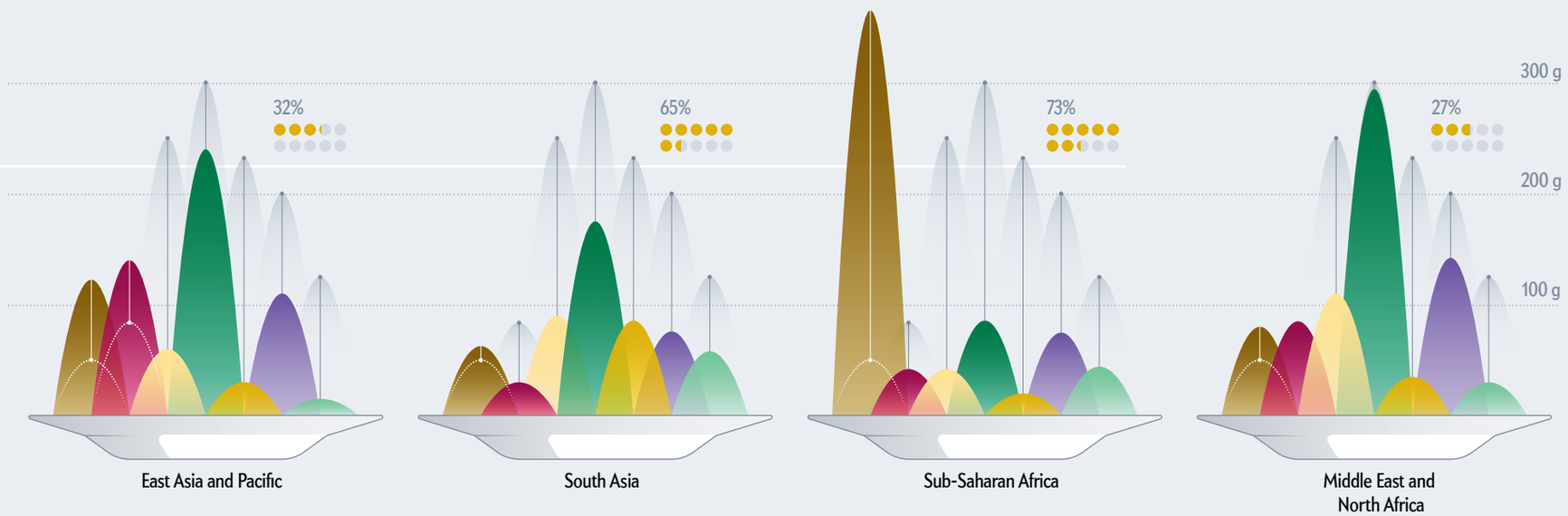


Planetary health diet
grams per day



Global average | North America | Latin America and Caribbean | Europe and Central Asia





East Asia and Pacific | South Asia | Sub-Saharan Africa | Middle East and North Africa

Sources: Intakes, Ref. 4; Costs, Ref. 12

Kerri Smith/Design by Jasiek Krzysztofiak; "What Humanity Should Eat to Stay Healthy and Save the Planet," by Gayathri Vaidyanathan, in *Nature*, Vol. 600; December 2021

including carbon emissions, biodiversity loss and the use of fresh water, land, nitrogen and phosphorus. Breaching such environmental limits could make the planet inhospitable to humans.

They ended up with a diverse and mainly plant-based meal plan. The maximum red meat the 2,500-calorie per day diet allows in a week for an average-weight 30-year-old is 100 grams, or the equivalent of one serving of red meat. That is less than one quarter of what a typical American consumes. Ultraprocessed foods, such as soft drinks, frozen dinners and reconstituted meats, sugars and fats are mostly avoided.

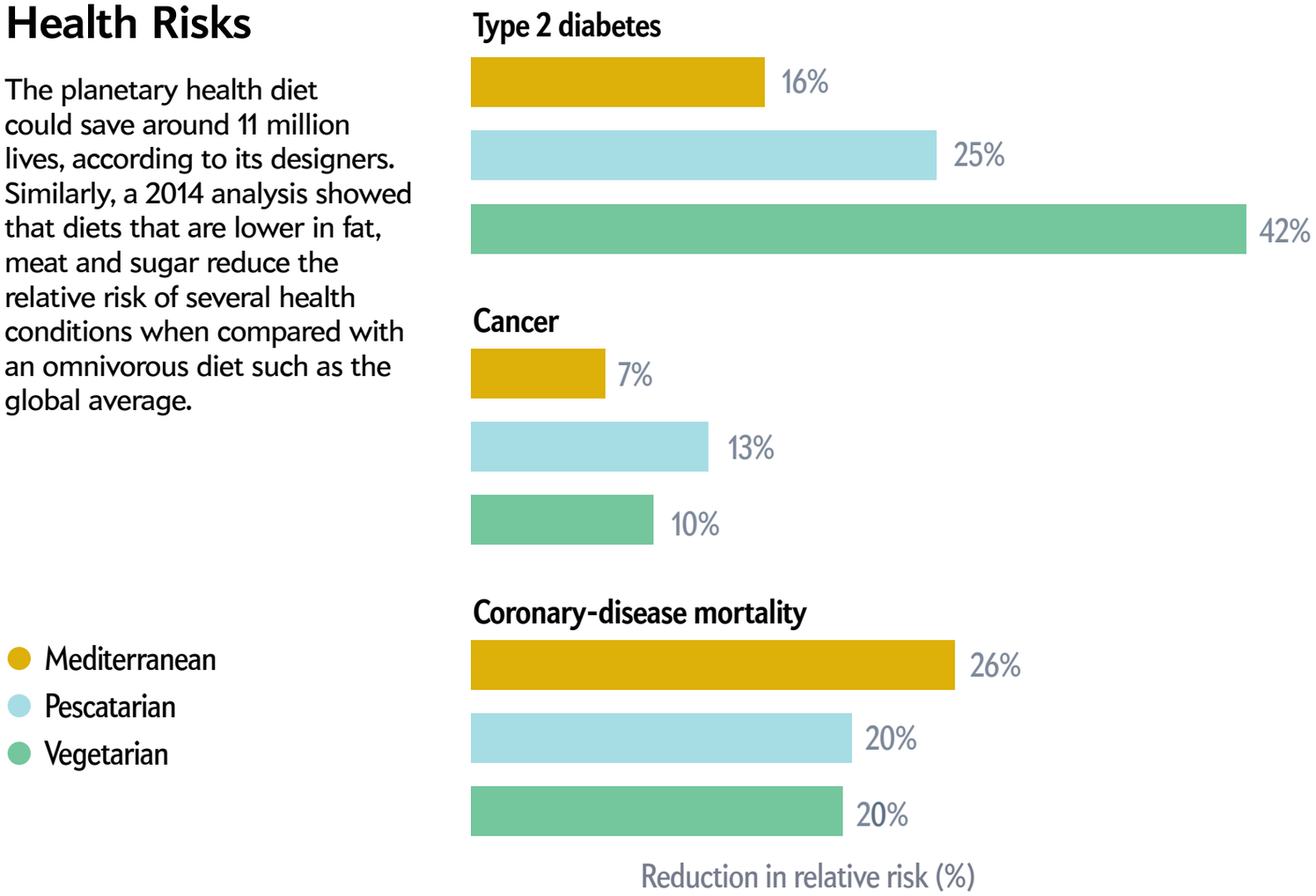
This diet would save the lives of about 11 million people every year, the commission estimated. "It is possible to feed 10 billion people healthily, without destroying ecosystems further," says Tim Lang, food-policy researcher at the City University of London and a co-author of the EAT-*Lancet* report. "Whether the hardliners of the cattle and dairy industry like it or not, they are really on the back foot. Change is now inevitable."

