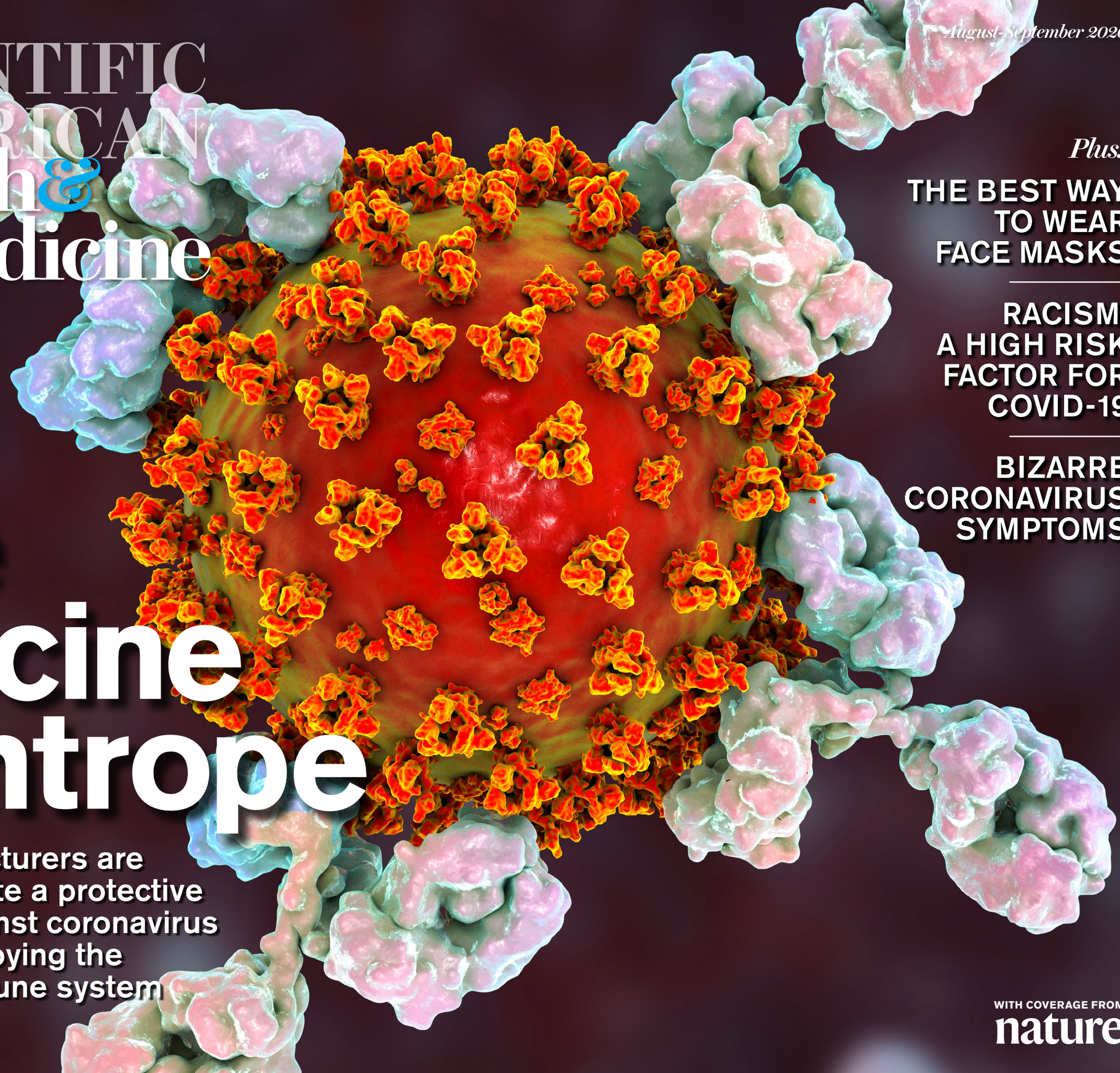
August-September 2020

SCIENTIFIC AMERICAN

Health & Medicine



The Vaccine Tightrope

Drug manufacturers are racing to create a protective measure against coronavirus without destroying the patient's immune system

Plus:

THE BEST WAY TO WEAR FACE MASKS

RACISM: A HIGH RISK FACTOR FOR COVID-19

BIZARRE CORONAVIRUS SYMPTOMS

WITH COVERAGE FROM nature

LIZ TORMES

Viral Learning Curve

As the public and policy makers anxiously await the arrival of a preventive treatment for SARS-CoV-2, the virus that causes COVID-19, researchers are racing to apply what they know about how coronaviruses stimulate the human immune system to create a barrier to prevent them from invading cells. The catch is the virus is tricky. It can co-opt the very molecules sent to disable it and launch a destructive immune reaction in the patient (see "COVID-19 Vaccine Developers Search for Antibodies That 'First Do No Harm' "). Reporter Esther Landhuis makes the astute observation that never before have the intricacies of immune function been a more central topic of conversation in everyday life. For those wishing they'd paid more attention in high school biology, there is plenty in this issue to help you catch up.

We on the editorial team worried that our primer on how to properly wear a face mask would be old news by the time it published. But virus cases are surging across the U.S., and new mask-wearing ordinances went into effect only recently in states such as South Carolina and California. Check out graphics designer Katie Peek's excellent illustrated guide in "How to Use Masks during the Coronavirus Pandemic." And epidemiologist Camara Phyllis Jones explains the socioeconomic conditions that make it more likely that people of color in America are more likely to die from the novel coronavirus (see "Why Racism, Not Race, Is a Risk Factor for Dying of COVID-19").
Mask up, and be well.

Andrea Gawrylewski
Collections Editor
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Health & Medicine

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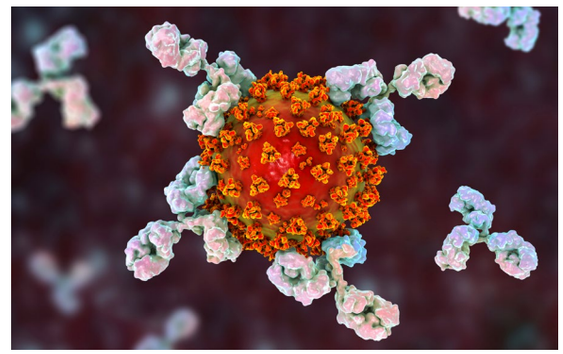

KATERYNA KON *GETTY IMAGES*

On the Cover

Illustration of antibodies (*white, Y-shaped objects*) responding to an infection with SARS-CoV-2 (*orange*)

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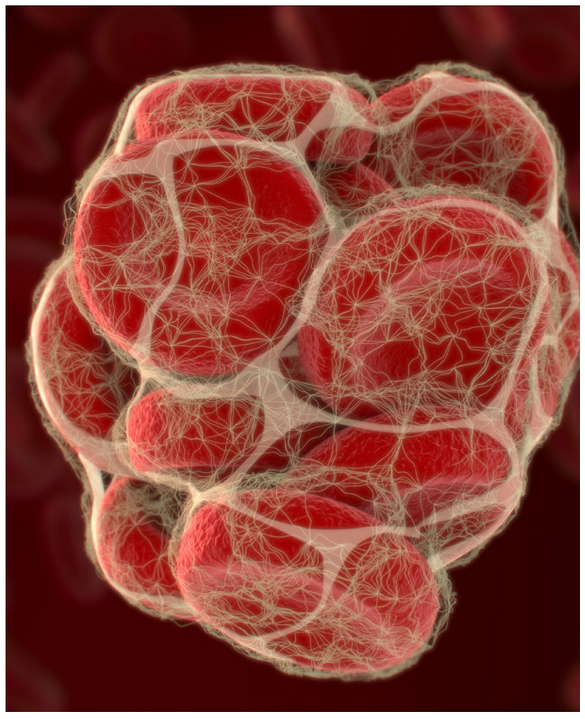

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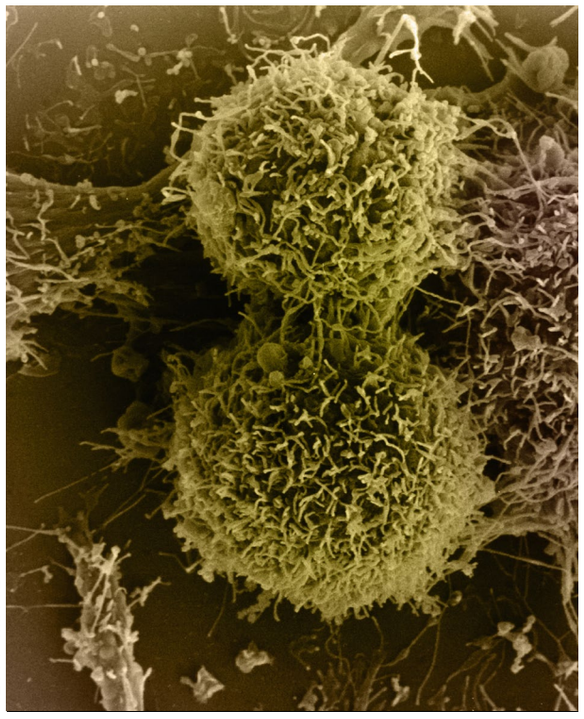

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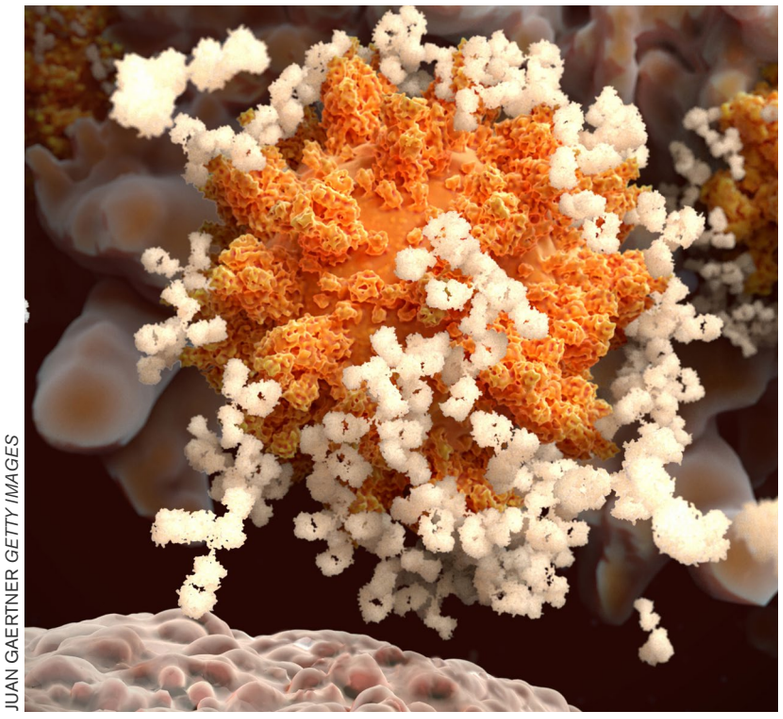


JUAN GAERTNER *GETTY IMAGES*

NEWS

FEATURES

OPINION

From Headaches to "COVID Toes," Coronavirus Symptoms Are a Bizarre Mix

Blood clots and inflammation may underlie many of these complications

The new coronavirus that has infected millions of people around the globe can wreak havoc far beyond the lungs. Some of the symptoms of the disease it causes, COVID-19, are predictable enough: cough, fever, chills, headache. But the pathogen's effects by no means stop there. The virus can cause problems in almost every organ, including the brain, heart, kidneys, gastrointestinal tract and skin.

Physicians have been taken aback by what they now call silent hypoxia or happy hypoxia, a phenomenon in which people with dangerously low levels of blood oxygen are astonish-

Blood clot

GETTY IMAGES

ingly not struggling to breathe. And there is "COVID toe," painful swelling of the skin called chilblains. In rare cases, children—who were previously thought to be relatively spared from severe illness—come down with symptoms akin to those of Kawasaki disease, which leads to inflamed blood vessels throughout the body. Complications associated with blood clots, such as strokes and pulmonary embolisms (blockages of blood vessels in the lungs), also turn up. "It's interesting that a respiratory virus will cause such a diverse array of clinical sequelae," says Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine.

One of the reasons for the unusual manifestations of COVID-19 may simply be the more than 10 million confirmed cases worldwide of a wholly new illness. Some of these symptoms have appeared during other viral infections—for example, researchers have seen blood clots in some patients infected with the original SARS coronavirus or the H1N1 influenza virus. "There are so many cases in the world now that we may be picking up on minor variants," says Stanley Perlman, a professor of microbiology and immunology at the University of Iowa. "It makes you wonder: If in other infections you look at two [million] to three million [cases], how many of these kinds of events would occur? Or is [the situation] really special for COVID-19?"

Scientists are still trying to pin down the exact mechanism underlying the wide range of complications. There seem to be two key leading suspects, however. The first is the immune system's defensive inflammatory response to foreign invaders such as viruses and bacteria. That reaction, in turn, may lead to the second culprit: blood clotting. The disease's impact on blood vasculature appears to underlie some of the more bewildering effects COVID-19 patients encounter.

Reports of clotting-related complications such as pulmonary embolism and stroke among COVID-19 patients in intensive care units have come from several countries, including China, France, Italy and the U.S. The overall frequency of such issues remains unclear, but some assessments suggest that they appear in as many as 30 percent of critically ill patients. In rare cases, strokes have turned up in people in their 30s and 40s, alarming doctors.

