October–November 2021

SCIENTIFIC AMERICAN

Health & Medicine

Designer DNA Revolution

GENE EDITING IS POISED TO CURE AN ARRAY OF DISEASES

Plus:

DOES VITAMIN D PROTECT YOU FROM COVID?

REVERSING GRAY HAIR

ICU PHYSICIANS IN CRISIS

WITH COVERAGE FROM nature

Liz Tormes

The Blueprints of Health

Medicine accomplished a huge feat at the start of 2020, when researchers produced the first mRNA vaccine to protect humans from SARS-CoV-2 infection. It was certainly not new technology–the vaccine platform had been under development for more than a decade and tested against multiple diseases, from flu to rabies. It represents our rapidly advancing understanding of how the body manufactures proteins, the molecules that are coded for by our genes. The potential to manipulate the very blueprints that our cells use to build the molecules and cells at the heart of disease is undoubtedly a game changer. Beyond vaccines, researchers have been devising treatments for cancer, lymphoma, AIDS, cystic fibrosis, and more, aided by new gene-editing technology, as physician Carolyn Barber (see "How Designer DNA Is Changing Medicine ") profiles in this collection. The next generation of lifesaving treatments may be manufactured right in our own bodies.

Such genetic advancements are being hyped as a way for prospective parents to screen their embryos for future diseases–but the technology might not be ready for primetime, as genetic counselor Laura Hercher writes (see "A New Era of Designer Babies May Be Based on Overhyped Science"). And as always we have updates on the latest COVID news–from breakthrough infections (see " 'Breakthrough' Infections Do Not Mean COVID Vaccines Are Failing) to a surprising COVID risk (see "People with COVID Often Infect Their Pets"). Here's to your health, now and in the future!

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Health & Medicine

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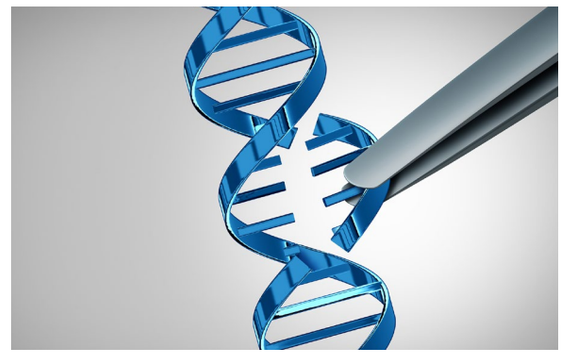

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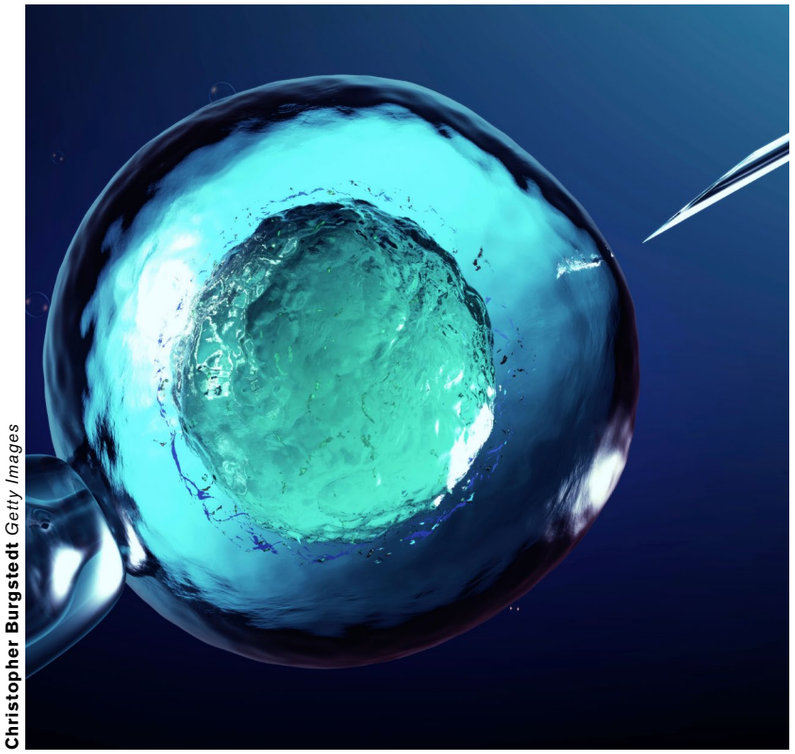

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NEWS

“Breakthrough” Infections Do Not Mean COVID Vaccines Are Failing

Getting flu again postinoculation is more common than a return case after a COVID shot

Nurse administers a Moderna COVID-19 vaccination.

Ethan Miller *Getty Images*

Endless news cycles and viral social media warn of “breakthrough infections” in people already vaccinated for COVID-19. These reports leave the mistaken impression that protections afforded by the vaccines are not working—and they can fuel reticence among the millions of people in the U.S. who have yet to get a shot. But such infections are not only known to occur after COVID vaccination. They frequently happen following inoculation against influenza, measles and many other diseases.

SARS-CoV-2, the virus that causes COVID, is special in one way, though: more than any other pathogen, it has provided the public at large with lessons in immunology—and terms such as “breakthrough infections” and “herd immunity” have gained a broad familiarity. “It almost feels not just like a microscope but an electron microscope on every single thing that happens with the COVID vaccines,” says Kawsar Talaat, an associate professor in the department of international health at the Johns Hopkins Bloomberg School of Public Health. No vaccine is 100 percent effective, she notes, and “although some are better than others, most of them have some breakthrough infections.”

A “breakthrough” simply means that a vaccinated person has tested

positive for the disease-causing agent, not that they will become ill or transmit the infection to someone else. Most vaccinated people who are infected do not have symptoms, and those that do tend to have mild illness. Even with the Delta variant of SARS-CoV-2, the vaccines show good protection against symptomatic disease and death.

Nationally, as of August 2, the U.S. Centers for Disease Control and Prevention reported that more than 164 million people have been fully vaccinated, just under half of the total population. Yet 97 percent of those who are being hospitalized for COVID-19 are unvaccinated.

The numbers underscore how reality sometimes becomes distorted in the public consciousness. "Anecdotally, from talking to my friends and family and on social media, I think people are more concerned about these breakthrough infections than their prevalence would lead you to be," says Tara Smith, a professor of epidemiology in the College of Public Health at Kent State University.