Many scientists say the EAT-*Lancet* diet is excellent for wealthy nations, where the average person eats 2.6 times more meat than their counterpart in low-income countries and whose eating habits are unsustainable. But others question whether the diet is nutritious enough for those in lower-resource settings. Ty Beal, a scientist based in Washington, D.C., with the Global Alliance for Improved Nutrition, has analyzed the diet in unpublished calculations and found that it provides 78 percent of the recommended zinc intake and 86 percent of calcium for those older than 25 years and only 55 percent of the iron requirement for women of reproductive age.

Despite these critiques, the diet has put environmental concerns front and center. "Until EAT-*Lancet,* I don't think it had been at the top of policy makers' minds that sustainability should be integrated into this global conversation about dietary change," says Anne Elise Stratton, a food-systems scientist at the University of Michigan. The diet is not a one-size-fits-all recommendation, stresses Marco Springmann, a food scientist at the University of Oxford who was part of the EAT-*Lancet* core modeling team. Since the report was published, public health scientists around the world have been studying how to make the diet realistic for people the world over, whether an overweight adult or an undernourished child.

Health Risks

The planetary health diet could save around 11 million lives, according to its designers. Similarly, a 2014 analysis showed that diets that are lower in fat, meat and sugar reduce the relative risk of several health conditions when compared with an omnivorous diet such as the global average.



Source: Ref. 6

RICH DIETS

Nutrition researchers know that most consumers do not follow dietary guidelines. So some scientists are exploring ways to convince people to adopt healthy, sustainable diets. In Sweden, Patricia Eustachio Colombo, a nutrition scientist at the Karolinska Institute in Stockholm, and her colleagues are quietly testing a sustainable diet in schools. Their work piggybacks on a social movement that began in Scandinavian countries called the New Nordic Diet, which promotes consumption of traditional, sustainable foods such as seasonal vegetables and free-range meat.

Eustachio Colombo and her colleagues used a computer algorithm to analyze existing school lunches at a primary school with about 2,000 students. The algorithm

Kerri Smith/Design by Jasiek Krzysztofiak; "What Humanity Should Eat to Stay Healthy and Save the Planet," by Gayathri Vaidyanathan, in *Nature*, Vol. 600; December 2021

suggested ways to make them more nutritious and climate-friendly, such as reducing the amount of meat in a typical stew and adding more beans and vegetables. The children and parents were informed that lunches were being improved but did not know details, Eustachio Colombo says. Most kids did not notice, and there was no more food waste than earlier. The same experiment is now being rerun in 2,800 children.

"School meals are a near unique opportunity to foster sustainable dietary habits. The dietary habits we develop as children, we tend to stick to them into adulthood," Eustachio Colombo says.

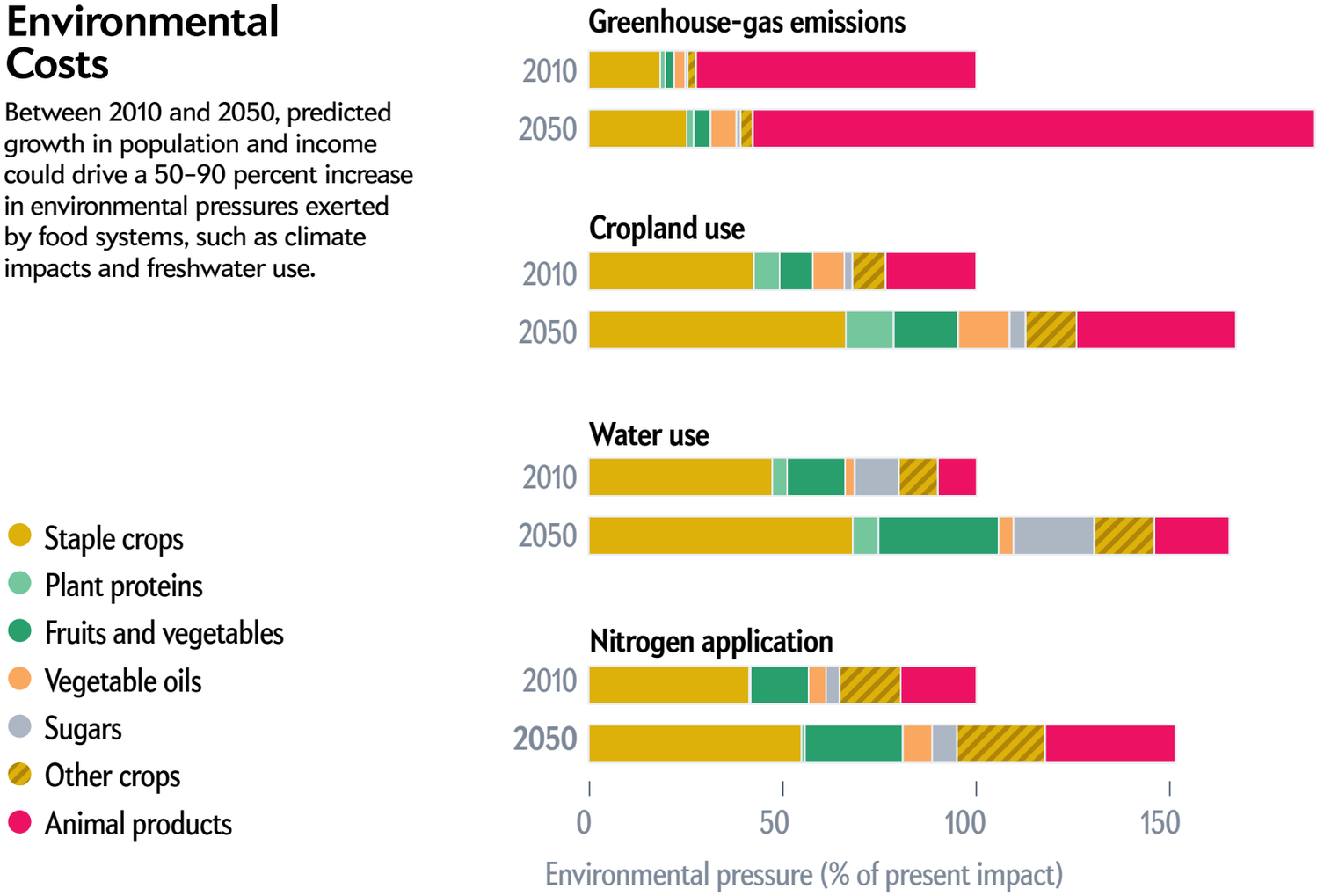
The diet is very different from the EAT-*Lancet* one, she says. It is cheaper and includes more starchy foods such as potatoes, which are a staple of Swedish cuisine. It is also more nutritious and culturally acceptable, she says. "This highlights the importance of tailoring the EAT-*Lancet* diet to the local circumstances in each country or even within countries," she says.

Across the Atlantic, some academics and restaurateurs are trialing the diet in low-income settings. In Baltimore, a collaboration between a catering business and a restaurant, both forced to close during the COVID-19 pandemic, started taking donations and providing free meals based on the EAT-*Lancet* diet to families who live in food deserts—areas where there is little access to affordable, nutritious food. One meal had salmon cakes with mixed seasonal vegetables, Israeli couscous and creamy pesto sauce.

Researchers at the Johns Hopkins University School of Medicine surveyed 500 people who tried the meals and found that 93 percent of the 242 people who completed the survey said they either loved or liked it. The downside? Each donation-funded meal cost $10—five times the amount currently provided by the U.S. food-stamp program. "It's very clear that if you have a huge shift in diets, you could swing the environment impact for the better, but there are cultural barriers and economic barriers to that," Griffin says.

Environmental Costs

Between 2010 and 2050, predicted growth in population and income could drive a 50–90 percent increase in environmental pressures exerted by food systems, such as climate impacts and freshwater use.



Source: M. Springmann et al. in *Nature*, Vol. 562, No. 519–525; 2018

HARD TO STOMACH

For researchers exploring future diets in some low- or middle-income nations, one hurdle is finding out what people are eating in the first place. "It's literally like a black box to me right now," says Purnima Menon of the International Food Policy Research Institute in Delhi, who has been studying diets in India. The data on what people are eating are a decade old, she says.