"We're seeing lots of different coagulation abnormalities" in the patients admitted to the ICU, says Margaret Pisani, an associate professor specializing in pulmonary and critical care medicine at the Yale School of Medicine. "We've seen strokes, myocardial infarctions, pulmonary embolisms—clots in places that we don't normally see in otherwise healthy people who come in with a viral infection."

Clotting-related issues are not specific to COVID-19, says Yvonne Maldonado, a professor of pediatric infectious diseases at Stanford University. A condition known as disseminated intravascular coagulation, in which abnormal clotting occurs throughout the blood vessels, has previously been reported in people with infectious diseases who experience sepsis (a life-threatening immune response to a contagion). "What's unusual here is that it seems to happen with this disease more often than with other diseases," she says.

In addition to clots in large blood vessels, researchers have reported clotting within smaller blood vessels known as capillaries. COVID-19 "is a vascular problem" says Frank Ruschitzka, a cardiologist at University Hospital Zurich. "The lung is the main battlefield, but it's a disease of the blood vessels."

Scientists have yet to pin down the cause of the clotting. Inflammation seems to be a likely culprit, however. Researchers have found, for example, the presence of complement proteins—molecules involved in activating the immune response—within clotted blood vessels. Across many of COVID-19's myriad symptoms, the common mechanism appears to be the inflammation of the endothelium, the layer of cells that make up the inner lining of blood vessels, says Luciano Gattinoni, a visiting professor in the departments of anesthesiology and intensive care at the University Medical Center Göttingen in Germany. "As the endothelium is present everywhere, you can explain why the symptoms are so different."

Some of the mysterious symptoms linked to COVID-19 start to make sense when they are viewed as manifestations of a vascular disorder. Take silent hypoxia, a condition Gattinoni drew attention to in April

as being related not to lung oxygen capacity but rather to impaired blood flow through the organ.

Many other odd manifestations of COVID-19, including kidney problems that require dialysis (in some cases, clotted blood has reportedly clogged filters in dialysis machines), chilblains in toes and Kawasaki-like symptoms in children, have been associated with vascular complications as well. "This is an extremely rapidly evolving field, but the vascular component of the disease is obvious," Ruschitzka says—although he cautions that "there is never one mechanism alone."

Whether the vascular problems associated with COVID-19 arise from direct effects of the virus or from the body's immune response remains an open question. Some evidence suggests that SARS-CoV-2, the coronavirus behind COVID-19, can directly attack the endothelial cells. In April, Ruschitzka and his colleagues published a paper in the *Lancet* that chronicled three autopsies. They found the presence of viral particles in kidney endothelia and an accumulation of inflammatory immune cells within the endothelia of various organs, including the kidney, heart and lungs. Ruschitzka, however, says that that the body's immune response, not the virus itself, is the more likely explanation for the excessive clotting. "What we see everywhere is pronounced inflammation," he adds.

Still, it is too early to rule out direct effects of the virus. "There are a lot of conditions that cause inflammation where you don't see these kinds of clotting disorders," Hotez says, raising the prospect that the virus may be directly involved in spurring blood abnormalities. The diversity of symptoms, he suggests, may have to do with the ACE2 receptors that SARS-CoV-2 binds to. These receptors are present on the surfaces of cells of multiple organs affected by COVID-19.

Alex Richter, an immunologist at the University of Birmingham in England, notes that the timing of a symptom may hint at whether it is caused by the virus itself or the body's immune response to it. A frequent early symptom—the loss of taste and smell—may be a more likely direct effect of the virus than the clotting complications or Kawasaki-like symptoms that appear later. "There's almost a time line of how we're getting these symptoms and how likely they are to be a direct effect of the virus or because of a hyperimmune response," she says.

"There's almost a time line of how we're getting these symptoms and how likely they are to be a direct effect of the virus or because of a hyperimmune response."

—Alex Richter

Richter notes that what is particularly strange about the Kawasaki-like symptoms seen in children is that they seem to appear several weeks after initial exposure to the virus. She and her team are currently investigating samples from affected children to pinpoint how their immune system might be generating these effects. So far they have found evidence that these individuals possess antibodies suggestive of a well-developed immune response, indicating that the infection likely occurred weeks prior to the onset of symptoms.

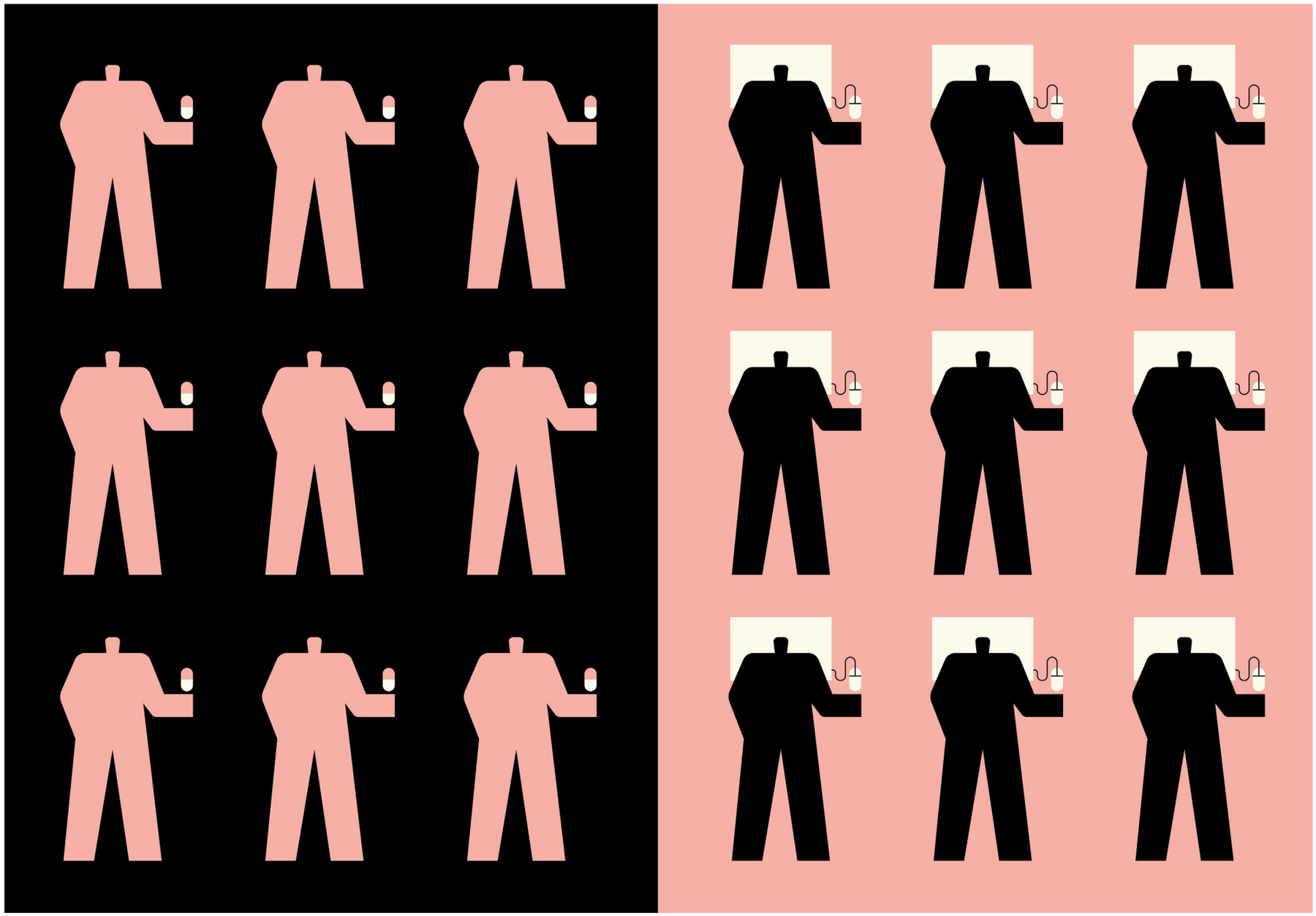
Richter says this observation is distinct from what has been seen in adult cases, in which the immune system seems to react much more immediately to the contagion.

Despite the wide range of COVID-19 symptoms, the emerging understanding of the infection hints at a set of common underlying factors that may be at work. "It could be that it's actually just a few things that are going on, and depending on where they manifest, you see all these different symptoms," Perlman says. "Then the question is: Why does it manifest differently in different people?" Most people who are infected with SARS-CoV-2 will not need to be admitted to the ICU, but those who are hospitalized confront an illness that continues to hold surprises for the medical community. Clear risk factors presage severe disease, including age, obesity and heart conditions. But scientists are still looking for inflammatory biomarkers and other biochemical signposts to help physicians predict who will get better on their own and who will become severely ill, Maldonado says. "Everybody's trying to figure that out."

—Diana Kwon

The Coronavirus Outbreak Could Make It Quicker and Easier to Trial Drugs

Remote clinical trials and other changes could permanently alter pharmaceutical development



Jonathan Cotliar knew he was ahead of the curve four years ago when he joined Science 37, a company that supports virtual clinical trials conducted mostly online. The firm, based in Los Angeles, was growing slowly before March, receiving about a dozen calls a week from potential clients. But since the COVID-19 pandemic began, Science 37 has been running at fever pitch.

Cotliar, the company's chief medical officer, says Science 37 now receives hundreds of inquiries every week from potential clients such as pharmaceutical companies, medical centers and even individual investigators. With hospitals forming the epicenters of COVID-19 outbreaks around the world, clinical-trial participants have become reluctant to attend routine checkups and monitoring visits, and health care workers are stretched beyond their capacity. This has caused researchers to put many clinical trials on hold or to shift to a virtual trial structure by performing consultations online and collecting as much paperwork and data as possible remotely.

The pandemic might hasten the kind of change in clinical trials that Cotliar and Science 37 were hoping to make anyway. And there could be

other lasting effects on drug development: companies that are usually competitors are now collaborating, and many are trying to make their supply chains more robust to deal with disruption. Some researchers and companies in the drug-development field say the system might never be the same again.

The pandemic has touched nearly all aspects of the industry, says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development. “This has really turned upside down the whole drug-development process,” he says. “The entire investigative world is focused just on developing treatments for COVID-19.”

Some changes are likely to be temporary, Kaitin predicts. Drug regulators in the U.S. and in other countries have acted fast to approve clinical trials of therapies and to allow new uses of existing medicines to fight COVID-19, without demanding as much data and paperwork as they normally would. Such changes are likely to stick only for as long as the outbreak lasts. “The flexibilities that are being granted for clinical-trial development are being granted under the auspices of a public health declaration,” says Esther Krofah, executive director of FasterCures, a Washington, D.C., think tank. “That, to me, is very much an emergency operation.”

And Kaitin points out that these changes shave only a few months off the drug-development time line—crucial in the middle of a pandemic but unlikely to make a significant dent in the lengthy process of developing a therapy, which can stretch out over years.

The pandemic could catalyze lasting change in other ways. What might linger, Krofah says, is the culture of collaboration across government, industry and academia that has emerged during the outbreak. “We have traditional competitors working together in new ways,” she says. An alliance of more than a dozen companies—including Gilead in Foster City, Calif., Novartis in Basel, Switzerland, and WuXi AppTec in Shanghai, China—has been working to discover and test antiviral treatments by sharing data about early results and basic science, as well as by collaborating on designs for clinical trials. If these group efforts bear fruit, they might continue, Krofah says.

Researchers at Sinovac Biotech in Beijing at work on a vaccine for COVID-19. Drug development has sped up during the pandemic, but it is unclear whether the pace will last.

NICOLAS ASFOURI *GETTY IMAGES*

Pharmaceutical companies might also make long-lasting adjustments to their supply chains, says David Simchi-Levi, who studies operations management at the Massachusetts Institute of Technology. Over the past few decades drugmakers have increasingly shifted their manufacturing away from the U.S. and Europe to countries such as India and China,

which can produce the drugs at lower cost. But over the past few years many firms have begun to look for ways to diversify their supplies of services and raw materials, to reduce the risk of supply interruptions in the event of a U.S.-China trade war, Simchi-Levi says. The coronavirus outbreak could accelerate that trend. "Some shocks were anticipated but not at this scale," Krofah says. "This is going to cause a fundamental reexamination of that risk."

Momentum for a shift toward virtual clinical trials has been building gradually for years. But progress had been hindered by a lack of clear guidance from regulators such as the U.S. Food and Drug Administration and by a reluctance to invest in the technology needed to run such trials—until the pandemic hit, Cotliar says. Companies such as Science 37 are suddenly seeing their popularity skyrocket. "It's exponentially accelerated the adoption curve of what we were already doing," Cotliar says. "That's been a bit surreal."

At the University of Minnesota, for example, infectious disease specialist David Boulware and his colleagues conducted a randomized, controlled, virtual trial of the malaria drug hydroxychloroquine to find out whether it can protect people who are at high risk of contracting COVID-19. The trial, which included more than 800 people and found that the treatment had no benefit, sent participants medicine by FedEx delivery and monitored their health remotely.

Patient advocates have long pushed for more virtual trials, which ease the burden of clinical-trial participation. If the trend catches on, it could speed up the enrollment of participants—a significant piece of the drug-development time line.