Another worry with breakthrough cases is passing the virus to others. But people infected "tend to be less likely to transmit, no matter what we're looking at," Smith says. "We see this with viruses and bacteria—even with pertussis, one of the reasons that people try to 'cocoon' around infants" who cannot initially be vaccinated against that disease. "Cocooning" refers to vaccinating those who spend time with the infant as a protective barrier because the pertussis vaccine is not administered before the age of two months.

COVID vaccines are expected to reduce transmission among those with an asymptomatic breakthrough infection, says Nick Grassly, a professor in the department of infectious disease epidemiology at Imperial College London. "So you already have the fact that you're immunized and less likely to become infected, and even if you are infected, your risk of transmitting the virus is reduced," he adds.

One reason is that the amount of the coronavirus, its viral load, is lower in such infections, so there is less of it to transmit. How this pattern looks with the Delta variant is not clear. A Centers for Disease Control and Prevention study published in late July pointed to similar viral counts among vaccinated and unvaccinated people. In that study, however, the researchers did not conduct tests to confirm true viral loads or report data on transmission from vaccinated people, and the "unvaccinated" group included people who were partially vaccinated.

Breakthrough cases do not occur because the vaccines are ineffective. Immunity can wane over time, and a vaccine might be less effective for a given pathogen. The measles-mumps-rubella (MMR) vaccine is one example: its protection against measles is strong, but the immunity to mumps it confers is less so, Talaat says.

Even the mighty measles vaccine has a breakthrough infection history. One measles outbreak in the late 1980s that largely involved vaccinated young people led to a policy change calling for two doses instead of one. The first MMR dose confers about 90 percent protection for a lifetime, Talaat says, but the second dose covers about half of the remaining 10 percent. Given the high contagiousness of measles, getting the highest possible coverage is crucial.

Influenza vaccines are the inoculations that are most associated with breakthrough infections. If such cases of flu were tracked as closely as breakthrough SARS-CoV-2 infections, "there would be so many more" of the former, Smith says, because "we know the flu vaccine is not as effective." Breakthrough COVID cases, she says, are "just another Wednesday," compared with those that occur with other vaccines.

The COVID vaccines appear to be faring better than those for influenza usually do. The shots neutralize COVID variants quite effectively so far. Grassly says that, in fact, COVID does not overcome immunity as much as influenza viruses do. And some types of influenza are just better at dodging what human ingenuity throws at them, making for some flu seasons with very low-efficacy vaccines and plenty of breakthrough cases.

Talaat notes that with the flu, "we're not calling it 'breakthrough' but saying, 'It's 47 percent effective this year' or '60 percent….' We talk about efficacy." But even though influenza vaccines have relatively poor efficacy, she says, they are "better than nothing," saving lives and preventing hospitalizations.

Breakthrough rates can increase if the vaccinated population is small

and there are high case counts in the community. Conversely, high vaccine uptake means that the vaccinated population makes up a larger proportion of overall cases. If almost everyone is vaccinated, any cases that do occur are likelier to be in someone who's immunized. That was the situation in an outbreak in Massachusetts in which 74 percent of people testing positive were vaccinated in a region where some 69 percent of eligible residents had received shots.

Other factors contribute to an overrepresentation of vaccinated patients with breakthrough infections, including age and health conditions associated with a weakened immune system. Often the level of immunity for these patients produces a blunted response to the vaccine, so they may be at a higher risk than younger unaffected people who are not immunized.

Similar to those that are routinely administered for pertussis, booster shots for COVID may be needed for people with a suppressed immune system or for gradually waning immunity. Talaat points to reports of good responses to a third COVID vaccine dose in patients who had an organ transplant. France and Israel have already added a recommended third dose for some immunocompromised recipients, and the U.K. is considering doing so. The CDC's Advisory Committee on Immunization Practices met on July 22 to review data related to booster shots in people who are immunocompromised and concluded that a third dose might be in order for this patient population.

In an earnings call in late July, Pfizer cited unpublished, preliminary results for 23 clinical trial participants that showed increased protection against the Delta variant after a third dose of its mRNA vaccine. The company submitted its third-dose findings to the FDA in mid-August in a bid to obtain emergency-use authorization for a booster.

In the meantime, "we don't know if boosters will work, but if we vaccinate everybody, then that will protect the 2.7 percent of people in this country who are immunocompromised," Talaat says. "And they won't have to worry about how well or how badly their immune system works to protect against the virus."

—Emily Willingham

Gray Hair Can Return to Its Original Color—and Stress Is Involved, of Course

The universal marker of aging is not always a one-way process

Few harbingers of old age are clearer than the sight of gray hair. As we grow older, black, brown, blonde or red strands lose their youthful hue. Although this may seem like a permanent change, new research reveals that the graying process can be undone—at least temporarily.

Hints that gray hairs could spontaneously regain color have existed as isolated case studies within the scientific literature for decades. In one 1972 paper, the late dermatologist Stanley Comaish reported an encounter with a 38-year-old man who had what he described as a "most unusual feature." Although the vast majority of the individual's hairs were either all black or all white, three strands were light near the ends but dark near the roots. This signaled a reversal in the normal graying process, which begins at the root.

In a study published in June in *eLife*, a group of researchers provide the most robust evidence of this phenomenon to date in hair from around a dozen people of various ages, ethnicities and sexes. It also aligns patterns of graying and reversal to periods of stress, which implies that this aging-related process is closely associated with our psychological well-being.

These findings suggest "that there is a window of opportunity during which graying is probably much more reversible than had been thought for a long time," says study co-author Ralf Paus, a dermatologist at the University of Miami.

Around four years ago Martin Picard, a mitochondrial psychobiologist at Columbia University, was pondering the way our cells grow old in a multistep manner in which some of them begin to show signs of aging at much earlier time points than others. This patchwork process, he realized, was clearly visible on our head, where our hairs do not all turn gray at the same time. "It seemed like the hair, in a way, recapitulated what we know happens at the cellular level," Picard says. "Maybe there's something to learn there. Maybe the

hairs that turn white first are the more vulnerable or least resilient."

While discussing these ideas with his partner, Picard mentioned something in passing: if one could find a hair that was only partially gray—and then calculate how fast that hair was growing—it might be possible to pinpoint the period in which the hair began aging and thus ask the question of what happened in the individual's life to trigger this change. "I was thinking about this almost as a fictive idea," Picard recalls. Unexpectedly, however, his partner turned to him and said she had seen such two-colored hairs on her head. "She went to the bathroom and actually plucked a couple—that's when this project started," he says.

Picard and his team began searching for others with two-colored hairs through local ads, on social media and by word of mouth. Eventually, they were able to find 14 people—men and women ranging from nine to 65 years old with various ethnic backgrounds (although the majority were white). Those individuals provided both single- and two-colored hair strands from different parts of the body, including the scalp, face and pubic area.