Getting that information is crucial because India ranks 101 out of 116 countries in the Global Hunger Index and has the greatest number of children who are too thin for their height.

Using what is available, Abhishek Chaudhary, a food-systems scientist at the Indian Institute of Technology Kanpur, who was part of the EAT-*Lancet* team, and his colleague Vaibhav Krishna of the Swiss Federal Institute of Technology in Zurich used a computer program and local environmental data on water, emissions, land use, and phosphorus and nitrogen use to design diets for all of India's states. The algorithm suggested diets that would meet nutritional requirements, cut food-related

Kerri Smith/Design by Jasiek Krzysztofiak; "What Humanity Should Eat to Save the Planet," by Gayathri Vaidyanathan, in *Nature*, Vol. 600; December 2021

"The farmer in the highlands of Ethiopia doing dairy has three or four animals in his or her backyard, and each of these animals is a member of the family—they have names."
—Jimmy Smith

emissions by 35 percent and wouldn't stress other environmental resources. But to grow the required amount of food would require 35 percent more land—which is impractical in the overcrowded nation—or higher yields. And food costs would be 50 percent higher.

Healthy, sustainable diets are expensive elsewhere, too. The dietary diversity advised by EAT-*Lancet* —nuts, fish, eggs, dairy, and more—is impossible to access for millions of people, Iannotti says.

In fact, for the average person to eat the diet in 2011—the most recent data set available on food prices—would have cost a global average of $2.84 per day, about 1.6 times higher on average than the cost of a basic nutritious meal.

There are other impracticalities. Take restrictions on meat, for instance. In places with nutrient deficiencies and where the diet's prescribed foods are not available, animal-source products are a crucial source of easily bioavailable nutrients in addition to plants, Iannotti says. In many places in low-income nations, farming systems are on a small scale and include both crops and domesticated animals, which can be sold in times of family need, says Jimmy Smith, director-general of the International Livestock Research Institute in Nairobi. "The farmer in the highlands of Ethiopia doing dairy has three or four animals in his or her backyard, and each of these animals is a member of the family—they have names," he says.

Menon says that for now scientists in low- and middle-income regions are more concerned about delivering nutrition than preserving the environment. The FAO has organized a committee to do a much more comprehensive analysis than EAT-*Lancet*'s. The new analysis will be more globally inclusive and include topics such as food security and sustainability of the livestock sector, says Iannotti, who is part of the committee. It will be published in 2024. "They don't feel as if it was entirely balanced or holistic in its review of the evidence," she says. "Let's go further and make sure we have evidence from around the world."

The way to find sustainable diets in poor nations is by working closely with communities and farmers, as in Kilifi, scientists say. Clark, having mapped out diets at a global scale using model-based projections, thinks that food-system scientists now need to find the local adjustments and fixes to get people to eat better.

"People working in food sustainability need to go into communities and ask, 'Hey, what's good for you?'" he says. "And then, given that baseline, how can we start working toward outcomes that those communities are interested in?" SA

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These Are the Latest COVID Treatments

But shortages mean that new antivirals and other drugs may be hard to come by

By Esther Landhuis

Close-up photoillustration of dexamethasone tablets

John Phillips/Getty Images

Esther Landhuis is a freelance science and health journalist based in the San Francisco Bay Area. Follow her on Twitter @elandhuis

TWO YEARS INTO THE COVID PANDEMIC, as the highly contagious Omicron variant pushes infections to record highs, U.S. physicians have a growing arsenal of therapies to keep mild disease from worsening. At the same time, limited availability and challenging logistics are complicating decisions about which patients receive them. Here is a rundown of what is on hand for hospitalized patients, as well as for people who are primarily recovering at home.

TREATMENTS FOR NONHOSPITALIZED PATIENTS

Monoclonal antibodies: For newly diagnosed patients at high risk for severe COVID-19, the recommended therapy has generally been monoclonal antibodies—lab-made proteins that bind to SARS-CoV-2, the virus that causes COVID, and keep it from grabbing onto and infecting cells. If administered within 10 days of diagnosis, either intravenously or as a series of shots under the skin, monoclonal antibodies can cut hospitalizations and deaths by more than 80 percent.

Several companies make these antibody treatments, which started to receive emergency use authorization from the U.S. Food and Drug Administration in late 2020. Yet with most COVID cases in the U.S. currently caused by fast-spreading Omicron, a new coronavirus variant with mutations in the part of SARS-CoV-2 targeted by monoclonals, "there's only one [antibody] that actually works," says Michelle Barron, a professor of medicine at the University of Colorado School of Medicine and senior medical director of infection prevention and control at the nonprofit health system UCHealth.

That treatment—a monoclonal antibody called sotrovimab that is made by GlaxoSmithKline and Vir Biotechnology—can only be administered intravenously. "So from a logistics standpoint, that's a little different than giving you shots in your leg or arm," Barron says. "You have to be there at least an hour for the infusion, and you have to be able to get to the location." And on the provider end, she adds, "you have to figure out where to do it from the U.S. Food and Drug Administration in late 2020. Yet with most COVID cases in the U.S. currently caused by fast-spreading Omicron, a new coronavirus variant with mutations in the part of SARS-CoV-2 targeted by monoclonals, "there's only one [antibody] that actually works," says Michelle Barron, a professor of medicine at the University of Colorado School of Medicine and senior medical director of infection prevention and control at the nonprofit health system UCHealth. That treatment—a monoclonal antibody called sotrovimab that is made by GlaxoSmithKline and Vir Biotechnology—can only be administered intravenously. "So from a logistics standpoint, that's a little different than giving you shots in your leg or arm," Barron says. "You have to be there at least an hour for the infusion, and you have to be able to get to the location." And on the provider end, she adds, "you have to figure out where to do it because you obviously don't want these individuals who have COVID walking through a very populated waiting room."

Antiviral pills: In December 2021 the FDA authorized emergency use of two antiviral treatments that can be taken at home as pills: Pfizer's Paxlovid and Merck and Ridgeback Biotherapeutics' molnupiravir. In studies of high-risk adults who started these treatments within their first five days of COVID symptoms, Paxlovid cut the risk of hospitalization or death by 89 percent, and molnupiravir cut these sufferings by 30 percent, compared with placebo pills.

One issue with Paxlovid is that it consists of the antiviral nirmatrelvir given in combination with ritonavir, "an old HIV drug that's known to interact with everything," Barron says. "A lot of our highest-risk patients will potentially have a medication that will interact." A pharmacist has to review all of a patient's other medications before filling a prescription.

Access: But the biggest challenge with most of these outpatient treatments is short supply. In the fall of 2021 the monoclonal antibody sotrovimab was available directly through a wholesaler, making them easier for physicians and medical facilities to procure. But as monoclonal antibody use surged because of a rise in COVID cases caused by the Omicron variant, the U.S. Department of Health and Human Services began overseeing distribution to states and territories. Each state receives a limited allocation in accordance with COVID rates and hospitalizations, and federal guidelines now expect states to prioritize giving antibodies to immunosuppressed or elderly individuals at highest risk for severe disease. And because sotrovimab is the only monoclonal found to work well against Omicron, it is particularly in demand.

Antiviral pills are also scarce and similarly prioritized for highest-risk outpatients. "Yesterday our health system just prescribed our first Paxlovid dose—for one person," said David Boulware, an infectious disease physician-scientist at the University of Minnesota Medical School, when he was interviewed for *Scientific American* on January 7.

As of January 10, Zuckerberg San Francisco General Hospital and Trauma Center, which serves 100,000 patients every year and provides 20 percent of the city's inpatient care, had received 20 courses of Paxlovid, says Monica Gandhi, an HIV and infectious disease physician at the University of California, San Francisco.

New York City, with a population of more than eight million and more than 30,000 infections a day in early January, had received about 1,600 doses of Paxlovid as of the first full week of January, says Celine Gounder, a physician and infectious disease expert at the New York University Grossman School of Medicine. The U.S. Department of Health and Human Services is allocating the pills per capita rather than based on infection rates, she says.