And now that the pandemic has driven medical centers to set up much needed technology and forced the FDA to release guidelines for virtual trials during the pandemic, it is hard to imagine clinical research going back to the way it was before, Krofah says. "We're going to see this as a new, normal part of clinical research," she says. "The cat is out of the bag." *—Heidi Ledford*

Heat and Humidity Are Already Reaching the Limits of Human Tolerance

Events with extreme temperatures and humidity are occurring twice as often now as they were 40 years ago

Over the hundreds of thousands of years of our existence on the planet, modern humans have managed to adapt to a huge range of climates—from the arid heat of the Sahara Desert to the icy chill of the Arctic. But we have our limits. If temperatures and humidity rise high enough, even a robustly healthy person sitting still in the shade with access to water will succumb to the heat.

As heat waves have grown hotter and more frequent, research has suggested that some places will begin to see events that reach the limit of human tolerance in the coming decades. But now a new study shows they already have. The findings, published in May in *Science Advances*, underscore the need to rapidly curtail emissions of heat-trapping greenhouse gases and to develop policies that will help vulnerable populations stay cool.

High temperatures prompt the human body to produce sweat, which cools the skin as it evaporates. But when sky-high humidity is also involved, evaporation slows down and eventually stops. That point comes when the so-called wet-bulb temperature—a measure that combines air temperature and humidity—reaches 35 degrees Celsius (95 degrees Fahrenheit).

Previous analyses using climate models suggested that parts of the Persian Gulf region, the Indian subcontinent and eastern China would regularly see heat waves breaching this limit by later in the century. But they looked at broad areas over several hours, which can mask more localized, shorter-term spikes in extreme conditions. To see what other researchers might be missing, "we decided to zoom in a little bit closer," says Colin Raymond, who conducted the new study when he was a Ph.D. student at Columbia University.

Raymond and his co-authors examined temperature data from more than 7,000 weather stations

around the world going back to 1979. They found that extreme humid heat occurs twice as often now as it did four decades ago and that the severity of this heat is increasing. Many places have hit wet-bulb temperatures of 31 degrees C and higher. And several have recorded readings above the crucial 35-degree mark. Identifying that trend is "important because it builds on [weather] station data, which is the most direct evidence that we usually have," says Massachusetts Institute of Technology climate scientist Elfatih Eltahir, who was not involved in the new research but has done previous work on the topic.

These humid heat extremes have already emerged in the same places that earlier modeling studies had identified as future hotspots. Most are coastal areas that are both near warm bodies of water, which can supply abundant moisture, and subject to soaring overland temperatures. Others, particularly in the Indian subcontinent, are regions where monsoon winds usher in moisture-laden air.

Given the paucity of weather stations in some of the involved places, such as parts of Pakistan, "there's probably even higher [wet-bulb] values out there," says Raymond, who now works at NASA's Jet Propulsion Laboratory. The highest extremes were typically reached only for an hour or two, so they do not yet necessarily hit the limit of human tolerance. But such events will start to last longer and cover larger areas in a warmer future. Also, even much lower wet-bulb temperatures can be deadly, particularly to the elderly or those with underlying health conditions. The historic heat waves that killed thousands of people across much of Europe in 2003 and in Russia in 2010 never had a wet-bulb temperature above 28 degrees C. "These are very, very nasty conditions," Eltahir says.

The new paper also found that parts of the world will regularly see wet-bulb temperatures higher than the 35-degree limit if global average temperatures rise just 2.5 degrees C above those of the preindustrial climate. The world has already warmed to about 1 degree C above that level. "These kinds of events can become a regular occurrence with not much more warming than we've experienced," says Kristina Dahl, a senior climate scientist at the Union of Concerned Scientists, who was not involved with the study.

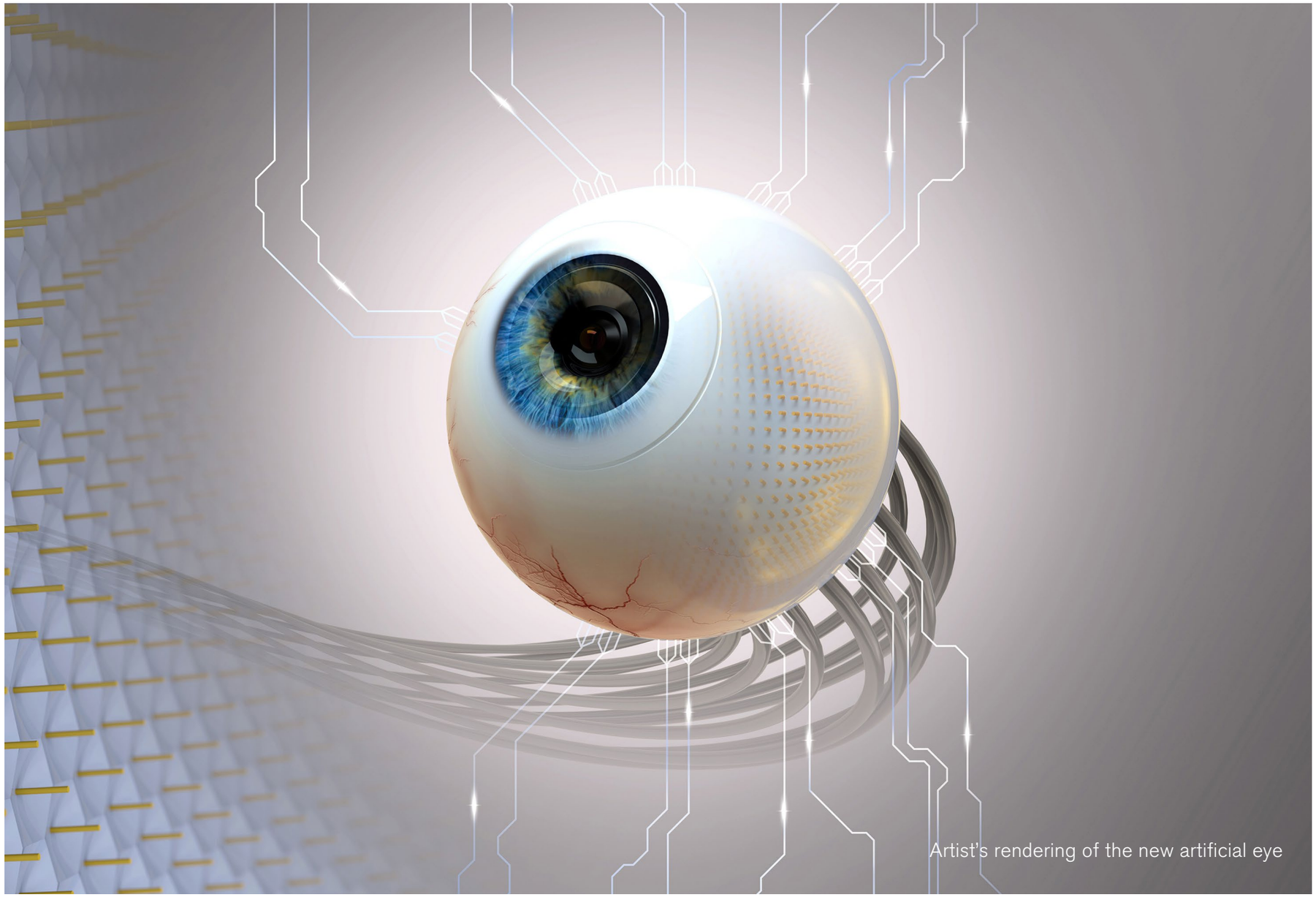
That projection underscores the need to rapidly reduce greenhouse gas emissions to limit global warming as much as possible, which would restrict how often such events might happen in the future. It also raises several questions about, for example, the policies governments will need to develop to safeguard vulnerable groups, such as establishing cooling centers for elderly residents or sending out warnings before heat waves. And industries whose workers toil outdoors—such as agriculture and construction—may need to shift their schedules to cooler times of day. Even in the abundantly air-conditioned U.S., heat currently kills more people than cold, floods or hurricanes do. *—Andrea Thompson*

Man stands in the spray of a broken water pipe during a heat wave in Karachi, Pakistan, on June 29, 2015. The heat wave reached 45 degrees Celsius (113 degrees Fahrenheit).

ASIM HAFEEZ *GETTY IMAGES*

New Artificial Eye Mimics a Retina's Natural Curve

Researchers have crafted a device that replicates the shape of the eye's sensory membrane



Artist's rendering of the new artificial eye

LEILEI GU AND FANTASTIC COLOR ANIMATION TECHNOLOGY CO., LTD

The human eye is a sophisticated instrument: images enter through a curved lens at the front of the sphere and pass through its gooey vitreous liquid before reaching the light-sensitive retina—which relays the signal to the optic nerve that carries the picture to the brain. Engineers have attempted to replicate this structure for about a decade. Now a new artificial eye successfully mimics the natural instrument's spherical shape. Researchers hope this achievement could lead to sharper robotic vision and prosthetic devices. A paper on the development was published in May in *Nature*.

The research built on the fact that perovskite, a conductive and light-sensitive material used in solar cells, can be used to create extremely thin nanowires several thousandths of a millimeter in length. These wires mimic the structure of the eye's long, thin photoreceptor cells, says study co-author Zhiyong Fan, an electronic and computer engineer at the Hong Kong University of Science and Technology. "But the difficulty is: How can we fabricate an array of the nanowires in a hemispherical substrate to form this hemispherical retina?" he adds. Constructing a curved retina is important because light hits it only after passing through a curved lens. "When you try to image something, the image that forms after the lens is actually

curved," says Hongrui Jiang, an electrical engineer at the University of Wisconsin–Madison, who reviewed the new paper but was not directly involved in the work. "If you have a flat sensor, then the image cannot be focused very sharply." The retina is curved, but electronic light sensors are rigid and flat.

To solve the problem, Fan and his colleagues deformed soft aluminum foil into a hemispherical shape. Then they treated the metal with an electrochemical process that converted it into an insulator called aluminum oxide. This process also left the material studded with nanoscale pores. As a result, the researchers were left with a curved hemisphere that had convenient densely clustered holes in which they could "grow" perovskite nanowires. "The density of the nanowires is very high," Jiang says. "It's comparable—it's actually even higher—than the density of the photoreceptors in human eyes."

Once they had their curved "retina," the scientists incorporated it into an artificial eye that included a curved lens at the front. Inspired by the specialized liquid in a real eye, the team filled its biomimetic version with an ionic liquid, a type of liquid salt in which charged particles can move. "One very important component inside is in the cavity we filled [with] ionic liquids," Fan says. "Once these nanowires generate charges, the charge will be exchanged with some ions." This electrical exchange allows the perovskite nanowires to carry out the electrochemical function of detecting light and sending that signal to external image-processing electronics.

When the team tested the artificial eye, it managed to process patterns of light in as little as 19 milliseconds—half the time required by a human eye. And it produced images that had greater contrast and clearer edges than those generated by a flat image sensor with a similar number of pixels. In some ways, the artificial eye improved on natural vision: it could pick up a greater range of wavelengths and lacked a blind spot.

Fan hopes to work with medical researchers to build prosthetic devices based on his team's design. Doing so could require much more development, however. The artificial eye is "really elegant; it looks like amazing work," says Jessy Dorn, vice president of clinical and scientific affairs at biomedical company Second Sight, who was not involved in the research. "But [the study authors] don't talk about how it could possibly be connected to the human visual system." She works on blindness-treating devices, including a retinal prosthesis called the Argus II, and points out that developing the electronic interface is only the first step. Such a device will need to interact with the human brain to produce images. "That's one of the bigger challenges: how to get any kind of high-resolution interface safely and reliably implanted and then [to] work with the human visual system."

"Mimicking the natural eyes has been a dream for many optical engineers."

—Hongrui Jiang

Furthermore, there are different types of blindness, and perfect eyes may not always produce perfect vision. For example, brain development during infancy and childhood is crucial to the processing of visual input—so a person who is born blind may never have the brain wiring required to see through prosthetic eyes later in life. Dorn notes that recipients of the Argus II implant are all adults who lost their vision much later in life. And even they have different levels of success: some only gain the ability to differentiate light and shadow, whereas others can process shapes. Still, she says that any visual connection to the environment can result in more independence and greater freedom of movement. And prostheses are not the only valuable application of artificial eyes: such devices could have immediate applications in robotic vision.

"Mimicking the natural eyes has been a dream for many optical engineers," Jiang says, noting that some researchers seek to imitate mammalian eyes and that others work with insectlike compound ones. The field is finally beginning to have real breakthroughs, he adds. "I think in about 10 years we should see some very tangible practical applications of these bionic eyes."

—Sophie Bushwick

Coronavirus and the Flu: A Looming Double Threat

The two could come together, making things worse—or our new hygiene habits may actually reduce the flu's spread

Uncertainty about the future seems to be the one sure thing in the coronavirus pandemic. No one knows whether COVID-19 will persist at its current pace or whether recent increased interactions among people will spawn an onslaught of smaller outbreaks or a larger second wave. But a few things are clear: the virus that causes the disease is likely to continue circulating through the population until there is a vaccine, and flu season is only a few months away.

The overlap of COVID-19 and influenza has epidemiologists and some policy makers concerned. The U.S. may soon face two epidemics at the same time, they worry, and this combination could precipitate a crisis unlike any other. "The worst-case scenario is both [the coronavirus and the flu] are spreading fast and causing severe disease, complicating diagnoses and presenting a double burden on the health care system," says Marc Lipsitch, an epidemiologist at Harvard University. A few states are planning for extra capacity in hospitals to deal with both illnesses.

Yet another, more favorable future also might be possible as these viruses cross paths, Lipsitch and other infectious disease forecasters say. The behavioral changes people have already adopted to flatten the curve of COVID-19—such as social distancing, handwashing and mask wearing—could lessen the impact of the flu.