The researchers then developed a technique to digitize and quantify the subtle changes in color, which they dubbed hair pigmentation patterns, along each strand. These patterns revealed something surprising: In 10 of these participants, who were between age nine and 39, some graying hairs regained color. The team also found that this occurred not just on the head but in other bodily regions as well. "When we saw this in pubic hair, we thought, 'Okay, this is real,'" Picard says. "This happens not just in one person or on the head but across the whole body." He adds that because the reversibility only appeared in some hair follicles, however, it is likely limited to specific periods when changes are still able to occur.

Most people start noticing their first gray hairs in their 30s—although some may find them in their late 20s.This period, when graying has just begun, is probably when the process is most reversible, according to Paus. In those with a full head of gray hair, most of the strands have presumably reached a "point of no return," but the possibility remains that some hair follicles may still be malleable to change, he says.

Getty Images

"What was most remarkable was the fact that they were able to show convincingly that, at the individual hair level, graying is actually reversible," says Matt Kaeberlein, a biogerontologist at the University of Washington, who was one of the editors of the new paper but was not involved in the work. "What we're learning is that, not just in hair but in a variety of tissues, the biological changes that happen with age are, in many cases, reversible—this is a nice example of that."

The team also investigated the association between hair graying and psychological stress because prior research hinted that such factors may accelerate the hair's aging process. Anecdotes of such a connection are also visible throughout history: according to legend, the hair of Marie Antoinette, the 18th-century queen of France, turned white overnight just before her execution at the guillotine.

In a small subset of participants, the researchers pinpointed segments in single hairs where color changes occurred in the pigmentation patterns. Then they calculated the times when the change happened using the known average growth rate of human hair: approximately one centimeter per month. These participants also provided a history of the most stressful events they had experienced over the course of a year.

This analysis revealed that the times when graying or reversal occurred corresponded to periods of significant stress or relaxation. In one individual, a 35-year-old man with auburn hair, five strands of hair underwent graying reversal during the same time span, which coincided with a two-week vacation. Another subject, a 30-year-old woman with black hair, had one strand that contained a white segment that corresponded to two months during which she underwent marital separation and relocation—her highest stress period in the year.

Eva Peters, a psychoneuroimmunologist at the University Hospital of Giessen and Marburg in Germany, who was not involved in this work, says that this is a "very creative and well-conceptualized study." But, she adds, because the number of cases the researchers were able to look at was relatively small—particularly in the stress-related portion of the study—further research is needed to confirm these findings.

For now the next step is to look more carefully at the link between stress and graying. Picard, Paus and their colleagues are currently putting together a grant to conduct another study that would examine changes in hair and stress levels prospectively—which means tracking participants over a specified period rather than asking them to recall life events from the past.

Eventually, Picard says, one could envision hair as a powerful tool to assess the effects of earlier life events on aging—because, much like the rings of a tree, hair provides a kind of physical record of elapsed events. "It's pretty clear that the hair encodes part of your biological history in some way," he says. "Hair grows out of the body, and then it crystallizes into this hard, stable [structure] that holds the memory of your past."

—Diana Kwon

People with COVID Often Infect Their Pets

New unpublished studies show that dogs and cats with COVID-positive owners frequently have SARS-CoV-2 antibodies

Dogs or cats that live in a household with people who have COVID often become infected and sick themselves. Experts advise infected individuals to keep a distance from their animals if possible.

New research shows that people who become infected with the novel coronavirus, or SARS-CoV-2, and fall ill often pass the pathogen on to their pets. The animals sometimes also become sick from the infection, occasionally severely, according to the results of two separate studies presented at this year's European Congress of Clinical Microbiology and Infectious Diseases. The papers have not yet been published in scientific journals.

A team led by veterinarian Dorothee Bienzle of the University of Guelph in Ontario investigated potential COVID infection in 198 cats and 54 dogs. All of the dogs and 48 of the cats came from a household in which at least one person had COVID, and the rest of the cats came from an animal shelter or neuter clinic. The team found that two out of three cats and two out of five dogs whose owners had COVID had antibodies against SARS-CoV-2, indicating they had been infected with the virus at some point, too. But in the shelter group, less than one in 10 cats had these antibodies. And in the neuter clinic, the figure was less than one in 38.

Dogs and cats that came from households in which owners had COVID also often developed symptoms of the disease, Bienzle and her team report. Between 20 and 30 percent of the animals experienced loss of energy and appetite, coughing, diarrhea, runny nose and respiratory problems. The complications were mostly mild and short term, but they were severe in three cases. In cats, the risk of infection was higher in those that were closely cuddled by their owners, according to behavioral surveys the researchers conducted in addition to the antibody tests. This cuddling correlation

was not observed in dogs.

Veterinarian Els Broens of Utrecht University in the Netherlands and her colleagues conducted similar studies on 156 dogs and 154 cats from about 200 households with human COVID patients. The researchers found that animals in one in five of these households had become infected with the virus—results identified by positive polymerase chain reaction (PCR) or antibody tests. Disease symptoms, especially respiratory and gastrointestinal complications, also occurred in the animals but were mostly mild.

Both Bienzle's and Broens's groups conclude that humans often transmit SARS-CoV-2 to their pets. "This is not at all surprising," says Sarah Hamer, a veterinary epidemiologist at Texas A&M University, who is conducting similar studies on COVID-positive pets in the U.S. As research rolls in, she says, the international veterinary field is finding that pet owners transmitting the virus to their furry friends is more common than originally thought. "The findings are consistent: it's just not that hard for these animals to get infected," Hamer says. That result makes sense, she explains, given the closeness of person-pet relationships. "Often we're snuggling and even sleeping in the same beds with them," Hamer says.

"The findings are consistent: it's just not that hard for these animals to get infected."
—Sarah Hamer

The role pets and livestock play in the COVID pandemic has been debated for some time. Several studies have shown that pigs, cows, ducks and chickens seem to be largely resistant to the virus. Cats frequently become infected at higher rates than dogs, Hamer notes, and pass the pathogen on to fellow felines. Beyond the pathogen posing a risk to our pets' health, researchers worry that it will multiply in the animals and possibly mutate, jumping back into humans at some point. "The main concern is … the potential risk that pets could act as a reservoir of the virus and reintroduce it into the human population," Broens says. Mink have been shown to retransmit SARS-CoV-2 to humans, leading some countries to take drastic measures to prevent the pathogen from spreading on mink farms. Denmark and the Netherlands culled their mink stocks, killing almost 20 million of the furry animals in total to stop the virus from spreading further.