For every patient who manages to receive antiviral pills, many other immunocompromised, high-risk patients cannot get them, Boulware says. "'Okay, they don't have this; they don't have that. What do you recommend?' I've been called about that," he adds. Plus, Paxlovid and sotrovimab are not authorized for children under 12 years of age, and the FDA limits molnupiravir to adults age 18 and up.

In these situations, Boulware suggests considering fluvoxamine or budesonide—widely available, low-cost drugs for other conditions that have published data suggesting benefits in nonhospitalized COVID patients.

Repurposed drugs: Fluvoxamine, an antidepressant pill that is approved in the U.S. for obsessive-compulsive disorder, can tame inflammatory responses, which typically arise in severe COVID. In a randomized trial of 1,497 high-risk COVID outpatients in Brazil, those who tolerated a 10-day course of fluvoxamine suffered about 90 percent fewer deaths, and their need for emergency care fell by 65 percent, compared with patients who were randomly assigned placebo pills.

"The one thing we've all learned is to be flexible. What we do today may not be what we do tomorrow, and you just gotta be okay with that."
—Michelle Barron

Budesonide, an inhaled steroid that is used to prevent asthma symptoms, showed modest benefits in a large, open-label study in the U.K. that enrolled older, nonhospitalized patients with comorbidities such as high blood pressure and diabetes. Those who started to use the inhaler within two weeks of developing COVID symptoms saw an approximately three-day reduction in symptom duration. "So there's a mild benefit, particularly during the second week of illness," Boulware says.

Treatments for that enrolled older, nonhospitalized patients with comorbidities such as high blood pressure and diabetes. Those who started to use the inhaler within two weeks of developing COVID symptoms saw an approximately three-day reduction in symptom duration. "So there's a mild benefit, particularly during the second week of illness," Boulware says. Treatments for Hospitalized Patients.

For hospitalized COVID patients whose blood oxygen has dropped low enough to require monitoring, the National Institutes of Health recommends the widely available and relatively inexpensive steroid dexamethasone, which can be taken as oral tablets or intravenously. Remdesivir, an intravenous antiviral, is also offered, often concurrently, to hospitalized patients who are in the severe inflammatory stage of COVID. "It's better when given earlier," Boulware says. "By the time you get in the ICU on a ventilator, there's less benefit."

To keep COVID from worsening to that stage, NIH guidelines updated this month are also recommending high doses of intravenous heparin, a drug used to prevent blood clots, in some patients. "What's new is that therapeutic-dose heparin is now recommended for patients before they get to the ICU," says Farid Jalali, a gastroenterologist in Laguna Hills, Calif., whose theories about COVID lung injury have been featured in the emergency medicine blog REBEL EM.

Several arthritis drugs, such as baricitinib or tocilizumab, can be given to dampen inflammation as disease progresses in hospitalized COVID patients two years of age or older. Baricitinib is a tablet taken by mouth, and tocilizumab is given through the vein as a drip infusion.

NEW HOPE FOR "OLD" COVID DRUGS

New research suggests remdesivir could also be helpful in COVID outpatients. In a randomized trial published last December in the *New England Journal of Medicine,*

COVID-related hospitalizations and deaths were 87 percent lower in 279 symptomatic, nonhospitalized patients who received remdesivir, compared with 283 in the placebo group. "It looked really good, and supplies are not an issue," Barron says. She notes, however, that "logistics are a little challenging because it's three days of infusions."

Similar logistical hurdles, as well as unclear findings from past research, have raised questions about the utility of the once eagerly studied convalescent plasma—collected from the blood of donors who have recovered from COVID, compared with 283 in the placebo group. "It looked really good, and supplies are not an issue," Barron says. She notes, however, that "logistics are a little challenging because it's three days of infusions." Similar logistical hurdles, as well as unclear findings from past research, have raised questions about the utility of the once eagerly studied convalescent plasma—collected from the blood of donors who have recovered from COVID. "It's kind of falling out of favor right now," Barron says.

Yet new research could be reviving interest in this treatment, especially given the limited supplies of outpatient therapies. The findings, posted on December 21, 2021, as a not yet peer-reviewed preprint paper, revealed that in a study of 1,181 patients, convalescent plasma cut hospitalizations by 54 percent when administered within the first eight days of COVID symptoms.

"The one thing we've all learned is to be flexible," Barron says. "What we do today may not be what we do tomorrow, and you just gotta be okay with that." SA

People Have Been Having Less Sex–Whether They're Teenagers or Fortysomethings

Among the young, social media, gaming and "rough sex" may contribute to this trend

By Emily Willingham

Hase-Hoch-2/Getty Images

Emily Willingham is a science writer and author of *Phallacy: Life Lessons from the Animal Penis* (Avery, Penguin Publishing Group, 2020). Her latest book is *The Tailored Brain: From Ketamine, to Keto, to Companionship: A User's Guide to Feeling Better and Thinking Smarter* (Basic Books, 2021). Follow her on Twitter @ejwillingham

Human sexual activity affects cognitive function, health, happiness and overall quality of life—and, yes, there is also the matter of reproduction. The huge range of benefits is one reason researchers have become alarmed at declines in sexual activity around the world, from Japan to Europe to Australia. A recent study evaluating what is happening in the U.S. has added to the pile of evidence, showing declines from 2009 to 2018 in all forms of partnered sexual activity, including penile-vaginal intercourse, anal sex and partnered masturbation. The findings show that adolescents report less solo masturbation as well.

The decreases "aren't trivial," as the authors wrote in the study, published on November 19, 2021, in *Archives of Sexual Behavior*. Between 2009 and 2018, the proportion of adolescents reporting no sexual activity, either alone or with partners, rose from 28.8 to 44.2 percent among young men and from 49.5 percent in 2009 to 74 percent among young women. The researchers obtained the self-reported information from the National Survey of Sexual Health and Behavior and used responses from 4,155 people in 2009 and 4,547 people in 2018. These respondents to the confidential survey ranged in age from 14 to 49 years.

The study itself did not probe the reasons for this trend. But *Scientific American* spoke with its first author Debby Herbenick, a professor at the Indiana University School of Public Health–Bloomington, and Tsung-chieh (Jane) Fu, a co-author of the paper and a research associate at the school, about underlying factors that might explain these changes.

[*An edited transcript of the interview follows.*]

Given that research in other parts of the world has already indicated decreases in partnered sex, what do your recent findings add to the picture?

HERBENICK: Our study tracks the declines, too, and extends the research because Jane [Fu] and our larger team tracked sex behaviors in really detailed ways. We looked at penile-vaginal sex, partnered masturbation, and giving and receiving oral sex. And we saw declines across all categories. And we included adolescents, too. The decline in adolescent masturbation is interesting, and we were the first to include it. That one deserves a lot more attention.

What might explain declines among young people?

FU: We need more studies to tell us why. But for young people, computer games, increasing social media use, video games—something is replacing that time. During that period from 2009 to 2018, different types of social media emerged. This is always evolving, especially for younger people.

HERBENICK: We don't expect there to be one explanation or one driver in these decreases. We fully expect that there are multiple things going on for different age groups, different partnership status, different genders. You don't need those individual pieces to explain a big part of a notable decrease, but … each one [might] explain a percentage point or two.

Is there any contribution from increases in people expressing an asexual identity?

HERBENICK: We don't know why more people are identifying as asexual, but I do think more people are aware of it as a valid identity. Even compared with when I started teaching human sexuality in 2003, I routinely had one student in my class who might identify as asexual. Now I have three or four. That's striking to me. I love that young people are aware of so many different ways to put into words how they feel about themselves. For many of them, they feel that it's okay to opt out of sex.

In your paper, you bring up increases in "rough sex" as potentially contributing to declines. Can you explain what you mean by rough sex, and how it could be playing a role in these changes?