"It is hard to predict," says Sarah Cobey, an epidemiologist at the University of Chicago. Not only is it unknown whether the coronavirus will ebb and flow as seasons change, but "what's really hard is that I don't have a good forecast for human behavior and policy decisions that are going to be made over the next couple of months," she says.

Jeffrey Shaman, an epidemiologist at Columbia University, says that if SARS-CoV-2 follows seasonal patterns like some other coronaviruses and influenza viruses do, it could subside in the summer. "But that could come back to haunt us," he adds. "We might get complacent; we might not be prepared." Four flu virus pandemics over the past 100 years—H1N1 in 1918, H2N2 in 1957, H3N2 in 1968 and H1N1 in 2009—had a deadly second wave around the fall and early winter. COVID-19 could do the same. "The concern that we might have a double whammy of flu and coronavirus is legitimate," Shaman says.

Every year influenza sickens millions of people in the U.S. In particularly bad years, flu surges overwhelm hospitals and health care systems. During the 2017–2018 flu season, local news outlets reported that hospitals across the country flew in nurses from other states, erected tents in parking lots and sent incoming ambulances to other facilities because of the overload of patients. The U.S. Centers for Disease Control and Prevention

GETTY IMAGES

estimates that between 46,000 and 95,000 Americans died from the illness that season.

Although the new coronavirus and influenza viruses can cause some of the same symptoms—such as fever, cough and fatigue—these similarities are mostly superficial. The pathogens use different receptors on cells to gain access to our bodies. As a result, SARS-CoV-2 could enter one way while a flu virus slips in another. A study of about 1,200 patients, conducted in northern California and published in *JAMA* in April, found that one in five people who were diagnosed with COVID-19 were coinfected with another respiratory virus. The risk of such coinfections is typically low, says Ben Cowling, an epidemiologist at the University of Hong Kong, but it gets higher when two viruses are circulating heavily in the same region. "It's possible you could get infected with both at the exact same time—if you're having a really bad day," he says.

Cowling and some other epidemiologists think that the way viruses interact and interfere with each other could reduce the impact of any coronavirus-influenza collision, however. They have tracked epidemics for decades and have found that outbreaks of respiratory viruses usually do not reach their peaks during the same time period. A study published last year in the *Proceedings of the National Academy of Sciences USA* hypothesized that temporary bursts of immunity to different viruses on the cellular level could shift the course of future epidemics, although no one knows exactly why. For example, an outbreak of a rhinovirus—the cause of a common cold—appears to have delayed the arrival of the 2009 influenza pandemic in Europe. And that effect, in turn, likely postponed epidemics of another disease: respiratory syncytial virus.

"Right now COVID-19 has a huge fraction of the population susceptible to it," Cobey says. "Assuming that we're not incredibly diligent about stopping transmission, it's going to continue burning through populations, leaving this wake of immunity that might be slightly effective against other viruses." She admits that this idea sits on the "speculative side of hypotheses." And the theoretical immunity would not be strong enough for, say, someone who has recovered from a coronavirus to shrug off the flu, or vice versa. But on a population level, it could mean that other viruses might not spread as quickly as normal, so their epidemic peaks could be delayed.

Another reason that the collision might not be dramatic has less to do with virology and more to do with human behavior: both COVID-19 and the flu are transmitted, for the most part, by respiratory droplets, so the same prevention strategies used to reduce the spread of the former will also work for the latter.

In a study published in the *Lancet* in April, Cowling showed that the public health measures introduced in Hong Kong to contain the coronavirus—such as border restrictions, quarantine and isolation, social distancing, mask wearing and handwashing—led to a rapid decline in flu activity. In the U.S., new flu cases plummeted a few weeks after COVID-19 was declared a global pandemic. The 2019–2020 flu season, once on track to be among the worst in decades, ended six weeks early.

But as states in the U.S. ease restrictions on activity and travel, people's behaviors could change in ways that ease virus transmission, so a double threat is still possible. And it is not clear what, if any, federal response is being mounted to prepare for it. In April, Robert Redfield, director of the CDC, told the *Washington Post* that "we're going to have the flu epidemic and the coronavirus epidemic at the same time." After President Donald Trump claimed that Redfield was misquoted, the director walked his statement back, saying he did not mean that the current crisis would be worse, just "more difficult and potentially complicated." (The CDC did not respond to *Scientific American*'s requests for further comment.)

In late May a group of Democratic senators sent a letter to the White House asking it to prepare for the worst overlap scenario. "We urge you to begin planning for and activating the resources of the federal government now," they wrote, "to increase capacity, supplies, and vaccinations to prevent public health and medical systems from being overwhelmed by simultaneous peaks of both of these deadly infectious diseases in the fall."

On the state level, some are updating hospital surge plans and expanding infectious disease surveillance programs to include both the flu and COVID-19. North Carolina's state

health director Elizabeth Tilson, who co-chairs the state's coronavirus task force, has been working with health systems to develop plans for increasing their surge capacity by converting unused facilities, procuring extra beds or hiring extra staff. "Thankfully, we haven't had to pull the trigger on any of our emergency med surge plans. But we have all those plans in place, whether it be COVID-19 or COVID-19 and flu," she says.

Cobey has been trying to convince the government of her home state of Illinois to set up a sentinel surveillance plan that could alert officials to coming surges of COVID-19 and flu cases. But she says her suggestions have received little traction. Such surveillance systems already exist in other states, including North Carolina and Michigan. The CDC also tracks both illnesses on the national level and releases a weekly surveillance report on the viruses that cause them.

Tilson points out that whatever happens, there is one basic step people can take that may alter the trajectory of either epidemic. "Look, we don't have a vaccine for COVID-19," she says. "We do have a vaccine for flu. Get the vaccine."

—Marla Broadfoot

Early Coronavirus-Immunity Data Fuel Promise for a Vaccine

Researchers found that COVID-19 infection produces a strong T cell response. Here's why they say that is good news

As the world grapples with how to safely reopen society in the midst of the coronavirus pandemic, scientists have been racing to understand whether COVID-19 infection confers immunity—and how long such immunity might last. A lot hangs in the balance: A strong immune response could mean people who have already been infected would be able to safely return to work. And it would also bode well for vaccine-development efforts.

A small but suggestive new study found that individuals who have had COVID-19 produce a robust response in immune cells called T cells. The adaptive immune system contains several main components: antibody-creating B cells, helper T cells and killer T cells. The latter two are important for recognizing and destroying a particular virus, respectively. Alessandro Sette and Shane Crotty, both professors at the La Jolla Institute for Immunology, and their colleagues found that of a group of 20 people who had recovered from COVID-19, 70 percent had killer T cells and 100 percent had helper T cells that were specific to the SARS-CoV-2 virus, which causes COVID-19. More important, the researchers observed a strong T cell response to the "spike" protein the virus uses to bind to and infect cells (and which most vaccine candidates target). They additionally detected a helper T cell response to SARS-CoV-2 in about half of blood samples they examined that had been drawn before the virus began circulating. This observation, they say, hints that exposure to seasonal common cold coronaviruses may confer some protection against the new pathogen.

The findings build on earlier studies showing that infection with the novel coronavirus produces protective, or "neutralizing," antibodies. Taken together, these results suggest that people who have had COVID-19 possess at least some immunity—an encouraging sign for the dozens of vaccines under development. Separately, in May the company Moderna announced early results from a trial of its coronavirus vaccine candidate: eight individuals who received the vaccine produced antibodies to the virus at levels similar to those of people who had had the disease.

Scientific American spoke with Sette and Crotty about what their study means for immunity to COVID-19, possible protection from seasonal cold infections and the prospects for a SARS-CoV-2 vaccine.

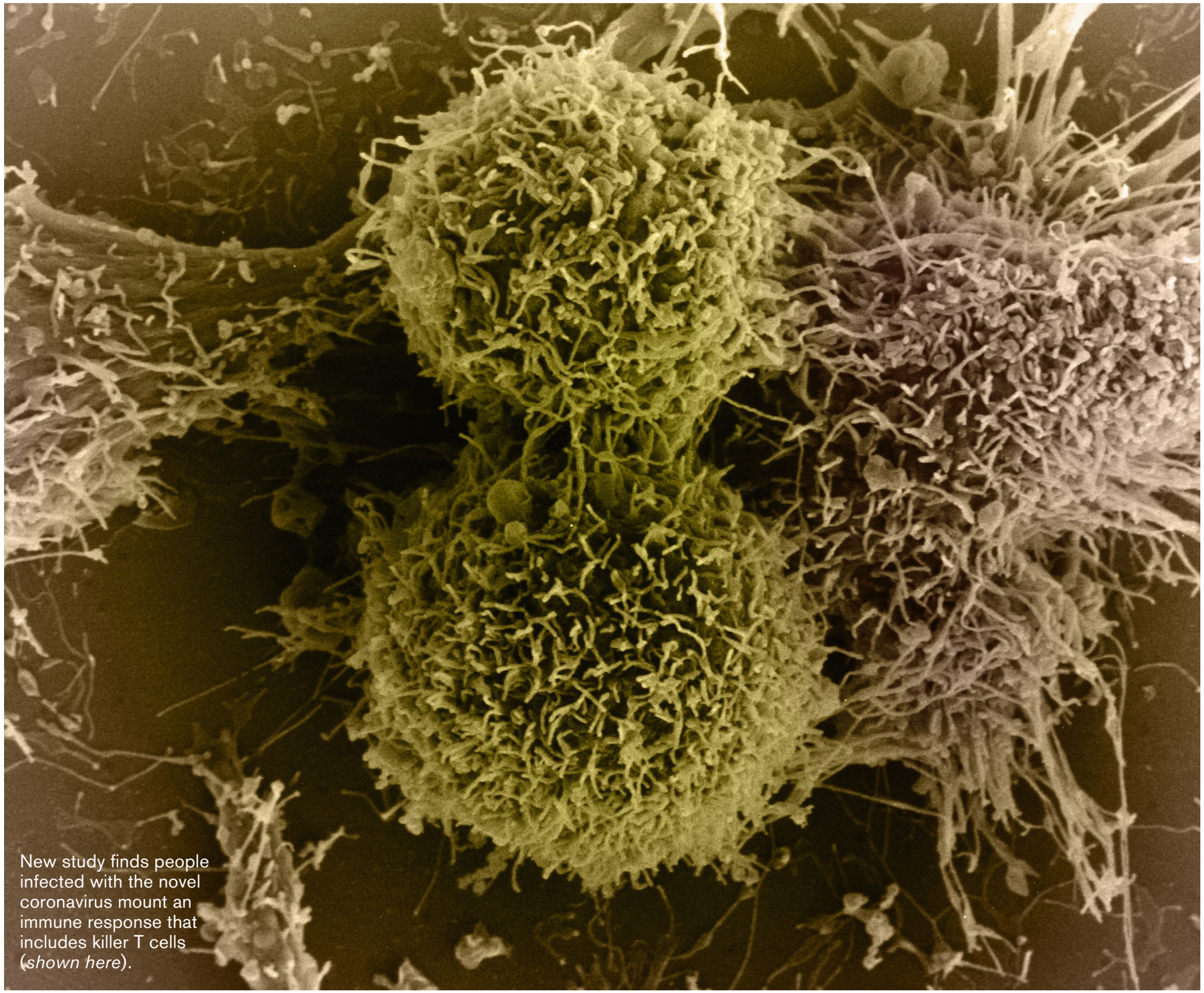
[*An edited transcript of the interview follows.*]

What do we know so far about immunity to COVID-19? And why is it so important?

CROTTY: There's just been a huge amount of uncertainty about immunity to COVID-19. And that question about immunity has two major implications: one, for just understanding the disease itself, and two, for vaccine development. It's clearly been a world-on-fire type of situation. And so it has made sense for these 100-odd different vaccine programs to get going and just try moving things forward. The normal way you would try and make a successful

vaccine would be to look at what gets you good protective immunity to that disease and copy that. A disease such as COVID-19 is normally an acute infection, and most people control and clear it without a lot of problems. That's a good sign that indicates that the human immune system normally makes a good response to that virus and controls it.

But the immune system is a big, complicated place, with lots of different cell types with lots of different functions. And some are useful or important in one context versus another. For a vaccine, you'd want to know which components of the immune response are the important ones for protection against this disease. And without that information, you can very much go totally in the wrong direction with a vaccine program, in terms of either the type of immune response you're trying to get or the [vaccine's molecular] target. And both of those have been things that worried [Sette] and me and other people about these ongoing vaccine efforts. We really wanted to generate information that would help [us] understand the disease itself—and also generate information about which vaccine strategies are likely to



New study finds people infected with the novel coronavirus mount an immune response that includes killer T cells (*shown here*).

GETTY IMAGES

be better or worse ones and whether people are getting the right [molecular target] or not. Our goal was to look at essentially average cases of COVID-19—ones where people definitely are making successful immune responses—and ask, "Okay, what does that immune response look like?"

Can you describe the different parts of the immune response and how they work?

CROTTY: Quite a few labs around the world have looked at antibody responses. Those are generally easier to measure and look at. But really there are three parts of the adaptive immune system: you've basically got antibodies, you've got helper T cells, and you've got killer T cells. The T cells are tougher to measure, but they do very important things. You've got to have the helper T cells to get an antibody response. For example, in animal models, [helper T cells] are important for protecting against [severe acute respiratory syndrome (SARS)]. And the killer T cells are important for most viral infections. You don't want to go forward without understanding anything about the T cell response. And [Sette] is the world's expert in predicting and identifying T cell [targets], particularly in humans. So we collaborated to get COVID-19 patient blood samples as quickly as possible and to try and get information about those questions. We mostly have concluded it's good news: things have largely looked the ways we would expect.