Adrienne Elliot *Getty Images*

So far, Broens says, there is no evidence of such retransmission from dogs and cats back into humans. But Hamer notes the current studies simply are not set up to answer that exact question. In the meantime, the researchers recommend pet owners exercise caution. "If you have COVID-19, my advice is to keep your distance from your pet and don't let them into your bedroom," Bienzle says. Hamer reiterates that the recommendations are the same as with any other humans in your household: if you're infected, stay as far away as possible.

—Frank Schubert

This article originally appeared in Spektrum der Wissenschaft *and was reproduced with permission, with additional reporting by Tess Joosse.*

Why Extreme Heat Is So Deadly

Heat waves kill more people than any other type of severe weather in the U.S. And climate change is making them more frequent and unpredictable

In June a massive "heat dome" smothered the famously temperate Pacific Northwest, subjecting parts of Washington State, Oregon and western Canada to blistering and unprecedented temperatures. Lytton, British Columbia, set an all-time Canadian record with a searing 121.3 degrees Fahrenheit (49.6 degrees Celsius). A day later most of that village was destroyed by a huge wildfire. During another western heat wave in early July, California's Death Valley reached a scorching 130 degrees F (54 degrees C)—just shy of its record of 134 degrees F (57 degrees C), which was reported in 1913 (and is somewhat disputed now). Following that, a third heat wave blanketed the U.S. and the Canadian West.

It is virtually impossible that heat waves like the Pacific Northwest's June scorcher would have occurred without climate change, according to a recent analysis by the World Weather Attribution collaboration. Scientists estimate it was a one-in-1,000-year event, says Kristie L. Ebi, a professor of environmental and occupational health at the University of Washington and a co-author of the report. "And that's an 'at least,' " she notes. "It could be more rare than that, because it was so far outside where the climate model said temperatures would get to in this region." If warming reaches two degrees C above preindustrial levels—the threshold that most national governments have agreed to try to avoid in hopes of reducing climate change impacts—"that event could occur every five to 10 years," Ebi says.

These heat waves pose a major risk to public health. "In an average year in the U.S., heat kills more people than any other type of extreme weather," says Kristina Dahl, a senior climate scientist at the Union of Concerned Scientists. Hundreds of people died in the recent Pacific Northwest heat wave, according to estimates: there were at least 486 deaths in British Columbia, 116 in Oregon and 78 in Washington (by comparison, hurricanes have killed an average total of 46 people a year in the U.S. over the past 30 years). A recent U.S. Centers for Disease Control and Prevention report found there were more than 3,500 emergency department visits for heat-related illness this past May and June in a region that includes Alaska, Idaho, Oregon and Washington State. Nearly 80 percent of these visits occurred between June 25 and 30, when Oregon and Washington were experiencing the worst of the wave.

In July, California's Death Valley reached a blistering 130 degrees Fahrenheit (54 degrees Celsius), only a few degrees below the record set in 1913.

Kyle Grillot *Getty Images*

The human body functions best at 98.6 degrees F (37 degrees C). When it overheats and becomes dehydrated, the blood thickens. The heart has to pump harder, and it and other organs can be seriously damaged. The body has mechanisms to rid itself of excess heat—most notably sweating. But at a certain point, that fails to work, especially if humidity is high and perspiration cannot evaporate. "Once your thermal stress or heat gain becomes too much, even sweating is not going to keep up with getting rid of the additional heat," says JohnEric W. Smith, an associate professor of exercise physiology at Mississippi State University. This situation can result in heat exhaustion (a dangerous condition characterized by symptoms that include nausea, muscle cramps and dizziness) and the deadlier heatstroke, which can cause delirium, hot and dry skin, and loss of consciousness.

People can eventually acclimatize to some level of heat. If you live in a hot climate or work in hot conditions for a period of weeks or months, your body becomes more efficient at sweating and cooling itself down, Smith says. This process takes time, however. When severe heat hits places where most people are unaccustomed to it, such as the Pacific Northwest, it can be especially deadly. Elderly people, children and those with already existing conditions such as heart, respiratory or kidney disease are particularly vulnerable, according to Smith. Furthermore, common medications (beta blockers, for example) can affect the body's ability to sweat.

Farm laborers, construction workers and others who toil outdoors can be exposed to potentially fatal heat for many hours a day. A farm worker in Oregon died while working in the extreme heat on June 26. Dehydration is among the dangers—there have been cases of farm workers developing severe kidney disease after hours of sweating in the sun. Many outdoor workers are paid by the hour and may feel that they cannot afford to take a day off because of the weather. Only two states—California and Washington—have permanent heat-protection standards for outdoor workers, according to the Union of Concerned Scientists' Dahl (Oregon has adopted emergency ones). At the federal level, versions of a bill recently introduced in the U.S. House and Senate would direct the Occupational Safety and Health Administration to issue national standards protecting workers from heat-related illness.

Athletes are also at increased risk because their body produces excess heat from muscle activity. In 2001 National Football League (NFL) player Korey Stringer died from heatstroke during training in Minnesota. The institute that bears his name now studies ways to prevent heat-related illness and death among athletes, members of the military and physical laborers.

There are well-known ways to mitigate the risks of extreme heat. Staying in cool buildings with air-conditioning is a great option for those who have it. For those who do not, either because they cannot afford it or because they live in places known for gentle summers (such as Seattle), some cities have established cooling centers. But people need to be able to access these resources. That is not always easy if they have to take public transit, which heat waves can also disrupt. If you lack access to air-conditioning or a cooling center or have to work outside, at least try to seek shade. Direct sun warms the skin and makes you even hotter, so wear long sleeves and loose-fitting clothing to cover up. If you have to exert yourself, take frequent breaks and drink plenty of water.

Communities should have heat action plans, says the University of Washington's Ebi. She adds that these plans should include an early-warning-and-response system. In addition to forecasting extreme heat events, such systems should detail appropriate ways to deal with them—including how to help the most vulnerable people, who are often disproportionately affected. State and federal agencies could help support communities, but heat-response systems should be locally based, Ebi says.

As the planet warms, heat waves like those that have occurred in the U.S. and Canadian West this year are becoming frighteningly common—and catching climate scientists off guard. "Even a lot of our climate models that project out how frequent extreme heat will be in the future wouldn't have necessarily predicted this level of heat for that part of the country," Dahl says. "But then to realize that I am seeing it in my lifetime, and living it right now, is really terrifying." —*Tanya Lewis*

Can Vitamin D Help Protect against COVID?