HERBENICK: Especially for those 18 to 29 years old, there have been increases in what many people call rough sex behaviors. Limited research suggests that an earlier idea of this was what I would consider fairly vanilla rough sex: pulling hair, a little light spanking. What we see now in studies of thousands of randomly sampled college students is choking or strangling during sex. The behavior seems to be a majority behavior for college-age students. For many people, it's consensual and wanted and asked for, but it's also scary to many people, even if they learn to enjoy it or want it. It's a major line of

research for our team: to understand how they feel, what the health risks are and how that fits into the larger sexual landscapes.

FU: We have seen what seem to be real shifts in those behaviors. We don't know to what extent that may be driving some people to opt out, but we do know that some people are feeling frightened and don't know what to make of what's being presented to them, especially young adults. They could consent to sex, but something like choking might happen without them being asked before. We see a lot of gender effects in a lot of behaviors for different nonheterosexual identities. For example, bisexual women experience a lot more of these aggressive behaviors.

HERBENICK: We have really been trying to untangle that, too, because it's not clear from our research how much of those elevated rates are wanted and pleasurable or unwanted, because bisexual women also report higher rates of sexual victimization.

In the report, you note that there are probably multiple reasons that people's sexual expression has changed.

HERBENICK: Various studies around the world have proposed different explanations, such as economic status. Lower income is associated with greater declines. One study looked at use of computer games among young people [as a possible explanation]. Some folks have tracked declines in alcohol use, and we know that [alcohol use] can be associated with disinhibition. We have seen, somewhat, [an] increase in sex toy use—from what we looked at, not a massive increase. If there is a change, it's probably just going to contribute to one of the blips. I don't expect it to be the explanation.

Do you have suggestions for people who might be reading this interview and wondering, "Should I do something with this information right now?"—maybe from the perspective of themselves, their partner or partners, or discussions with their children?

FU: For parents, it would be great to have open conversations with their children, especially teens, about sex. Sex in recent years looks very different, whether it's the emergence of technologies or of new sexual behaviors. We hope that parents can play an active role in guiding their children, not just to warn them of the risk of various sexual behaviors but also to educate them on how to have meaningful relationships and eventually satisfying and pleasurable sex.

HERBENICK: For many of us, I think it is worth asking a few things: How do I feel about my sexual life? How does my partner feel? Ask them! Some people may look around and feel like the sexual interactions they do have are pleasurable, connecting, joyful and make up a satisfying sex life for them. Others might look around and say, "You know, 10 to 15 years ago, when we couldn't stream as many fun shows on TV, we watched a lot less television, and we had sex more often. I wonder how we might have sex more often?"

More generally, could you elaborate a bit about how sexual activity with or without partners intersects with other aspects of health and what "sexual health" looks like?

HERBENICK: Sexuality is such an important part of life, and understanding changes that occur matters to how we understand what is shifting about the human experience. We know that sexual activity can help people to relax, fall asleep, reduce stress, feel intimate and connected, and thereby improve their relationships—and may even help to boost their immune system. And sex can also just be fun, pleasurable and joyful—a way to express oneself in vulnerable ways. Sexual health is multidimensional and not just about the presence or absence of infections or disease but about the potential for pleasure, access to accurate information about sexuality, bodily autonomy, and ability to have sexual experiences that are free from violence or coercion.

What sorts of effects on these behaviors do you already see or anticipate from the pandemic, which of course was not tracked in your study?

FU: We know that things are changing a lot when people are at home. Being able to work from home has allowed some long-distance partners to spend more time together or even live together. But for partners who do not live together and do not have that option of working remotely, difficulties in travel may lead to even less time together. For those living with their partner, more time spent together at home may not necessarily lead to more and more satisfying or pleasurable sex. Moreover, being quarantined, social distancing, financial difficulties, working from home could all lead to strains in the relationship. Loss of or the instability of child care because of the pandemic can restrict the sex lives of those who are parents.

HERBENICK: Certainly people who do not live with partners have, by and large, been more constrained in partnered sex over the past two years, with some relaxation of that since the widespread availability of vaccines and vaccine boosters. But ultimately we don't live in a vacuum, and our sex lives don't occur in a vacuum, so there are myriad factors.

The past two years have also brought lots of grief for people who have lost family members to COVID. Many people are dealing with long COVID and related health challenges, job loss and financial strain. And more people of all ages are dealing with anxiety and depression since the pandemic. So these all have influences on sexual interest and sex drive, too. SN

Steven W. Thrasher is a *Scientific American* columnist and professor at Northwestern University in the Medill School of Journalism and the Institute of Sexual and Gender Minority Health and Wellbeing. He is author of the forthcoming book *The Viral Underclass: The Human Toll When Inequality and Disease Collide* from Celdaon Books and Macmillan Publishing. Follow him on Twitter @thrasherxy

There Is Nothing Normal about One Million People Dead from COVID

Mass media and policy makers are pushing for a return to pre-COVID times while trying to normalize a staggering death toll

Sometime in the next few weeks, the official death toll for the two-year COVID pandemic in the U.S. will reach one million. Despite being the wealthiest nation on the planet, the U.S. has continued to have the most COVID infections and deaths per country, by far, and it has the highest per capita death rate of any wealthy nation.

This is an unfathomable number of people dead, yet, mass media are downplaying it. This is despite an empathetic *New York Times* headline in May 2020 of "U.S. Deaths Near 100,000, an Incalculable Loss," and using its entire front page to print names of some of the deceased. As Luppe B. Luppen noted on Twitter, the newspaper's more recent headline was the cruel and callous "900,000 Dead, but Many Americans Move On."

The *Times* is not alone; several large mainstream

A woman watches white flags on the National Mall in September 2021 in Washington, D.C. More than 660,000 white flags were installed here to honor Americans who have lost their lives to COVID-19 epidemic.

Chen Mengtong/China News Service via Getty Images

publications, in complicity with politicians of both major political parties, have been beating a death knell of a drum for getting "back to normal" for months. The effect is the manufactured consent to normalize mass death and suffering—to subtly suggest to Americans that they want to move on.

News media are helping to shape public opinion in order for business to return to the very circumstances that have created this ongoing crisis. A return to normal will allow profits to be reaped by people working relatively safely from their homes (the target audience of many news organizations' advertisers) at the expense of people working or studying in person who are more vulnerable.

A few weeks ago David Leonhardt, the writer of the *Times*'s newsletter "The Morning," asked Michael Barbaro, the host of the company's podcast "The Daily": "If [COVID] is starting to look like a regular respiratory virus, is it *rational* [emphasis by the *Times*] to treat it like something completely different—to disrupt all our lives in all these big and consequential ways[?]"

I was dismayed. That rhetorical move is a familiar one to me: Two white men frame what they think is rational, deeming any questioning of their stand as irrational.

Meanwhile some 140,000 children in the U.S. have lost a caregiver—about one in every 500 children. That is a big and consequential loss, and those children are probably not among the many who are ready to "move on" (another nearly one million Americans can't move on, because they're already dead). During this pandemic, Black people have been disproportionately killed by this virus. About 50,000 people have died each month of COVID, meaning several Black children are being orphaned by SARS-CoV-2 this month, as you read this.

"We are now faced with the fact that tomorrow is today. We are confronted with the fierce urgency of now. In this unfolding conundrum of life and history, there is such a thing as being too late. Procrastination is still the thief of time."
—Martin Luther King, Jr.

So is it rational? To be calling for the end of lifesaving mitigation efforts and saying they harm children when so many have been orphaned here and worldwide?

Is it rational for Democrats, Republicans and much of the news media to press on toward what writer Tom Scocca calls a policy of "unlimited" COVID? The Democratically controlled state governments of California, New Jersey, New York and Connecticut all moved to drop indoor mask mandates just days after a near-record 3,958 people died of COVID on a single day, February 4. Even the White House reportedly has "begun hinting at an impending 'new normal,' in a conscious messaging shift meant to get people comfortable with a scenario where the virus remains widespread yet at more manageable levels."