Do we know how long the immune response to the new virus lasts?

SETTE: What we certainly can say is that the infection induces a robust immune response, and this is in people who successfully deal with the virus and don't get very sick. The question [of] how long this response lasts obviously takes time, because we have been dealing with this virus for only a few months, and we cannot possibly know what is going to happen a year down the line. But what we've seen thus far is encouraging, because these T cells look healthy, look happy. They are not exhausted, and they don't express some of the molecular features that are associated with cells that are about to die.

In general, immunological memory is like any other memory in the sense that the intensity of the event dictates how strong the memory is. Pretty much like any event in your life: if it was a life-threatening situation—for example, you almost got run over by a truck—you remember. If it was instead what kind of socks you wore, you might not remember. It's the same for the immune system in the sense that a very strong infection with a microbe that reproduces to high levels generates a strong level of immune response, which then creates a long-lasting impression. I would speculate that the memory generated by SARS or [Middle East respiratory syndrome (MERS)] could be somewhat different from one generated from a common cold, which is fairly adapted to not cause much trouble in the human host.

"Quite a few labs around the world have looked at antibody responses."

—Shane Crotty

You also saw some T cell responses, or "cross-reactivity," to the new coronavirus in blood from people who were never exposed to it, correct?

SETTE: We looked at the COVID-19 patients, and then we looked at a control group. We purposely went after blood donations that were obtained in 2015 to 2018—before any SARS-CoV-2 was around. Surprisingly, in about half of these people, we could see some T cell reactivity. And we looked at the data hard from the left and from the right and convinced ourselves that this was real. We do not know at this point exactly what this cross-reactivity means, but it's reasonable to assume that it is the result of people having been exposed to common cold coronaviruses that are different from SARS-CoV-2 but have some similarity [to it]. This potentially has very strong implications because one of the things that is unknown and everybody wants to gain more information about is why there is such a spectrum of different COVID-19 outcomes: some people are totally asymptomatic, whereas other people die. Of course, age and other health issues are factors, but one element could be immunological:

If someone has some T cells that can cross-react to SARS-CoV-2, their immune system has an advantage. They can get going to generate antibody responses faster, maybe, and that could give a better outcome. In the context of vaccination, this is also very important, because imagine that you have a group of people and half of them have this coronavirus cross-reactivity and half of them don't. Now you give these people a vaccine. It could be that the people that have the common cold cross-reactivity will respond a lot faster and a lot better to the vaccine compared with the other ones.

One piece of data that is encouraging in speculating that some preexisting immunity may be beneficial is data from the 2009 H1N1 "swine flu" pandemic. You might recall that in that case older people did better than younger people. And in fact it turned out that the age of the people who did better correlated with when another H1N1 strain, a cousin of the swine flu pandemic strain, had circulated—so that the people who had been exposed in the 1950s to this other strain, their immune system still remembered a bit. Not that the people didn't get sick, of course, but they got less sick. And they fared better than people who were totally naive and had never seen this particular subtype of influenza.

Do we know whether people who had asymptomatic COVID-19 infections might be less protected against reinfection than people who had a very severe case?

CROTTY: We did this study with people who didn't have bad diseases—sort of average cases who definitely got well. Asymptomatic cases are definitely a big unknown. We have no idea [if they will be protected against reinfection].

Can you comment on the Moderna results from the phase I trial of its coronavirus vaccine candidate and the prospects for a vaccine in general?

CROTTY: There are actually three human vaccine candidates that have been tested in monkeys that gave what seems to be pretty good protection: one's an inactivated-virus vaccine; another is a chimpanzee adenovirus vector [a type of double-stranded DNA virus used to harmlessly deliver genetic material to a host]; and a third one is a DNA vaccine [a DNA sequence that stimulates the host to produce part of the virus and mount an immune response against it]. And then there's the Moderna vaccine, which hasn't been tested in monkeys but has been tested in a mouse model and in humans to measure their immune response. So those are the three examples of interesting vaccine candidate data that are available as of today. And I think if we combine those with the data from our paper showing that the T cell responses generally look good and data from a number of papers about people making neutralizing antibody responses overall, I would say those vaccine studies—particularly the two that were done in monkeys—suggest, so far, that it's not that hard to protect against this virus. I'm certainly encouraged based on the magnitude of the immune responses to the vaccines—and the magnitude of immune responses we're measuring in people who actually have disease and what happens in protection models. So far the available data are positive here.

"One encouraging thing is that there are so many different vaccines that are being developed."

—Alessandro Sette

SETTE: One encouraging thing is that there are so many different vaccines that are being developed. So our hope is that there is not going to be a winner but that there are going to be many different winners. The one thing that is important from our study is that the vast majority of these different vaccine concepts rely on one particular protein, which is the spike protein. And we saw very good responses, both in terms of killer and helper cells against the spike, which is really good news, because this was not a given. In this particular case, it so happens that it's a good target for all three different types of immune response—which bodes well for people who are developing the spike-based vaccines. At the same time, our data found that there were responses also against other pieces of the virus, which opens the way to thinking that maybe these other pieces could also be included to further fortify a vaccine concept.

—Tanya Lewis

COVID-19 Vaccine Developers Search for Antibodies That "First Do No Harm"

Biotechs and pharma want to protect patients without triggering immune system havoc

By Esther Landhuis

Illustration of antibodies (*white, Y-shaped objects*) responding to an infection with SARS-CoV-2 (*orange*)

JUAN GAERTNER *GETTY IMAGES*

Esther Landhuis is a freelance science journalist in the San Francisco Bay Area.

THE CORONAVIRUS PANDEMIC HAS PROVIDED THE WORLD WITH A QUICK STUDY in the intricacies of immunology. "Herd immunity" and "serological tests" have become household terms. Front and center among these concepts are antibodies. These immune proteins typically emerge during the second or third week after an infection, glomming on to invaders and preventing them from sneaking into human cells. If antibodies targeting a particular virus turn up in a blood sample, their appearance provides confirmation of an immune response that may protect against reinfection.

Eliciting the right antibodies to disarm SARS-CoV-2, the virus responsible for the current pandemic, is the goal of dozens of vaccine developers, several of which have already launched human trials in record time. But public health officials and scientists caution against moving too quickly. In rare instances, these immune defenders can exacerbate disease rather than guard against it.

That concern has not yet materialized in the early stages of making a COVID-19 vaccine. Yet based on research related to past coronavirus outbreaks, vaccine manufacturers do not view the hurdle as purely theoretical.

Typically SARS-CoV-2 and the related coronavirus SARS-CoV make their way into cells through a docking site: a cell-surface receptor called ACE2. Vaccines that provide the sought-after immunization make "neutralizing" antibodies against viral proteins, blocking the pathogen's entrance through the ACE2 portal.

But just because an antibody can keep a virus from entering cells in a lab dish does not necessarily mean it will behave that way in the body, says Akiko Iwasaki, an immunologist at Yale University. In scenarios she describes in a recent *Nature Reviews Immunology* commentary, antibodies may occasionally help a virus invade and thwart immune cells that would normally engulf and help clear the pathogen.

If some of the antibodies produced do not bind to the virus well enough—or if they are not present in the right concentration—they can latch on to it and exacerbate disease through a process known as antibody-dependent enhancement (ADE). In ADE, antibody-coated viruses gain a "backdoor" entry through antibody receptors on macrophages and other members of the cellular cleanup crew—in essence disabling the very cells that would have chopped up those viruses and chemically disposed of them. In some cases, this process can trigger a harmful inflammatory response.

Indeed, it seems that some pathogens, including coronaviruses, have "found a way to use the antibody as a Trojan horse to infect disease-fighting cells," Iwasaki says. Her lab is working to understand the types of immune responses that help people recover from COVID-19 versus those that contribute to disease.

Through ADE, Iwasaki suggests, the virus can initiate an overproduction of inflammatory signaling proteins called cytokines, leading to "cytokine storms" that can promote acute respiratory distress syndrome and damage lung tissue. Similar problems can also be unleashed in some people with COVID-19 by other immune cells called neutrophils.

Scientists are not yet sure whether ADE actually promotes cytokine storms or immune-related tissue damage in COVID-19. They are connecting hypothetical dots based on past studies of experimental vaccines for previous outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), in which some immunized animals developed more severe disease. Plus, earlier work by Iwasaki and others suggests that pathogens entering cells through the back door get shunted to different cellular compartments that are rich in receptors that sense microbial threats and release molecules linked to cytokine storms. "That's a well-known fact," Iwasaki says. "Why wouldn't SARS-CoV-2 also be recognized this way?"

Some research from earlier coronavirus outbreaks does in fact lend support to the idea that antibodies could trigger inflammatory pathology by co-opting macrophages. In an analysis of monkeys published last year in *JCI Insight,* researchers in China showed that SARS-CoV anti-

bodies from serum in vaccinated animals were sufficient to trigger lung damage in a set of unvaccinated ones. The transferred antibodies worsened disease and seemed to switch lung macrophages from a protective to a pathogenic state, as judged by an examination of the immune cells' genetic activity.

ADE has cropped up as a suspected problem for other vaccines. Certain dengue and respiratory syncytial virus vaccines have provoked severe immune reactions. Antibodies could be one of the initiators, but vaccine scientists say immune-related tissue damage is a bigger potential concern. Liver and lung damage caused by an inflammatory reaction has occurred in animals infected with the SARS virus after vaccination. But ADE as a mechanism was documented in lab dish experiments, so the phenomenon "is a bit more theoretical," says Peter Hotez, co-director of the Texas Children's Hospital Center for Vaccine Development, which is building on its SARS vaccine work to create a COVID-19 vaccine.

Although it is possible that suboptimal antibodies could lead to inflammation and tissue damage, Hotez says these problems could also result from the aberrant activity of T cells, which serve as another virus fighter in the immune system's arsenal. A study published online on May 14 in *Cell* suggests that SARS-CoV-2-specific T cells, when functioning normally, may help people combat COVID-19.

Scientists are well aware of the potential danger of ADE. It is "something that may happen," says Paul Henri Lambert, a vaccine scientist at the University of Geneva and a consultant at the Coalition for Epidemic Preparedness Innovations (CEPI). "But at this stage, we do not have any evidence that this is a problem for vaccines against SARS-CoV-2."

Moderna, a Massachusetts biotech company that announced preliminary findings from an early-stage clinical trial of its RNA-based COVID-19 vaccine in May, has found no serious health problems in study participants.

It seems that some pathogens, including coronaviruses, have "found a way to use the antibody as a Trojan horse to infect disease-fighting cells."
—Akiko Iwasaki

Another COVID-19 vaccine that was tested in an early-stage trial in China appeared to be safe and produced neutralizing antibodies in some of the study's 108 participants, according to a study published online on May 22 in the *Lancet*.

Several additional COVID-19 vaccines have been tested in nonhuman primates. One was made from an inactivated virus by researchers in China, who reported on May 6 that the highest dose gave protection. The team found no evidence for disease enhancement in four monkeys analyzed seven days after they were infected with SARS-CoV-2. A nonpeer-reviewed paper on a second vaccine, developed using the SARS-CoV-2 protein responsible for viral entry into host cells, was posted on the preprint server bioRxiv on May 13. It also showed no signs of enhanced disease. And in a study of macaques immunized with another type of candidate (a DNA vaccine), published online on May 20, scientists reported that they "did not observe enhanced clinical disease even with the suboptimal vaccine constructs that failed to protect."

Stanley Perlman, a physician and viral immunologist at the University of Iowa, has participated in COVID-19 vaccine committees set up by both the National Institutes of Health and the World Health Organization. These committees have thoroughly discussed possible risks posed by ADE, he says. But given the urgency of the pandemic, Perlman adds, "people say, we've got to get a vaccine yesterday. And on the other hand, you have people saying, 'Oh no, we have to be really careful.' How to balance this? We can't open up the country until we have a vaccine, until we have herd immunity. So it becomes a difficult question: What's the most correct course of action?"

The real question is whether COVID-19 vaccines will cause ADE when they are given to hundreds of thousands of people. This concern is shared by researchers testing whether blood plasma from people who have recovered can safely treat patients hospitalized with the disease. ADE has not been reported thus far in a nationwide study of 5,000 patients given this convalescent plasma, which was posted on May 14 on the preprint server medRxiv.

Analyses of immune responses in early-stage clinical trial volunteers and in nonhuman primates studied before moving on to the next phase of a given investigation should be able to identify vaccines at potential risk for immune enhancement, Lambert says. Hotez thinks it will be important to watch for ADE and damaging inflammatory reactions when immunizing study participants in areas where the virus is spreading. "If you're going to see a problem, that's where you would see it," he says. "In individuals who are vaccinated and then exposed to the virus, you would want to monitor for liver and lung function to make sure there's no worsening."

Beyond vaccines, ADE could influence other aspects of the immune response to SARS-CoV-2. Jorge Caballero, a Stanford University anesthesiologist who organizes data and engineering support for COVID-19 surveillance testing, wonders whether the process could underlie other disease manifestations, including "COVID toes," respiratory distress linked to lung pathology, and a mysterious inflammatory condition striking some kids with the disease. Emerging data "suggest that the common link—Occam's razor, if you will—may be a little-understood phenomenon known as antibody-dependent enhancement," he says.