Some studies suggest an impact, particularly for those who are vitamin-deficient. But for now the jury is out

Grace Cary Getty Images

From the early days of the COVID-19 pandemic, researchers examining the question of why some people were better protected from the infection than others began to look at a possible role for vitamin D. The nutrient, which is obtained from food and exposure to sunlight, is known to contribute to a well-functioning immune system in a variety of ways, including defending the body from invading viruses and other pathogens. "Vitamin D is cheap, easily available and relatively safe," says genetic epidemiologist Fotios Drenos of Brunel University London. Investigating whether the vitamin could make a difference in COVID patients "was an important question to ask," he says.

Researchers already knew that vitamin D can be helpful in staving off respiratory infections. A 2017 meta-analysis of 25 randomized controlled trials involving about 11,000 people concluded that giving daily or weekly vitamin D supplements reduced the risk of acute respiratory infections—with the strongest impact predictably falling on those who started off with a serious deficiency of the vitamin. That meta-analysis, led by Adrian Martineau of Queen Mary University of London, was updated this year with data from a total of 46 trials and 75,500 participants. Martineau's team confirmed its earlier finding but determined that the impact of the supplements appears to be quite small.

Epidemiological data emerging early in the pandemic also suggested that the vitamin might be useful. People older than 65 and people of color are more likely to have lower levels of vitamin D. Both groups face a higher risk of poor outcomes from COVID-19, although the reasons for their vulnerability are multifaceted. In addition, studies have shown that countries farther away from the equator—where levels of the vitamin tend to be lower because of less sunlight—have higher COVID death rates than those closer to the equator.

Taken together, such data points are far from conclusive, but they served as a spur to investigate further. Fortunately, several large, potentially relevant studies of vitamin D were already underway when the pandemic struck, and others were swiftly begun.

In Brisbane, Australia, cancer researcher Rachel Neale of the QIMR Berghofer Medical Research Institute has been leading the massive D-Health Trial, a randomized controlled trial of five years of vitamin D supplementation in 21,315 older adults. It has compared monthly high doses of the vitamin (60,000 international units) with a placebo and has looked at a wide range of outcomes, including heart disease, cancer, bone fractures and overall mortality. Acute respiratory tract infection has also been among the outcomes measured in the study, and with the COVID pandemic raging, Neale and her colleagues decided to examine those data early. Their analysis, published in the *Lancet Diabetes & Endocrinology* in January, showed that vitamin D did not reduce the risk of acute respiratory tract infection but may have slightly reduced the duration of symptoms. Neale points out, however, that vitamin D levels tend to be high in Australia because of the long hours of sunshine, so supplementation may have a lower impact there than in less sunny places.

Another researcher who started looking at the vitamin early in the pandemic—but in a more northerly latitude—is David Meltzer, a health economist and a professor of medi-

cine at the University of Chicago.

"I got an e-mail in the first week of March [2020] talking about the [2017] Martineau paper, and I was struck by the results, particularly in people who are deficient in vitamin D," he recalls. "We had a lot of people being tested for COVID-19 in our hospital, and we had historical data from these individuals, so we cross-referenced the positive tests and the vitamin D data on record."

The results in a diverse population of 4,638 people were published in *JAMA Network Open* this past March. Meltzer and his colleagues found that the risk of a positive COVID test was 2.64 times greater for Black individuals with low levels of vitamin D than for those with higher levels. There was no significant correlation in white participants. "Chicago has long winters, and people with darker skin produce less vitamin D. Our northern location and the predominance of Black people attending the hospital allowed us to spot the link," Meltzer observes.

In England, Drenos also took a look at D levels and the risk of COVID infection but used a different methodology. He studied a group of people of European ancestry in the UK Biobank who were genetically predisposed to high or low levels of vitamin D and looked for correlations between their levels of the vitamin and their SARS-CoV-2 infection risk and COVID-19 severity. Like Neale's trial and in contrast with Meltzer's study, Drenos's analysis, published in January, showed no evidence of a preventive effect of higher vitamin levels. Still, he says, "I am keeping an open mind. I believe that large, well-controlled trials will be the gold standard, but this takes time."

The lack of a clear answer from existing studies could reflect limitations in trial design, including populations that are already replete with vitamin D, sample sizes that are too small, or inconsistencies in doses or methods of measurement. Some forthcoming trials may help fill in the gaps.

The U. K.'s CORONAVIT trial, with 6,200 participants, is looking at whether correcting vitamin D deficiency during the winter with a standard or high dose of the vitamin will reduce the risk or severity of COVID-19 and other acute respiratory infections. In France, the smaller CoVitTrial is assessing the impact of a single high dose or routine dose of vitamin D on high-risk older adults with COVID-19. Results of both trials should be available later this year.

Meanwhile Meltzer is leading three studies of vitamin D supplementation in populations with mixed ethnicity: one investigation in medically complex patients, a second in health-care workers and a third that is community-based. They will assess the impact of various dosages of the vitamin on COVID-19 symptoms and antibodies, as well as on symptoms of other respiratory diseases.

Given the results of Neale's large-scale study and the modest benefits found in Martineau's latest meta-analysis, it seems unlikely that vitamin D will prove to be a critical ingredient in fending off COVID-19 or modulating its severity. But these and other new trials may find it is useful in certain doses for certain populations. As Neale points out, "there are data that are suggestive" and enough smoke to indicate that you don't want to be vitamin-D-deficient in a pandemic.

—*Suzanne Elvidge*

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Cancer Clues Found in Gene behind "Lemon Frost" Gecko Color

Research has solved a macabre mystery, and the finding could one day help efforts to catch human melanomas earlier

When reptile breeder Steve Sykes saw that two particular leopard geckos were up for auction in 2015, he knew he had to have them. The chubby lizards' bodies were dappled with the black spots that gave their species its common name. And at eye level, they looked to be smiling. But unlike other members of *Eublepharis macularius,* these were "lemon frost" geckos: they were pastel yellow from the base of their head to the root of their tail, as if they had been dipped in lemon sherbet. A breeder had created this variety, also called a morph, just one generation earlier. The combination of rarity and beauty made the two geckos instantly appealing to Sykes. He purchased the pair and named

them Mr. and Ms. Frosty.

Leopard geckos are among the most common reptile pets. Native to the Middle East and South Asia, they have been so successfully bred in captivity that most sold today are not sourced from the wild. Instead owners create and mix dozens of morphs through selective breeding and random luck.

"It's a big deal when a brand-new base morph comes out, no matter what it is. So the fact that a lemon frost was available—that was definitely something that I wanted to add to my collection," says Sykes, who owns a business called Geckos Etc. Herpetoculture. "I had no idea that there was any issue with this morph when I first got involved with it."