Is it rational, when as many people who died of AIDS in its worst year (near 50,000 in 1995) are dying every month of COVID, to think of the novel coronavirus as a "regular respiratory virus"—and to think that the big and consequential disruptions to worry about are mask wearing and ventilation and not death and debilitation?

Is it rational to ignore the high communal viral load in American society and to not do more to lower it so that fewer people are exposed, become sick, transmit onward and possibly die?

Is it rational for the *Times* to be advertising an event happening in March hosted by Leonhardt called "The New Normal, a Virtual Event on Life and Love after Omicron," which might just coincide with the timing of the millionth American officially dying of COVID?

Well, it depends on what it is you are trying to rationalize.

If you're trying to get people to accept that what the nation is doing right now is okay, and 50,000 deaths per month should be normalized, then it's rational.

If you don't want people to wonder why in just two years, the U.S. death toll for COVID is about 130 percent the size of the death toll of four decades of HIV—while global COVID deaths are less than 20 percent of the world's AIDS deaths—then it's rational.

If you want to manufacture consent for looser pandemic measures in the U.S. rather than more

comprehensive ones as the communal viral rate demands, then making these claims is rational.

But it's not ethical to manufacture what I call a viral underclass, and it's incorrect to pretend as though the news media have no role in creating it nor in persuading the public that so many deaths are inevitable.

It's a shame that major news outlets are talking more about moving on and returning to normal and not running more pieces calling for an increase in government-funded mitigation efforts (more free high-quality masks and tests, upgraded ventilation in worksites and schools) to stem the tide of death. American norms (rampant incarceration, eviction, homelessness, lack of health care, poor ventilation and economic inequality) are fairly deadly as is.

Rushing for the "urgency of normal" is "wishful thinking," epidemiologist Gregg Gonsalves wrote in the *Nation*. Intentionally or unintentionally, "the urgency of normal"—a phrase cropping up a lot lately—is evocative of a phrase Martin Luther King, Jr., used in his 1967 speech "Beyond Vietnam" at Riverside Church, where he preached about "the fierce urgency of now":

"We are now faced with the fact that tomorrow is today. We are confronted with the fierce urgency of now. In this unfolding conundrum of life and history, there is such a thing as being too late. Procrastination is still the thief of time."

If he were still alive, do you think King would be fighting for the fierce urgency of the very normal that produced all this death?

Senator **Chris Coons** is a Democrat representing the state of Delaware. He has been in office since 2010. Follow him on Twitter @chriscoons
Senator **Jerry Moran** is a Republican representing the state of Kansas. He has been in office since 2011. Follow him on Twitter @jerrymoran

A $1-Billion Boost to the NCI Will Help Us Beat Cancer

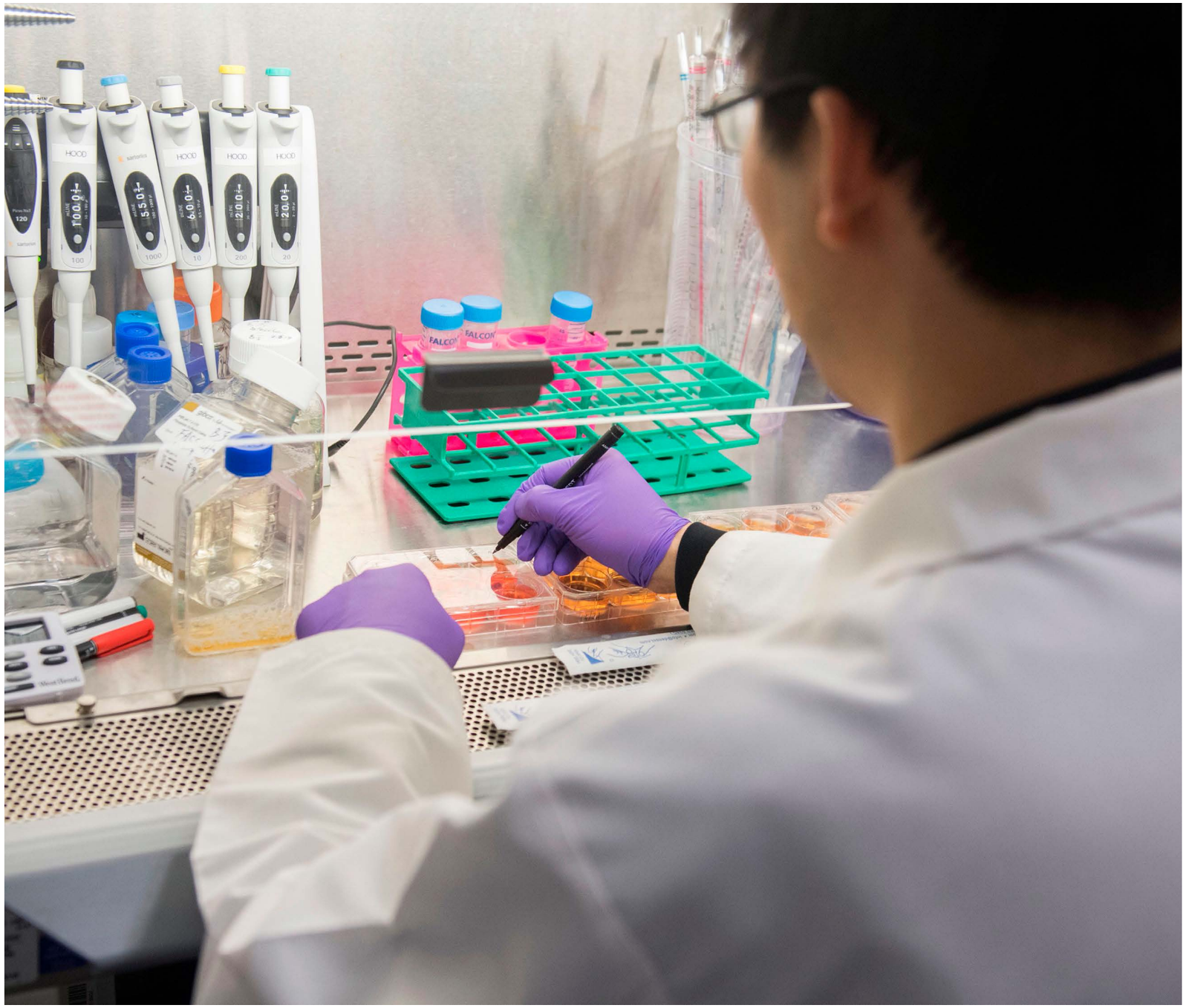
The organization's underfunding means critical research is not being done

While ideology and politics often divide Washington, D.C., Congress is steadfastly united in a common cause: curing cancer. As a Democrat from Delaware and a Republican from Kansas, both of our lives have been touched by this disease.

The U.S. has seen great advances in cancer treatment, but they are not enough. To ensure that our children and grandchildren will not be touched by the tragedy of the disease the way we have been, we must work together to treat cancer with the same urgency that we tackled the pandemic—starting with a robust, sustained investment in cancer research through the National Cancer Institute (NCI).

Nearly every American has shared in the heartbreaking experiences of a long battle with chemotherapy, an immeasurable wait for biopsy results or a mother, father, sibling or child lost too soon.

During our tenures in the Senate, we have



Benjamin Jin, a biologist working on immunotherapy for HPV+ cancers, works in the lab of Christian Hinrichs, an investigator at the National Cancer Institute at the National Institutes of Health.

Saul Loeb/AFP via Getty Images

worked for consistent increases to the National Institutes of Health's funding and are pleased with the work Congress has done to prioritize that funding over the past six years. An NIH program that funds researchers and workers across Delaware, the state that one of us (Coons) represents in the Senate, translates cutting-edge science into practical solutions for people with cancer.

But unfortunately, not all entities within the NIH have benefited equally from the recent budget increases, and the cancer research conducted via NCI funding is lagging behind. We believe a $1-billion boost this year and consistent increases going forward will allow the U.S. to remain the global scientific and economic leader in the development of cancer diagnostics and treatments that Americans will benefit from in the years ahead.