How to Use Masks during the Coronavirus Pandemic

What kinds of face coverings work for protection against COVID-19? How do you use them safely? A series of simple steps outlines the answers

By Katie Peek

JOSE A. BERNAT BACETE *GETTY IMAGES*

Katie Peek, formerly the information graphics editor at *Popular Science*, is a science journalist and data-visualization designer. Peek also holds advanced degrees in astrophysics.

ANY MASK WORN FOR day-to-day protection against COVID-19 is going to be imperfect, at least for now. Supplies of N95 respirators—the most effective mask type—should find their way to those in daily close contact with infected people. This requirement leaves the rest of us with reusable cloth face coverings and single-use paper surgical masks. (The latter are also in high demand for frontline folks, so if you are looking to buy, try to acquire fabric masks.)

"These are not going to be perfectly efficient," says Kirsten Koehler, an occupational and public health expert who studies personal protection at Johns Hopkins University. But they can still help limit the virus's circulation, especially if they are worn by those infected with the novel coronavirus—many of whom may be asymptomatic. "We're trying to prevent spreading disease to other people," Koehler says. "Hopefully the mask is helping to protect us, too." Even with our faces covered, she adds, we should continue to perform social distancing and isolation. A handful of best practices can help make the most of our imperfect personal protection.

BROWN BIRD DESIGN

How to Put On a Mask

❶ Wash your hands.

❷ Fit the mask across the bridge of your nose and under your chin.

❸ Loop the fasteners behind your ears or tie them behind your head, depending on your mask's style.

❹ Henceforth, consider the mask's surface contaminated inside and out. Don't touch it. Don't adjust it. (And wash your hands if you do.)

How to Wear a Mask

The mask should fit without gaps and fully cover your nose and mouth. Take special care to ensure a snug fit across the bridge of the nose. If your mask doesn't have a flexible wire built in, you may be able to MacGyver a pipe cleaner, a tie for a coffee bag or another object into the role. Are there special precautions bearded individuals should take? Koehler doesn't think so. "None of us are getting a perfect seal around our nose anyway," she says. "It shouldn't make that big of a difference."

If the mask is on correctly, air will pass through it rather than around it. Your breath will probably make it feel kind of humid and "swampy" inside.

When to Take a Mask Off

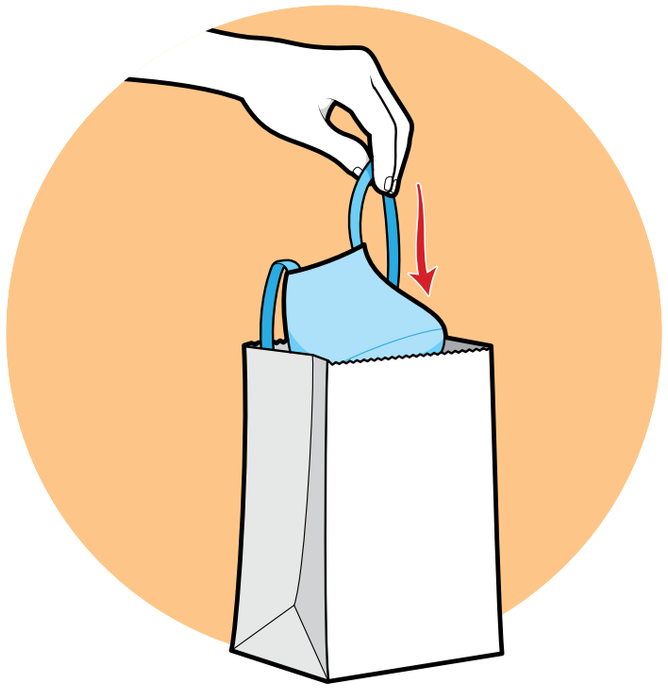
There are not a lot of data on how long a mask can be effectively worn. According to the World Health Organization, a face covering should be replaced when you have breathed through it enough for it to become damp. That is likely to happen only after several hours: For a trip to the grocery store, one mask will probably do. If you will be out longer, bring a spare if possible.

How to Take a Mask Off and Clean a Reusable Mask

Placing a cloth mask in a paper bag immediately after taking it off has two purposes: the container isolates the mask from accidental handling, and the paper allows it to dry out. Before wearing the covering again, let it sit in a warm spot—still in that paper bag—for two or three days. (The science here is nascent, but one study found that the coronavirus reaches undetectable levels on fabric after two days. After a week, levels were undetectable on the insides of surgical masks, although they remained detectable on the outsides.) Koehler recommends setting the paper bag on a sunny windowsill or in the natural oven of your car because the virus becomes inert faster at higher temperatures. Alternatively, if you have your own laundry facilities, you can pop a used mask straight into the washing machine with the regular laundry. A bag for washing delicates will keep mask ties from making a knot of the whole load. You can also wash a mask by hand: soak it in bleach suitable for disinfection for five minutes and then rinse it thoroughly. Face coverings should be decontaminated after each use—so have a few on hand if you are going out more often than your decontamination schedule allows.

❶ Don't touch the front!

❷ Untie the ties or remove the loops and lift the mask off your face by the ties or loops *only*.



❸ Place the mask in a closed container. If you will not be using it again, aim for a lidded trash can. For reusable masks, a paper bag works when it is folded closed.

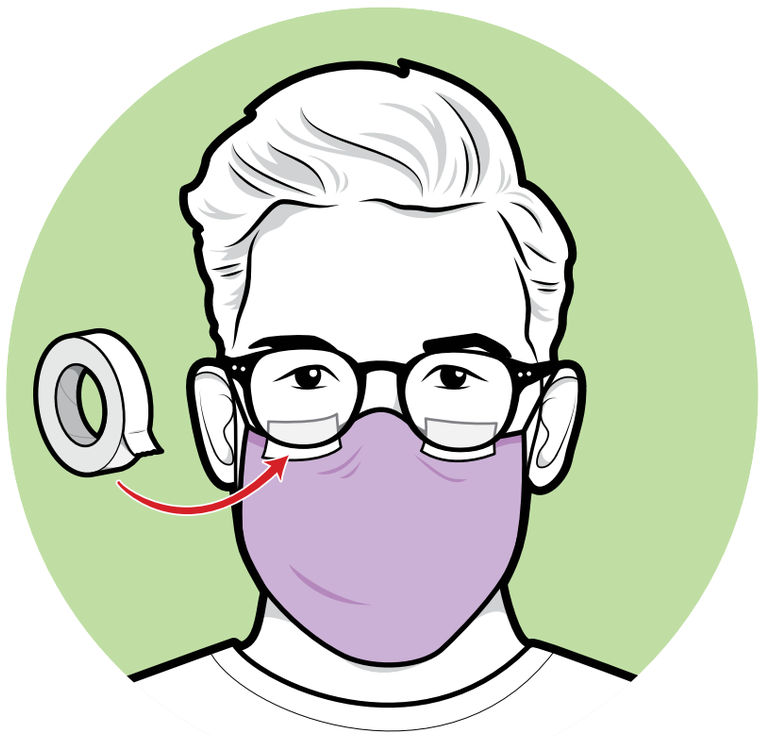
❹ Wash your hands.

How to Keep Your Glasses from Fogging

For the bespectacled among us, the foggy-glasses struggle is real. In general, it means your mask isn't fitting super well. If the material were tight across your nose, air would not be leaking from the top in the first place. Here are a few ideas to improve that fit:

Tissue

A piece of facial tissue tucked between the glasses and the mask can both push the latter into a tighter fit and prevent exhaled vapor from rising.



Tape

A bit of medical tape across the top of the mask can hold it more securely to your face at the cheeks.

Soap

A little soap on the insides of the lenses can keep fog from forming. One paper recommends dousing the inner surface with soapy water and allowing it to air-dry. A pinky nail's worth of liquid soap rubbed directly onto the insides of the lenses is another option.

Materials and Effectiveness

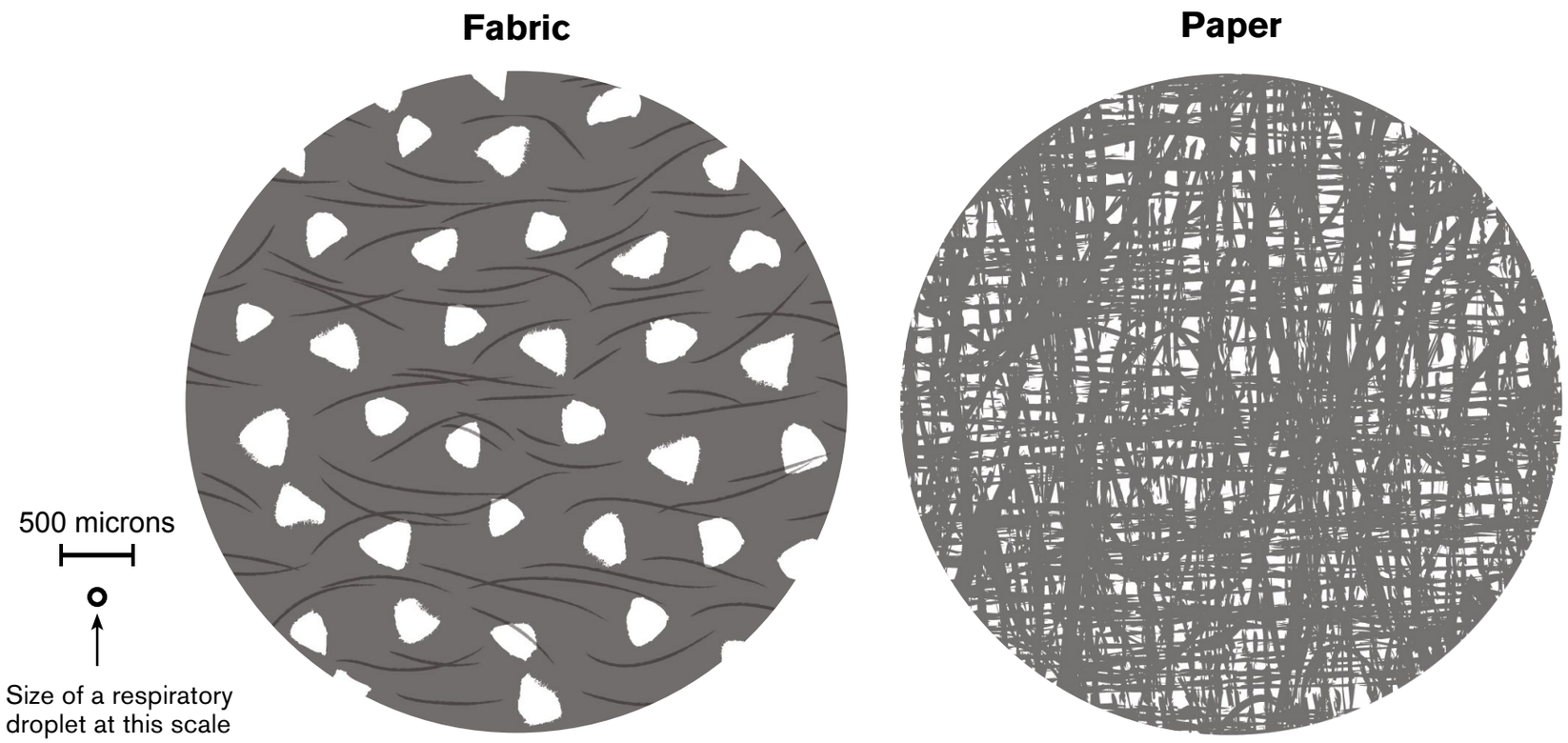
The science on mask efficacy is spotty. A few laboratory studies have examined how fabrics protect against particles of different sizes. They were mostly done in the pre-COVID-19 era to examine air pollution and the flu. But the medical gold standard—a randomized controlled trial of masks in daily use—is difficult and raises ethical concerns because it would require knowingly exposing people to pathogens or pollutants. That said, the existing lab studies have helped to teach researchers a lot about how particles interact with fabrics and paper.

Are paper or fabric masks more effective?

One study compared fabric and paper surgical masks' ability to filter air pollution. Researchers examined the materials under a microscope and found that fabric had a more open structure with bigger holes—often larger than the droplets believed to transmit the coronavirus. These droplets cover a huge size range from more than 100 microns—big enough to see as they fly out of a person's mouth—down to the submicron scale.

Another study found that paper masks were more effective than cloth ones at protecting against the flu. But there is more to consider than material. Fabric masks are typically sewn with two layers, which helps them trap more particles than a single cloth layer alone.

In general, even if paper face coverings are more effective, they have a shorter lifetime than cloth masks. And they are in high demand. Although the supply of surgical masks is starting to rebound, Koehler still advises the use of cloth ones. "We want to make sure that medical personnel have access to the supplies that they need," she explains.



BROWN BIRD DESIGN; SOURCE: "OPTICAL MICROSCOPIC STUDY OF SURFACE MORPHOLOGY AND FILTERING EFFICIENCY OF FACE MASKS," BY BHANU BHAKTA NEUPANE ET AL., IN *PEER J*; JUNE 26, 2019

Are masks for the protection of the wearer or those around that person?

Both. They are most effective at preventing an infected mask wearer from spreading the virus to others. But ideally, they can also provide some protection against incoming virus-laden droplets.

Droplets evaporate as they move through the air, so they are biggest when they are first coughed out. Because cloth masks are more effective at blocking larger particles, they are most efficient at stopping the spread if they stop the droplets at their source.

Have we proved that masks themselves significantly help? Or do mask wearers tend to simply be more careful in general?