Leopard geckos are one of the most common reptile pets.

Getty Images

The issue emerged with Mr. Frosty's offspring. Sykes had bred the male with other leopard geckos he owned to produce more of the coveted lemon frosts. A year after the auction, he noticed small, white bumps growing on the bodies of some of the babies. Over time, he says, it became clear that these bumps were tumors. In fact, it turns out that more than 80 percent of the geckos with this morph suffer from a rare skin cancer that arises from pigment-producing cells called iridophores.

Sykes wanted to know if there was a way to breed lemon frosts to avoid this fate. Were the cancer and unique color somehow inextricably linked? Evolutionary geneticist Leonid Kruglyak of the University of California, Los Angeles, and his colleagues used Sykes's geckos to crack the lemon frost genetic code—and found that a single gene controlled both the color and the cancer.

"There's been very little molecular genetic work done in reptiles, and so it's fantastic to see an instance where a group has been able to track down the genetic basis of a really interesting trait," says Douglas Menke, a geneticist at the University of Georgia, who was consulted for the study but was not directly involved in the work.

This research could also open new avenues for studying human melanoma, an aggressive cancer of our pigment-producing cells. It is newly diagnosed in about 100,000 people in the U.S. every year and kills more than 7,000 annually.

GECKO DETECTIVE WORK

In 2017, a short time after he discovered the lemon frost morph's proclivity to tumors, Sykes says he got a call from Longhua Guo, a postdoctoral researcher at Kruglyak's lab, who studies human genetics. Guo had seen photographs of leopard geckos online, and he became fascinated with how their genes control their vibrant and varied patterns. After a two-hour conversation, Guo says, Sykes convinced him to look into the lemon frost tumor mystery.

Because Sykes had already been breeding the geckos with the intent of selling them before he noticed the cancer, the researchers had access to dozens of Mr. Frosty's children and grandchildren. They collected DNA samples by cutting off a small piece of a gecko's tail or swabbing the inside of its cheek—relatively easy tasks, Guo says, because of the

lizards' relaxed temperament. Then, the team compared the sequenced genomes of the lemon frost geckos with an existing genome for a standard leopard gecko.

The results could not have been clearer: lemon frost geckos possessed one copy of a gene called *SPINT1* that had mutated. Their other copy of that gene, as well as both copies in non-lemon-frost leopard geckos, did not have those differences in the DNA sequence.

"It turns out that *SPINT1* can explain what is going on here because *SPINT1* has been reported in zebra fish, in mice and in humans. [Mutations in the gene] are associated with skin cell tumors," Guo says. Looking at the lemon frosts' tumors under a high-powered microscope revealed increased numbers of iridophores, which give some lizard scales a whitish appearance.

Guo and his team proposed that the mutated copy of *SPINT1* causes lemon frost geckos to overproduce these cells. That overproduction would lead to a whiter overall background that would make the animals' yellow color appear brighter and more visible—and that could also cause them to develop skin tumors later in life. The study, authored by Guo, Sykes, Kruglyak and their colleagues, was published in June in *PLOS Genetics.*

"Lemon frost" leopard gecko named Mr. Frosty.

A FROSTY MODEL ORGANISM

Researchers still do not know why some lemon frosts have more aggressive cancers than their siblings or why others (including Mr. Frosty himself) never develop visible tumors. "Why does gecko A develop no tumors at all while gecko B has very slight tumors that stay completely dormant for a very long time, and gecko C has tumors that are very fast-growing and very active?" Sykes asks. "That's always been a question for me."

Answering this question may help scientists better understand how some cancers develop in humans, says Lara Urban, a conservation genomics research fellow at the University of Otago in New Zealand, who was not involved in the study. "I do think it will have an impact on cancer research, in that we understand the conservedness of this [*SPINT1* genetic] pathway a little bit better now," she says. "It will also be a potential new model organism for studying the development of skin cancer and contributing to actual therapeutic development."

Perhaps there are tumor suppressor genes that keep the cancer at bay in some lizards but not others, Urban adds. And if the tumors are inevitable, they could exhibit certain chemical signatures that current methods do not detect. This raises the possibility of eventually creating diagnostics to catch preclinical melanoma in humans.

While the lemon frost morph might be bred as a research strain, Sykes says it is unlikely the lizards will ever be sold as hobbyist pets again.

"We've stopped breeding lemon frosts, and we have no intentions to start it up again in the future," he says. "My goal is to produce beautiful, perfect, healthy geckos. And it doesn't appear that it's possible to separate the lemon frost gene from this tumor phenotype."

—Maddie Bender

L. Guo et al., in *PLOS Genetics*, **2021**; *Steve Sykes*

"Inflammation Clock" Can Reveal Body's Biological Age

Using machine learning, researchers created a tool that might help doctors improve people's healthy lifespan

Thomas Barwick *Getty Images*

A new type of age "clock" can assess chronic inflammation to predict whether someone is at risk of developing age-related disorders such as cardiovascular and neurodegenerative disease. The clock measures "biological age," which takes health into consideration and can be higher or lower than a person's chronological age.

The inflammatory aging clock (iAge), reported on July 12 in *Nature Aging*, is one of the first tools of its kind to use inflammation to assess health. Other age clocks have used epigenetic markers, chemical groups that tag a person's DNA as they age and are passed along as cells divide. The researchers who developed iAge hope that, because inflammation is treatable, the tool could help doctors determine who would benefit from intervention—potentially extending the number of years a person lives in good health.

The study "is a further reinforcement of the fact that the immune system is critical, not only for predicting unhealthy aging but also as a mechanism driving it," says Vishwa Deep Dixit, an immunobiologist at the Yale School of Medicine, who was not involved in the work.

KEEPING TIME

iAge is based on the idea that as a person ages, their body experiences chronic, systemic inflammation because their cells become damaged and emit inflammation-causing molecules. This ultimately leads to wear and tear on their tissues and organs. People who have a healthy immune system will be able to neutralize this inflammation to some extent, whereas others will age faster.

To develop iAge, a team that included systems biologist David Furman and vascular specialist Nazish Sayed of Stanford University analyzed blood samples from 1,001 people aged eight to 96 who are part of the 1000 Immunomes Project, which aims to investigate how signatures of chronic, systemic

inflammation change as people age. The researchers used the participants' chronological ages and health information, combined with a machine-learning algorithm, to identify the protein markers in blood that most clearly signal systemic inflammation.