Because of the current funding lag, the NCI can fund only about one in eight meritorious research applications, according to data from the nonprofit ACT for NIH. This could leave many potential cures for various cancers on the cutting-room floor and leave young cancer scientists unable to get the financial backing they need to pursue innovative ideas. This in turn means that fewer promising scientists will enter the field of cancer research and that others will leave, leading to a brain drain in the field.

And Kansas, the state that one of us (Moran) represents in the Senate, is one of many that are home to universities and organizations conducting leading cancer research. Additional resources from the NCI would bolster those efforts, enabling renewed commitment on promising projects and a renewed hope for life-changing findings.

The funding gap is also the product of the remarkable momentum we have achieved in cancer innovation and the rise in applications to the institute for funding. During the past few decades, advances in cancer research have exploded. First, scientists learned how to use precision technology to target cancer in specific parts of the body. That innovation was followed by the development of immunotherapy, a technique by which doctors can use a patient's own immune system to identify and target individual cancer cells. The immunotherapy revolution is opening the next frontier in cancer research: scientists are beginning to understand how to use artificial intelligence and machine learning to predict patterns and diagnose and treat cancer patients earlier than we could have imagined 10 years ago.

As scientists learn more about immunotherapy and how to harness artificial intelligence to treat cancer, they are generating more and more ideas, any one of which could hold the answer we need to end cancer as we know it.

As NCI director Norman Sharpless recently told Congress, "You know, one of the things that's keeping me up at night, frankly, is the idea that there's this great investigator-initiated science in these pools of grants that we're not able to get to.... There may be a cure for pancreatic cancer in there, right?" But without adequate funding, the NCI cannot support these growing numbers of scientists.

Every year more than 600,000 Americans die from cancer, making it one of the leading causes of death in our nation. As a society, we now have the potential power and knowledge to diagnose and treat cancer in wholly new ways. We are heartened by the proposal to create the Advanced Research Projects Agency for Health, a new entity within the NIH that will bring innovations in cancer research to patients. And we believe those investments will produce the greatest value when paired with a robust, ongoing commitment to the NCI.

Our global competitors are already engaged in the battle against cancer and stand ready to reap the economic and health benefits of funding cures. Predictable and robust funding for the NIH, which oversees the NCI, is a critical part of our economy and an important driver of improving health outcomes for all Americans. Unless we take decisive steps to fund NCI at the level necessary to raise the number of research applications funded each year, we risk losing our position as the global leader in cancer research to other countries, including China. We instead support sustained robust investment in the NCI.

Francis Collins, who retired in December 2021 as director of the NIH, was a steady and strong leader who worked extremely well with Congress to prioritize the NCI and support public health and research. We encourage President Joe Biden to select a director who will continue to work together with Congress on our shared efforts of prioritizing resources for the NCI. Working together, we can leverage the growing field of cancer knowledge to end this disease as we know it.

Carolyn Barber has been an emergency department physician for 25 years. She is co-founder of the homeless work program Wheels of Change and author of many articles and the book *Runaway Medicine: What You Don't Know May Kill You*, which was recently Amazon's number-one Hot New Release in Health Care Administration. She received her M.D. at the Johns Hopkins University School of Medicine.

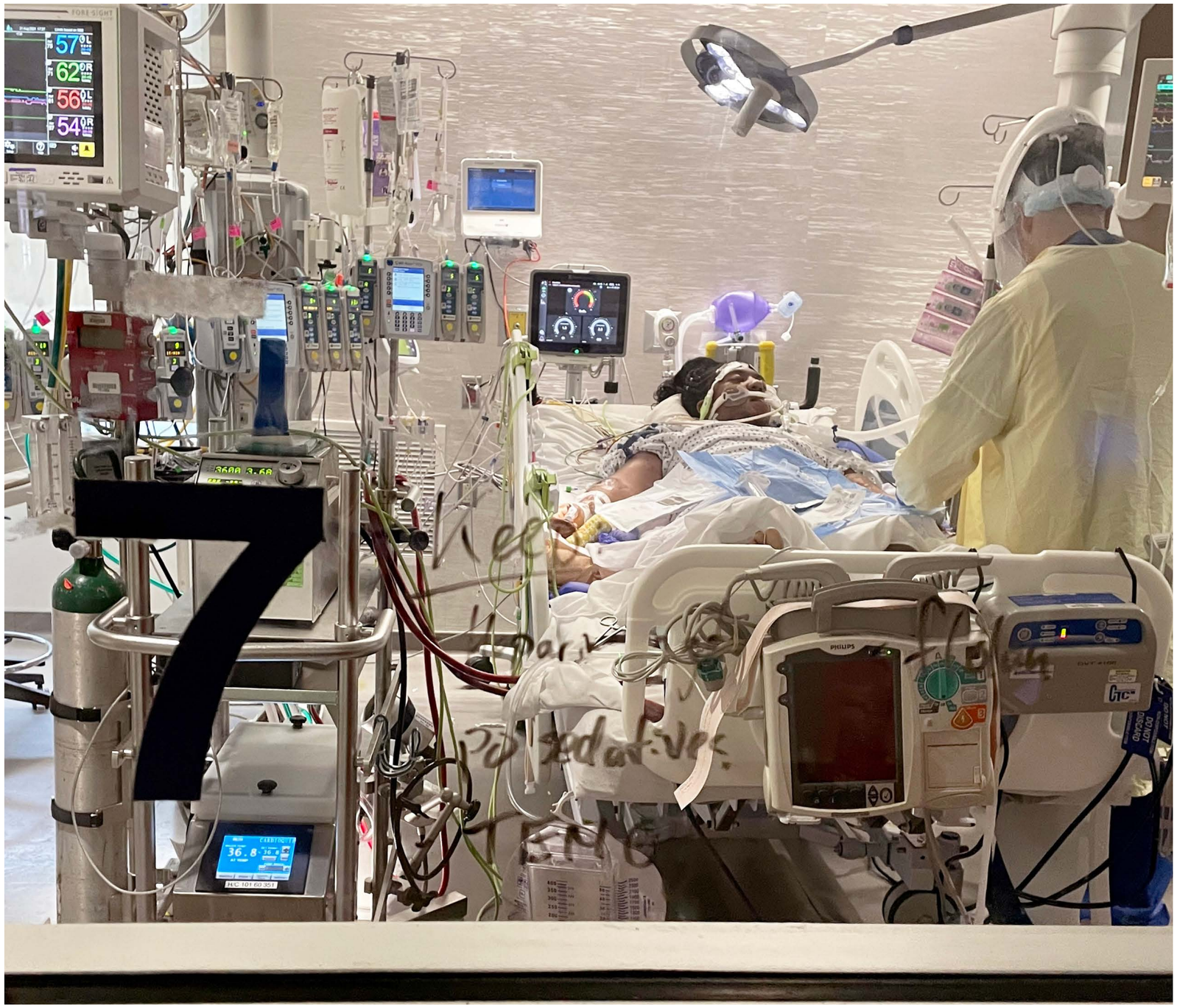
Some COVID Patients Need Amputations to Survive

Impaired blood flow leads to loss of limbs

In late summer 2021 Candice Davis and her brother, Starr, returned to Philadelphia from a trip to Mexico, and Davis quickly knew that something was wrong. Both she and Starr felt ill, and both subsequently tested positive for COVID-19. But Starr, who had been immunized, experienced only mild flulike symptoms and felt better within a few days. For his unvaccinated sister, a nightmare began to unfold.

Candice, 30, quarantined for two days but soon noticed that things were worsening. She started to feel her heart "skipping beats.... I was burning up," she tells me. She called an ambulance. At the Penn Presbyterian Medical Center, her blood pressure plunged to 70/50, and she was diagnosed with myocarditis, an inflammation of the heart muscle, caused by infection with the novel coronavirus.

In essence, Candice's heart was barely pumping.



Candice Davis, 30, in an intensive care unit. She was diagnosed with myocarditis and cardiogenic shock stemming from COVID, Davis spent weeks in a medically induced coma.