Randomized controlled studies have shown that mask wearing is indeed effective against the flu, but such trials do not currently exist for masks and the coronavirus. "The evidence isn't always as perfect as we would like it to be," Koehler says. "Based on the aerosol science, we know that the masks are going to help reduce the transmission of these particles. Can it be 100 percent effective? Maybe not. But can it help? I think so."

Okay, so what should I look for in a cloth mask?

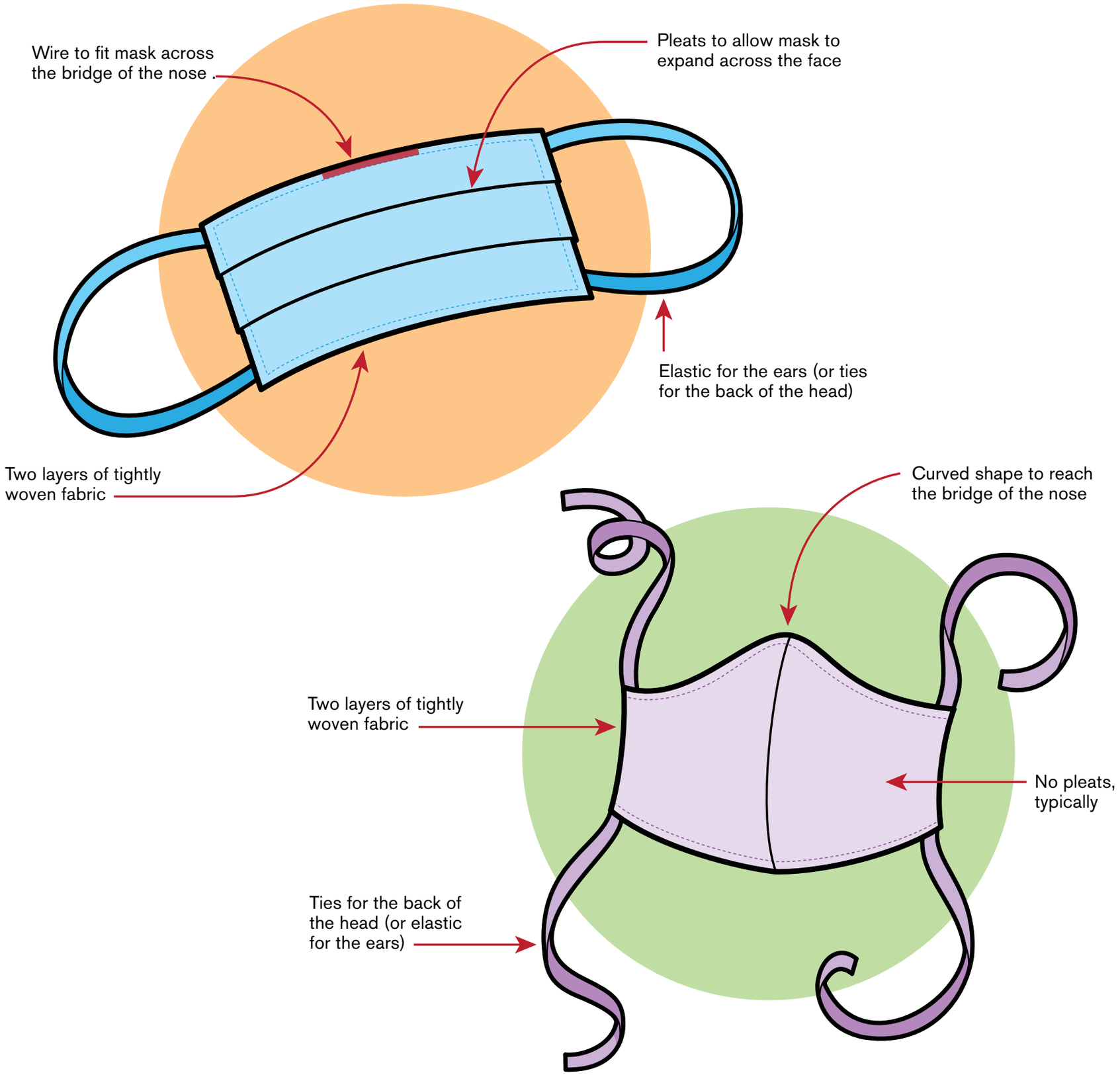
Whether you acquire one from someone else or make it yourself, there are a few things to pay attention to. The fabric should be high quality and tightly woven. In woven fabric, the fibers cross at right angles, whereas a knit's structure involves tiny V's of thread. Look for a right-angle weave and avoid knits.

A tight weave—such as one you might find in a fancy pillowcase—blocks most of the light if it is held up to a window. These are, of course, difficult properties to assess when buying online.

The shape of the mask should fit your face well. Rectangular coverings usually have a length of wire built into the top so they can be molded to your face, whereas those with a curved design rise up over the nose a little more.

If you want to make your own covering, the Centers for Disease Control and Prevention's Web site has several designs for different levels of crafting skill. Designs for curved-style cloth masks are fairly widespread as well.

Experts recommend that the public should avoid masks with built-in valves. They are designed to release air when the wearer exhales, reducing humidity but also allowing unfiltered breath to exit the coverings.



BROWN BIRD DESIGN

Why Racism, Not Race, Is a Risk Factor for Dying of COVID-19

Public health specialist and physician Camara Phyllis Jones talks about ways that jobs, communities and health care leave Black Americans more exposed and less protected

By Claudia Wallis

Camara Phyllis Jones

KEVIN GRADY *RADCLIFFE INSTITUTE*

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

COVID-19 is cutting a jarring and unequal path across the U.S. The disease is disproportionately killing people of color, particularly Black Americans, who have been dying at more than twice the rate of white people. In some places—Washington, D.C., Kansas, Wisconsin, Michigan and Missouri—the death rate is four to six times higher among Black people. Infection data are less reliable and less complete than information on mortality. Yet here, too, the discrepancies appear to be stark.

The reason for these disparities is not biological but is the result of the deep-rooted and pervasive impacts of racism, says epidemiologist and family physician Camara Phyllis Jones. Racism, she argues, has led people of color to be more exposed to and less protected from the virus and has burdened them with chronic diseases. For 14 years Jones worked at the Centers for Disease Control and Prevention as a medical officer and director of research on health inequities. As president of the American Public Health Association, she led a campaign in 2016 to explicitly name racism as a direct threat to public health. She is currently a fellow at Harvard University's Radcliffe Institute for Advanced Study and is writing a book about addressing racism.

As the country confronted the unequal impacts of COVID-19 and reeled from the killing of George Floyd and the ongoing legacy of racial injustice it represents, Jones spoke with contributing editor Claudia Wallis about the ways that discrimination has shaped the suffering produced by the pandemic.

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

Along with age, male gender and certain chronic conditions, race appears to be a risk factor for a severe outcome from COVID-19. Why is that?

Race doesn't put you at higher risk. Racism puts you at higher risk. It does so through two mechanisms: People of color are more infected because we are more exposed and less protected. Then, once infected, we are more likely to die because we carry a greater burden of chronic diseases from living in disinvested communities with poor food options [and] poisoned air and because we have less access to health care.

Why do you say Black, brown and Indigenous people are more exposed?

We are more exposed because of the kinds of jobs that we have: the frontline jobs of home health aides, postal workers, warehouse workers, meat packers, hospital orderlies. And those frontline jobs—which, for a long time, have been invisibilized and undervalued in terms of the pay—are now being categorized as essential work. The overrepresentation [of people of color] in these jobs doesn't just so happen. (Nothing differential by race just so happens.) It is tied to residential and educational segregation in this country. If you have a poor neighborhood, then you'll have poorly funded schools, which often results in poor education outcomes and another generation lost. When you have poor educational outcomes, you have limited employment opportunities.

We are also more exposed because we are overrepresented in prisons and jails—jails where people are often financial detainees because they can't make bail. And brown people are more exposed in immigration detention centers. We are also more likely to be unhoused—with no access to water to wash our hands—or to live in smaller, more cramped quarters in more densely populated neighborhoods. You're in a one-bedroom apartment with five people living there, and one is your grandmother, and you can't safely isolate from family members who are frontline workers.

And why are people of color less protected?

We are less protected because in these frontline jobs—but also in the nursing homes and in the jails, prisons and homeless shelters—the personal protective equipment [PPE] has been very, very slow in coming and still may not be there. Look at the meatpacking plants, for example. We are less protected because our roles and our lives are less valued—less valued in our job roles, less valued in our intellect and our humanity.

You've noted that once infected, people of color are more likely to have a poor outcome or die. Could you break down the reasons?

This has two buckets: First, we are more burdened with chronic diseases. Black people have 60 percent more diabetes and 40 percent more hypertension. That's not because we are not interested in health but because of the context of our lives. We are living in unhealthier places without the food choices we need: no grocery stores, so-called food deserts and what some people describe as "fast-food swamps." More polluted air, no place to exercise safely, toxic dump sites—

all of these things go into communities that have been disempowered. That's why we have more diseases, not because we don't want to be healthy. We very much want to be healthy. It's because of the burdens that racism has put on our bodies.

What is the second bucket that raises risks from COVID-19?

Health care. Even from the beginning, it was hard for Black folks to get tested because of where testing sites were initially located. They were in more affluent neighborhoods—or there was drive-through testing. What if you don't have a car? And there was the need to have a physician's order to get a test. We heard about people who were symptomatic and presented at emergency departments but were sent back home without getting a test. A lot of people died at home without ever having a confirmed diagnosis. So even though we know we are overrepresented, we may have been undercounted.

Once you get into the hospital, there's a whole spectrum of scarce resources, so different states and hospital systems had what they called "crisis standards of care." In Massachusetts they were very careful to say that you cannot use race or language or zip code to discriminate [on who gets a ventilator]. But you could use expected [long-term] survival. Then the question was: Do you have these preexisting conditions? This was going to systematically put Black and brown people at a lower priority or even disqualify them from access to these lifesaving therapies. [*Editor's note: Massachusetts has since changed its guidelines. But Jones says the revision is an incomplete fix.*]

What can be done to better protect people of color?

We need more PPE for all frontline workers; we need to value all of those lives. We need to offer hazard pay and something like conscientious objector status for frontline workers who feel it is too dangerous to go back into the poultry or meatpacking plant. We know that there are communities at higher risk, and we need to be doing more testing there.

Several states do not report racial and ethnic data on COVID-19 cases. Why is that a problem?

States should be reporting their data disaggregated by race, especially now that we know that Black and brown and Indigenous folks are at higher risk of being infected and then dying. It's not just to document it, not just to alarm or to arm some people with a false sense of security. It's because we need to provide resources according to need: health care resources, testing resources and prevention types of resources.

When we first spoke, on May 14, George Floyd was still alive and well in Minneapolis. In the wake of his killing and the public response, at the same time as the pandemic, do you see an opportunity for meaning ful change?

The outrage is encouraging because it has been expressed by folks from all parts of our population. The protests are effective mixing bowls for the virus. But at least they are not frivolous mixing bowls like pool parties. Participants in the protests are thinking not just about their individual health and well-being but about the collective power that they have now to possibly make things better for their children and grandchildren. This is both a treacherous time and a time of great promise.

Racism is a system of structuring opportunity and assigning value based on the social interpretation of how one looks (which is what we call "race") that unfairly disadvantages some individuals and communities, unfairly advantages other individuals and communities, and saps the strength of the whole society through the waste of human resources. Perhaps this nation is awakening to the realization that racism does indeed hurt us all.

Clayton M. Dalton is a Harvard University–affiliated emergency resident at Massachusetts General Hospital | Brigham & Women's Hospital.

PUBLIC HEALTH

So How Deadly *Is* COVID-19?

We still don't know, and it doesn't really matter right now; it's plenty deadly

GETTY IMAGES

We have learned an incredible amount about the novel coronavirus these past few months. It seems that people can transmit the virus without symptoms, that virus particles can spread through a lingering, mistlike aerosol, and that a deadened sense of taste is a surprisingly reliable indicator of infection. But we are still struggling to answer what may seem like the most pressing question of all: How deadly is it?

It is a question that has driven heated debate about whether lockdown measures cause more harm than good and about how we should reopen the country.

Here is my take as an emergency physician: it doesn't matter.

Let me back up for a minute before I tell you why. First we need to understand a few things about the mortality rate, which is a measure of how many people with the virus will die from it, and its limitations.

When the virus emerged as a serious threat in the city of Wuhan, early estimates for the mortality rate stood between 3 and 4 percent. But a few voices urged caution when interpreting this figure. People with mild symptoms (or no symptoms) were less likely to be tested for the virus and to be counted as confirmed cases. Because the mortality rate is the ratio of the number of deaths from the virus divided by the number of infections, an artificially low denominator from undetected cases would make the virus look deadlier than it was.

Months later scientists were still struggling to determine the mortality rate in Wuhan even as the virus spread rapidly around the world. In March researchers used a different approach to estimate the true number of infections in Wuhan and found that the mortality rate may have been closer to 1.4 percent. Then, in April, the number of

COVID-19 deaths in Wuhan was revised upward to three times the previous count, pushing the estimated mortality rate up again. So what was the true rate in Wuhan? We still do not really know.

Now, with the coronavirus endemic in the U.S., we are facing the same challenges. Given the excruciatingly slow effort to ramp up testing and the persistent testing problems even now, the total number of cases is almost certainly higher than the number of confirmed cases, possibly by a factor of 10 or even 20. We are not sure about the number of deaths, either. All-cause mortality during March and April was substantially higher in places hit hard by the virus, such as New York and New Jersey, than in previous years. Confirmed coronavirus deaths do not fully account for the difference, which suggests that we might be undercounting them. Alternatively, excess deaths could also be from things such as heart attacks or surgical emergencies if people were too frightened to seek medical attention. Both the numerator and the denominator needed to calculate a mortality rate remain fuzzy.