In particular, they pinpointed the immune-signaling protein, or cytokine, CXCL9 as a top contributor; it is mainly produced by the inner lining of blood vessels and has been associated with the development of heart disease.

Sayed says that CXCL9 being a key component of iAge gives new credence to the adage that "you're only as old as your arteries."

After developing it, the researchers tested iAge by collecting the blood of 19 people who had lived to at least 99 years old and using the tool to calculate their biological age. On average, the centenarians had an iAge 40 years lower than their actual age, according to a press release—aligning with the idea that people with healthier immune systems tend to live longer.

AGING GRACEFULLY

Scientists have long explored the idea of age clocks as a predictor of how healthy a person currently is. Epigenetics-based research in this area has shown some promise, but María Mittelbrunn, a molecular biologist at the Autonomous University of Madrid, says that evaluating a person's biological age by measuring epigenetic changes to their DNA can be complicated. Measuring inflammation with a blood test would be easier, making a tool such as iAge more practical for a clinical setting.

Furman hopes that iAge and other age clocks based on inflammation might enable personalized treatments, too.

When examining CXCL9 as a biomarker of systemic inflammation, Furman and his colleagues grew human endothelial cells, which make up the walls of blood vessels, in a dish and artificially aged them by letting them divide repeatedly. The researchers saw that high levels of the protein drove the cells into a dysfunctional state. When the team silenced expression of the gene that encodes CXCL9, the cells regained some function, suggesting that the protein's harmful effects might be reversible.

If caught early, "inflammation is one of the best things we can treat," Mittelbrun says. "We have developed amazing anti-inflammatory tools, so I think it's a biological process that we have a lot of knowledge about and can target easily." For instance, researchers have long known about salicylic acid (a starting material for making aspirin) and have more recently developed JAK/STAT inhibitors for inflammatory conditions such as rheumatoid arthritis.

Sayed envisions a future in which anyone can undergo inflammatory-biomarker profiling on a regular basis to keep tabs on their risk of developing age-related disease. "If we can control aging in a more impactful way," he says, "I think we can have a more graceful aging process."

—Max Kozlov

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A New Era of Designer Babies May Be Based on Overhyped Science

Genetic testing with IVF is being marketed as a means to choose a healthy embryo, despite questions about the soundness of the technology

By Laura Hercher

Christopher Burgstedt *Getty Images*

Laura Hercher is a genetic counselor and director of student research at the Joan H. Marks Graduate Program in Human Genetics at Sarah Lawrence College. She has written broadly on ethical, legal and social issues related to genetic medicine. Hercher is host of *The Beagle Has Landed*, a podcast for the clinical genetics community and other sci-curious individuals.

FOR BETTER OR WORSE, GENETIC TESTING OF EMBRYOS OFFERS A POTENTIAL gateway into a new era of human control over reproduction. Couples at risk of having a child with a severe or life-limiting disease such as cystic fibrosis or Duchenne muscular dystrophy have used preimplantation genetic testing (PGT) for decades to select among embryos created through in vitro fertilization (IVF) for those that do not carry the disease-causing gene. But what new iteration of genetic testing could tempt healthy, fertile couples to reject our traditional time-tested and wildly popular process of baby making in favor of hormone shots, egg extractions and DNA analysis?

A California-based start-up called Orchid Biosciences claims it has an answer to that question. The company offers prospective parents genetic testing prior to conception to calculate risk scores estimating their own likelihood of confronting common illnesses such as heart disease, diabetes and schizophrenia and the likelihood that they will pass such risks along to a future child. Parents-to-be can then use IVF, along with Orchid's upcoming embryo screening package, to identify the healthiest of their embryos for a pregnancy.

Orchid aims to use PGT and IVF to expand what is already a thriving marketplace in screening tests for prospective parents. Initially the only people offered tests to prevent genetic disease in the next generation were those whose ancestry put them at higher risk for a specific condition, such as Tay-Sachs disease in the Ashkenazi Jewish population. The first genetic screen intended for universal use and covering a wide range of diseases was introduced by Counsyl (now part of Myriad Genetics) in 2010. Today carrier screening is a $1.7-billion industry. These tests search for genetic problems that otherwise come to light only after the birth of an affected child. But diseases caused by a single gene are rare. Most children are born healthy, and most couples who do carrier screening come away reassured.

In contrast, Orchid's risk assessment includes common diseases, ensuring that a high percentage of prospective parents who do this version of preconception testing will find something to worry about. Those who choose to act on their concerns will soon have the option of paying for IVF plus Orchid's embryo-testing package. According to its promotional materials, the company will provide a scorecard intended to identify, among various embryos, the future children least likely to develop heart disease, breast cancer, prostate cancer, type 1 or 2 diabetes, and five other conditions that make up Orchid's current common disease risk portfolio.

With a marketing strategy that encourages routine use of IVF for those who can afford it, Orchid breaks new ground in introducing the first—but likely not the last—consumer-driven model of human reproduction. The ambitions of this new Silicon Valley venture into health care are backed by the imprimatur of health-tech luminaries, including 23andMe co-founder and Orchid investor Anne Wojcicki. Orchid's first product on the market is its "Couple Report," at a cost of $1,100. Phase two, scheduled for launch later this year, examines embryos conceived by IVF, allowing the couple to pick and choose among potential children in a process that Orchid CEO Noor Siddiqui, speaking in an interview on the podcast Mendelspod in April, referred to as "embryo prioritization." Siddiqui is a former Thiel Foundation Fellow whose interests lie in the use of technology in medicine. She did not respond to repeated requests for an interview from *Scientific American*.

Geneticists have greeted Orchid's launch with skepticism, in large part because of objections to the company's use of a technique called polygenic risk scores to assess an embryo's lifetime risk of common diseases. Heart disease runs in families just like musical ability or height, but only in exceptional cases can the inherited risk be traced to a single gene. Hundreds or even thousands of genes each contribute in a small way. Polygenic risk scores attempt to

sum up the overall likelihood of a particular outcome—such as getting a disease—by simply observing which patterns of variation in a genome are associated with a higher or lower probability of having the condition. In other words, this method gives us information about who might be more or less likely to get sick without explaining why. The statistical association is real but hardly definitive, and it tracks population-level trends that may not be relevant for the individual in question.

Researchers who work with polygenic risk scores are concerned about their use in this context. "We don't know what these variants are doing biologically," says Peter Kraft, a professor of epidemiology and biostatistics at the Harvard T. H. Chan School of Public Health. "Something that's associated with a decreased risk of breast cancer could be associated with all other kinds of things, some of which might actually increase your risk of something else. We just don't know enough yet."