Paige Davis

Davis with her brother, Starr, and mother, Paige. Starr Davis became infected on the same trip as Candice. Previously vaccinated, he recovered quickly and without complications.

Her treating physician, Nayelah Sultan, says the heart was functioning so poorly that her doctors considered her for a cardiac transplant. Candice also experienced atrial fibrillation, a sudden acceleration of her heartbeat. Her doctors shocked her heart back into a normal rhythm.

Doctors explained to Candice that she needed to have a breathing tube inserted and to be placed on a ventilator. “I freaked out,” she says, “because I had heard the stories.” After a conversation with her mother, she agreed to the procedure. Hours later she was also placed on extracorporeal membrane oxygenation (ECMO), a heart-lung machine for life support, because she remained critically ill. She was started, too, on an anticoagulant that thins the blood to help prevent clots.

“It was a hot mess,” says Paige Davis, Candice’s mother. Her daughter had lines going in and out of her groin, and she required fasciotomies (cuts made into the muscle) to treat possible compartment syndrome in her legs. “It started with the heart,” Paige says, “but as time went on, everything started to crash.”

Placed in a medically induced coma, Candice doesn’t remember much from those first few weeks. But she knows what she saw when she awoke: “My arms and my feet, super black and, like, dead,” she says. “It was terrible.”

Lack of blood flow to Candice’s extremities led to the amputation of one arm above the elbow, one arm below the elbow, one leg below her knee and half her right foot. Her COVID could have killed her, but these procedures saved her life.

Candice’s case shows one of the underappreciated dangers of the disease. As many reports have indicated, SARS-CoV-2, the virus that causes COVID, is associated with a risk of clotting complications such as acute limb ischemia, or ALI. This refers to a sudden decrease in blood flow to a limb, usually because of a blood clot—that is, a thrombosis or embolism—in an artery. When traffic comes to a standstill on one of these arterial

Starr Davis

thoroughfares, limb viability can be threatened. In Davis's case, "the prothrombotic state from COVID is probably the thing that made it so, so bad," says her vascular surgeon Julia Glaser.

How and why these arterial clots form in ALI is unclear, but some experts believe that inflammation and endothelial injury (damage to the inner lining of blood vessels) incited by the virus are likely contributors. "When the endothelium is not working well and its job is to keep keeping blood moving, it's more prone to clot," Glaser says.

Arterial blockages can be an embolic phenomenon, in which a blood clot originates from a more proximal source such as the heart, then travels and lodges in a smaller blood vessel, where it can limit or block flow. Alternatively, it may be a thrombus, where a blood clot forms and remains at that site within a blood vessel, hindering flow. Life-threatening complications resulting from arterial and venous clot formation may include ALI, heart attacks, deep venous thromboses (DVT), pulmonary emboli (PE), strokes and multiorgan dysfunction, among others.

When I ask about COVID vaccination, Candice, a flight attendant and nursing student, tells me that she was so busy working "that I just wasn't able to get it." Now, she adds, "this whole process has brought me to thinking that it's important to get vaccinated so you don't lose your limbs and you don't lose your life. I have lost three of my limbs and half of my foot. It's scary, and I'm only 30."

And her brother? "Well, he was vaccinated," she says. "He's doing very well. He didn't lose any limbs."

Davis worked full time as a flight attendant for Republic Airways and was also in school, studying to be a nurse, before COVID hit. "My faith and my family—I think that is what has carried me through," she says.

Starr Davis

The prevalence of these types of COVID cases is not well defined, but some of the numbers are worrisome. A Dutch study conducted early in the pandemic of 184 ICU patients found the cumulative incidence of thrombotic complications (PE, DVT, stroke, heart attack or arterial embolism) in COVID-19 patients to be 31 percent. Venous events were noted in 27 percent, and arterial thrombotic events were observed in 3.7 percent. Italian researchers, meanwhile, reported significantly higher numbers of patients presenting with ALI in 2020: 16.3 versus 1.8 percent for the same time frame in 2019, prepandemic. The experts with whom I spoke do not describe ALI as a common phenomenon but say it is occurring.

"There was a clear increase in the number of patients presenting with ALI that was associated with COVID infection itself," says Peter Faries, chief of vascular surgery at the Icahn School of Medicine in the Mount Sinai Health System. He and his colleagues reported on 27 patients who experienced thrombotic events (44 percent were ALI; 26 percent were acute on chronic ALI) out of 6,095 patients with lab-confirmed COVID in March and April 2020. That is an incidence of 0.4 percent. Faries says that the patients were often relatively young and without underlying peripheral arterial disease, unlike most non-COVID patients with ALI. "To date," he says, "we have not seen COVID-related ALI in a patient who has been vaccinated."

How Omicron plays into all of this is not yet clear. Clearly more transmissible than even the fast-moving Delta variant, Omicron's ability to

evade immune protection afforded by vaccines is resulting in many breakthrough cases, and experts warn that the unvaccinated remain more at risk of severe disease and hospitalization.

Wes Ely, a critical care specialist at Vanderbilt University Medical Center, recalls drawing blood from a COVID patient who was experiencing a pulmonary embolism. Despite the patient being on maximum blood thinners, "his blood clotted in the syringe before I could get it into the test tube," Ely says. "I've never seen anything like that in my whole life. It was just the craziest thing." Across the hall, a female COVID patient lost four limbs.

"During our initial response to COVID in early 2020, the amputation rate certainly increased," says Kenneth Ziegler, chief of vascular surgery a Los Angeles County + University of Southern California Medical Center. "These acute limb ischemias—unless it's a traumatic incident in a young person, I would not be seeing ALI in patients less than 50 years old except for COVID," he adds. "But the ones I've been seeing for COVID, we were seeing patients in their 30s, 40s."

Common symptoms of ALI may include an arm or a leg that has abrupt pain, numbness or tingling, coldness, blood blisters, purple discoloration of the skin, black toes or skin mottling. While some COVID patients with ALI have known risk factors or preexisting vascular disease, experts and studies show that others have little or no predisposing factors.

And not all patients with ALI are severely ill, experts say. It can occur in patients who have mild COVID or who have findings related to ALI but are otherwise asymptomatic. Data from 21 patients who had experienced major thrombotic events from COVID infection revealed that most had either mild (38 percent) or moderate (47 percent) disease.

"The mortality associated with infected patients with ALI is much higher than noninfected patients with ALI."
—George Galyfos

Concerningly, ALI has also been reported in patients who have completely recovered from the virus. And in multiple studies, men who were COVID-positive appeared to be much more commonly affected with ALI than women. A review of 12 studies of COVID limb ischemia found that 79 percent of patients were male. And a study from Spain noted 92 percent of those with ALI were male.

"The mortality associated with infected patients with ALI is much higher than noninfected patients with ALI," says George Galyfos, a vascular surgeon at Hippocration Hospital University in Athens, Greece. That figure, he says, is about 30 percent, versus somewhere between 5 and 9 percent for noninfected patients.

The World Health Organization recommends at least prophylactic doses of blood thinners in critically ill patients admitted to the hospital with COVID. For patients who develop ALI, the focus is on saving their limbs, but case management ultimately depends on multiple factors, experts say. Amputation is one such management tool, and in a recently published small study in the *Annals of Vascular Surgery,* researchers found more than a twofold increase in major amputations in vascular surgery patients after the arrival of the COVID-19 pandemic in 2020. "We do have to save life over limb," Ziegler says.

Her life dramatically altered, Candice Davis has begun her long process of rehabilitation. Only very recently was she deemed healthy enough to become vaccinated against COVID. "They need to get their shots, period," says Paige Davis, Candice's mother, when asked if she has anything she wished to share with the public. "It's not a good sight to watch your daughter lose her limbs. Get vaccinated."

Hospitalized since August 17, 2021, Candice says her primary goal "is getting out of here." But she also reminds herself to be encouraged "that everything is going to be okay and life is going to get better. I want people to know that serious COVID can be beat." Sometimes that victory comes at tremendous cost.

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