Mortality rates from other countries affected by the pandemic have added to confusion about how deadly the virus is. The rate is nearly 14 percent in Italy but is only 0.5 percent in Iceland. Germany stands at 4.5 percent, and South Korea is half that at 2.4 percent. The U.S. mortality rate is about 6 percent, slightly less than the global average of 6.8 percent.

This wide range does not get us closer to a "true" mortality rate. Instead it suggests something else that is important: the virus's lethality depends on a whole host of factors that are extrinsic to the virus itself. Put another way, even if we could count every single infection and every single death from the virus without missing anyone, the risk of dying from the virus would still vary from country to country, city to city and person to person. We know that the virus is more dangerous to the elderly, for example, so we expect mortality to be higher in countries with older populations such as Italy. We know that the virus is more dangerous if you have comorbidities such as hypertension or diabetes, so we might expect mortality to be higher in countries with more of these diseases, as in the U.S.

Hospital capacity also influences the risk of dying from the virus because the quality of medical care suffers when a hospital is overwhelmed. Capacity varies from country to country: Germany has eight hospital beds per 1,000 people, for instance, but the U.S. has fewer than three. Mortality rates can evolve over time, too. According to the WHO, mortality decreased in Wuhan because hospitals were inundated early on and then increased their capacity later in the outbreak.

So the mortality rate, instead of being a fixed number that distills the true essence of the virus's danger, is actually a protean, organic, fluid metric. The rate of fatalities among people with COVID-19 "is not a biological constant," according to a team of University of Oxford researchers. "Instead it reflects the severity of the disease in a particular context, at a particular time, in a particular population." Even with perfect data, the mortality rate is a living number, changing all the time, that is in part a reflection of ourselves. With these limitations in mind, we should be wary of using any one estimate of mortality in shaping our response to the pandemic.

Unfortunately, that has not stopped some commentators and even some scientists from trying. John Ioannidis, a respected scientist at Stanford University, was an early skeptic about the likelihood that the virus was any worse than the flu, which has a mortality rate of about 0.1 percent. In March, Ioannidis argued that a "reasonable" estimate of the mortality rate for the coronavirus could actually be lower than that for influenza and suggested that lockdown measures might be "totally irrational." "It's like an elephant being attacked by a house cat," he wrote. "Frustrated and trying to avoid the cat, the elephant accidentally jumps off a cliff and dies."

In late April, Ioannidis and his colleagues at Stanford released a preprint of a study purporting to support this claim. Released without peer review, the study's methods and conclusions have been ferociously criticized by other statisticians and scientists.

Even so, the study has added fuel to what has somehow become a highly partisan fire, with many conservatives latching on to any evidence suggesting a lower mortality rate, claiming that the virus is not as dangerous as billed and that we are cratering the economy for no good reason. On the other side, liberals have tended to align with public health authorities, who caution that we should go slow on reopening because the virus is dangerous, cases are still rising, and our capacity to test and trace remains inadequate. So who is right?

Now we are ready to come full circle. As we have seen, mortality exists on a spectrum instead

of as a single number, and persistent problems with testing and with categorizing deaths make estimates extremely tricky. This work is important because a better understanding of the virus's behavior can only help us.

But from my perspective as an emergency physician, precisely how deadly the virus is does not matter right now because the virus is deadly enough. I have stood on the front lines of the pandemic, and I know that this virus is no house cat. Every day for weeks my colleagues and I have faced wave after wave of COVID-19 patients in their 30s, 50s or 80s, many of them extraordinarily ill. Some of these people have died. The virulence of the disease is astonishing, at least among hospitalized patients. Experienced physicians know that this is nothing like the flu.

We know enough to understand the dangerous potential that this virus still holds. We know that the coronavirus spreads twice as fast as flu, or faster, and that if left unchecked it has the potential to race through populations like wildfire. We know that viral "dose" likely influences illness severity and that masks and social distancing can mitigate it. We know that a large majority of people probably remain unexposed and susceptible. We know that if infected, some of these people will die.

Wherever the mortality rates may settle, we have enough information to act responsibly, with carefully phased reopenings, robust testing and contact tracing.

We know enough to know that this virus is deadly serious.

Erik Parens is a senior research scholar at the Hastings Center, a bioethics research institute in Garrison, N.Y.

POLICY & ETHICS

The Inflated Promise of Genomic Medicine

COVID-19 has laid bare the need to reconsider the hope and money we invest in genetics research

HIROSHI WATANABE *GETTY IMAGES*

Since its birth 30 years ago, proponents of the Human Genome Project have promised that genetics research will yield untold health benefits for all of us. Indeed, in 1990 James Watson asserted that failing to move the project ahead and usher in those benefits as fast as possible would be "essentially immoral."

The COVID-19 crisis, however, offers a supremely unwished-for opportunity to scrutinize the proponents' promise and to recalibrate the hope and money we invest in genetics. Such scrutiny and recalibration can be small steps on the path to fulfilling our nation's professed commitment to the health of all of us.

Recalibration is not abandonment. In the midst of the crisis, genetics-based research tools offer some rare opportunities for optimism. They make it possible to track the spread of the virus and to test for the presence of the virus in individuals, and they may help to create a vaccine that will protect the health of all of us.

In the midst of this crisis, however, it is impossible to ignore the obscenely and grotesquely disproportionate impact that the virus has on the health of some of us. Yes, it is likely that some individuals are genetically predisposed to be less

or more susceptible to the virus. But no geneticist is suggesting that genetic differences are an important part of the explanation for why the virus impacts different social groups differently. No geneticist claims that genetic differences help to explain why a physician in northwestern Oregon says that Latinos have been found to be 20 times as likely as other patients to have the virus. Nor is any geneticist suggesting that genetic differences help to explain why, according to a *Washington Post* analysis, "counties that are majority-black have three times the rate of infections and almost six times the rate of deaths as counties where white residents are in the majority."

Rather it is a truism that those different impacts are the result of the different social conditions to which different groups are exposed. The less access members of those groups have to decent jobs, housing, education, nutrition, clean water and air, the greater the likelihood that they will be exposed to the virus, the more underlying health conditions that will afflict those groups, and the greater the negative health impacts on members of those social groups.

And yet we continue to overinvest our hope in genetics, notwithstanding that with every passing year we understand in more detail why genetics cannot deliver as much as it once promised. Recently geneticist Francis Collins, who once led the Human Genome Project and who now directs all 27 of the National Institutes of Health (NIH), said to the *Wall Street Journal,* with admirable frankness and breathtaking understatement, "The genetic architecture of common diseases is turning out to be more elaborate than we might have guessed." That is, because of the fabulous complexity of the pathways from genes to the kinds of common diseases (such as diabetes) that make people more vulnerable to COVID-19 infection, genetics has not been able to offer the kinds of health benefits that geneticists envisioned 30 years ago.

Despite the fact that we have known for years that genetics will not yield as many health benefits for any social group as were once envisioned, enthusiasm for genetics at the NIH has not flagged. In 2016, the year the NIH launched a major new genetics-focused research initiative, it spent well over half of its $26 billion budget for extramural research on investigations that could be linked to search terms that include "gene," "genome," "stem cells" or "regenerative medicine."

That program—called All of Us—aims to tailor medical care to the genomes of individuals, much as tailors create clothes to fit their customers. To achieve that end, the NIH is seeking to enroll one million people in the program and is doing so with rhetoric that departs strikingly from the rhetoric usually used to enlist people in health research.

Departing from the customary American invocation of autonomy in matters of health research, proponents of the All of Us program are appealing to the value of solidarity. As philosopher and bioethicist Carolyn Neuhaus puts it in a forthcoming essay in a special collection of the *Hastings Center Report,* the All of Us program appeals "to sense of civic duty—on each one of us—on you, on me—to improve the health of fellow and future Americans." That is, according to the All of Us program's rhetoric, we have a civic duty, a solidarity-based ethical obligation, to participate in this research project, including by donating our genomes to the project's database.

Moreover, the All of Us program is explicit in its commitment to improving the health care of those of us in historically discriminated-against social groups. In fact, enthusiasts about All of Us have gone so far as to suggest that the program will help "to reduce and eventually eliminate health disparities." The lead author of that piece worked not at the National Human Genome Research Institute but at the National Institute on Minority Health and Health Disparities.

The problem here is not a lack of good intentions or the lack of a beautiful vision of health for all of us. The problem is the lack of facts to support the hope that genetics can be key to realizing that vision. The Human Genome Project has produced some truly profound health benefits for some individuals, most of which have to do with testing for and treating inherited cancers. And, again, the tools of genetics research may be key to bringing our current health care crisis to an end. But those tools will not reduce, much less eliminate, the health disparities that are produced by the unjust social conditions that are so excruciatingly obvious in our current crisis.

Of course, just investing less money and hope in genetics will not reduce those disparities either. But it would be a small step in the right direction if our NIH were to develop a more realistic and forthright vision of the role that genetics can play in promoting the health of all of us.

Nora D. Volkow, director of the National Institute on Drug Abuse (NIDA) at the National Institutes of Health, pioneered the use of brain imaging to investigate the toxic effects and addictive properties of certain drugs. Her work has been instrumental in demonstrating that drug addiction is a chronic brain disorder.

BEHAVIOR & SOCIETY

Addressing the Stigma That Surrounds Addiction

Health care already has effective treatment tools, including medications, but many people who could benefit are reluctant to seek them out

PIXABAY

Untreated drug and alcohol use contributes to tens of thousands of deaths every year and impacts the lives of many more. Health care already has effective tools, including medications for opioid and alcohol use disorders, that could prevent many of these deaths, but they are not being utilized widely enough, and many people who could benefit do not even seek them out. One important reason is the stigma that surrounds people with addiction.

Stigma is a problem with health conditions ranging from cancer and HIV to many mental illnesses. Some gains have been made in reducing stigma around certain conditions; public education and widespread use of effective medications have demystified depression, for instance, making it somewhat less taboo now than it was for past generations. But little progress has been made in removing the stigma around substance use disorders. People with addiction continue to be blamed for their disease. Even though medicine long ago reached the consensus that addiction is a complex brain disorder with behavioral components, the public and even many in health care and the justice system continue to view it as a result of moral weakness and flawed character.

Stigma on the part of health care providers who see patients' drug or alcohol problems as their own fault can lead to substandard care or even to the rejection of individuals seeking treatment. People showing signs of acute intoxication or withdrawal symptoms are sometimes expelled from emergency rooms by staff fearful of their behavior or who assume they are only seeking drugs. People with addiction internalize this stigma, feeling shame and refusing to seek treatment as a result.

In a Perspective I published recently in the *New England Journal of Medicine*, I tell a story about a man I met during a visit to Puerto Rico several years ago who was injecting heroin into his leg at a "shooting gallery"—a makeshift injection site—in San Juan. His leg was severely infected, and I urged him to visit an ER—but he refused. He had been treated horribly on previous occasions and preferred risking his life, or probable amputation, to the prospect of repeating his humiliation.

This highlights a dimension of stigma that has been less remarked on in the literature and that is uniquely important for people with substance use disorders: beyond just impeding the provision or seeking of care, stigma may actually enhance or reinstate drug use, playing a key part in the vicious cycle that drives addicted people to continue using drugs.

Previously I highlighted research by Marco Venniro of the National Institute on Drug Abuse Intramural Research Program showing that rodents dependent on heroin or methamphetamine still choose social interaction over drug self-administration when given a choice, but when the social choice is punished, the animals revert to drug use. It is a profound finding that is very likely to be applicable to humans because we are highly social beings. Some of us respond to social as well as physical punishments by turning to substances to alleviate our pain. The humiliating rejection experienced by people who are stigmatized for their drug use acts as a powerful social punishment, driving them to continue and perhaps intensify their drug taking.

Even though medicine long ago reached the consensus that addiction is a complex brain disorder with behavioral components, the public and even many in health care and the justice system continue to view it as a result of moral weakness and flawed character.

The stigmatization of people with substance use disorders may be even more problematic in the current COVID-19 crisis. In addition to the greater risk associated with homelessness and with drug use itself, the legitimate fear around contagion may mean that bystanders or even first responders will be reluctant to administer naloxone to people who have overdosed. And there is a danger that overtaxed hospitals will preferentially pass over those with obvious drug problems when making difficult decisions about where to direct lifesaving personnel and resources.

Alleviating stigma is not easy, in part because the rejection of people with addiction or mental illness arises from unease over their violations of social norms. Without training in caring for people with substance use disorders, even people in health care may be at a loss as to how to interact with someone who is acting threateningly because of withdrawal or the effects of some drugs (for example, PCP). It is crucial that people across health care, from staff in emergency departments to physicians, nurses and physician assistants, be trained in caring compassionately and competently for people with substance use disorders. Treating patients with dignity and compassion is the first step.

There must be wider recognition that one's susceptibility to the brain changes associated with addiction is substantially influenced by factors outside an individual's control, such as genetics or the environment in which one was born and raised, and that medical care is often necessary to facilitate recovery as well as to avert the worst outcomes such as overdose. When people with addiction are stigmatized and rejected, especially by those in health care, it only contributes to the vicious cycle that makes their disease entrenched.

SCIENTIFIC AMERICAN
Health & Medicine

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