Some version of prenatal planning as envisioned by Orchid may be possible eventually, but few experts seem to share their optimism that today is that day. A July 1 special report in the *New England Journal of Medicine* pointed out the inherent weakness of using polygenic risk scores to distinguish among sibling embryos—which, unlike random individuals in a population, will be identical in 50 percent of the genetic variation that is examined to generate a score. The report concluded with recommendations on how to convey any purported benefits from polygenic scores in embryo selection responsibly—and the need to emphasize the underlying uncertainties in the data. "Any one of the issues discussed in this article would be difficult to communicate accurately—even to other scientists and clinicians," the authors noted. "Collectively, these issues constitute a formidable challenge for [companies selling these services], which must ensure that their customers understand what they are doing." The report also called for the Federal Trade Commission to look carefully at claims made by any company using polygenic scoring to pick embryos.

Current polygenic risk scores have limited predictive strength and reflect the shortcomings of genetic databases, which are overwhelmingly Eurocentric. Alicia Martin, an instructor at Massachusetts General Hospital and the Broad Institute of the Massachusetts Institute of Technology and Harvard University, says her research examining polygenic risk scores suggests "they don't transfer well to other populations that have been understudied." In fact, the National Institutes of Health announced in mid-June that it will be giving out $38 million in grants over five years to find ways to enhance disease prediction in diverse populations using polygenic risk scores. Speaking of Orchid, Martin says, "I think it is premature to try to roll this out."

In an interview about embryo screening and ethics featured on the company's Web site, Jonathan Anomaly, a University of Pennsylvania bioethicist, suggested the current biases are a problem to be solved by getting customers and doing the testing. "As I understand it," he said, "Orchid is actively building statistical models to improve ancestry adaptation and adjustments for genetic risk scores, which will increase accessibility of the product to all individuals."

Still, better data sets will not allay all concerns about embryo selection. The combined expense of testing and IVF means that unequal access to these technologies will continue to be an issue. In her Mendelspod interview, Siddiqui insisted, "We think that everyone who wants to have a baby should be able to, and we want our technology to be as accessible to everyone who wants it," adding that the lack of insurance coverage for IVF is a major problem that needs to be addressed in the U.S.

But should insurance companies pay for fertile couples to embryo-shop? This issue is complicated, especially in light of the fact that polygenic risk scores can generate predictions for more than just heart disease and cancer. They can be devised for any trait with a heritable component, and existing models offer predictions for educational attainment, neuroticism and same-sex sexual behavior, all with the same caveats and limitations as Orchid's current tests for major diseases. To be clear, tests for these behavioral traits are not part of Orchid's current genetic panel. But when talking about tests the company does offer, Siddiqui suggested that the ultimate decision makers should be the parents-to-be. "I think at the end of the day, you have to respect patient autonomy," she said.

Despite Orchid's hard lean into parental free choice, bioethicists such as Gabriel Lázaro-Muñoz of the Center for Medical Ethics and Health Policy at the Baylor College of Medicine worry that Orchid's system of ranking embryos may unduly influence prospective parents and replace a very necessary broader societal debate on what qualifies as a good life. It is problematic for that reason, according to Lázaro-Muñoz, to have these companies "bias the conversation."

Lurking in the background of every discussion on embryo selection and ethics is the specter of eugenics. "I think we have to be very aware of our history," Lázaro-Muñoz says, "in terms of sterilization and state-mandated programs in the past that were aimed at … exterminating individuals with some of these conditions."

Clearly, Orchid anticipates pushback. The company's promotional materials include guides to fertility planning and the genetics of irritable bowel disease but also a set of talking points for concerned relatives described as "How to respond to your family skeptics—playing God, designer babies, and genetic enhancement."

"Yes, we're going there," the guide says. Ethics? Bring it on. This is not a company in a defensive crouch. The "Our Principles" section of its Web site positions genetic testing as a human right. "From a reproductive freedom perspec-

tive, we stand for a couple's right to have access to information that enables them to mitigate disease risk for their future child," it says. Like other Silicon Valley health-care technology pioneers, Orchid presents itself less as a product than as a social justice movement with a little commercial venture on the side, like a gift shop.

Orchid dismisses suggestions from detractors that its marketing oversells what polygenic risk scores have to offer in the context of screening embryos. "Parents are asking for this information and deserve to know it," Siddiqui told Mendelspod, warning that those who stand in the way are "frankly being a little bit paternalistic." And if prospective parents are not asking, Siddiqui suggested, perhaps they should be. When it comes to the next generation, "we've been sort of just rolling the dice," Siddiqui said, while "the ability to actually stack the odds against disease is … sort of a new capability that humanity has just gotten online."

The suggestion that embryo selection is not only something people can do but something they should do raises perhaps one of the thorniest ethical issues of all. In the Mendelspod interview, Siddiqui drew a contrast between "earned" and "unearned" bad luck. "You can get hit by a car, right? That's totally out of your control. But what is earned bad luck?" she asked before answering her own question. "I mean, that's the idea of … you're going base jumping constantly, and then you break your leg.… You kind of exposed yourself to higher risk there."

Ultimately, if technology allows Orchid to offer a product that meaningfully reduces the risk of disease susceptibility in the next generation, does that mean that anyone who can't or won't use it deserves their bad luck? If the basic, no-frills version of human reproduction comes to be seen as a form of careless parenting, it invites a callous parsing of who does and does not deserve their fate—and, by extension, who does and does not deserve resources and support. SA

Trailblazing Transgender Doctor Saved Countless Lives

After transitioning in 1917, Alan L. Hart helped alter medical history

By Leo DeLuca

Alan L. Hart, circa 1922

Gay & Lesbian Archives of the Pacific Northwest

Leo DeLuca is an award-winning writer from Dayton, Ohio. A graduate of the Columbia Journalism School's science concentration, DeLuca is currently writing a historical book concerning systemic racism and classism. He lives in New York City.

IN FEBRUARY 1918 ALAN L. HART WAS A TALENTED, UP-AND-COMING 27-YEAR-OLD intern at San Francisco Hospital. Hart, who stood at 5'4" and weighed about 120 pounds, mixed well with his colleagues at work and afterward—smoking, drinking, swearing and playing cards. His round glasses hemmed in his pensive eyes, a high white collar often flanked his dark tie, and his short hair was slicked neatly to the right. Though the young doctor's alabaster face was smooth, he could deftly go through the motions of shaving with a safety razor. A photograph of a woman, who he had told colleagues was his wife, hung on his boarding-room wall.

Then, one day that February, Hart was gone. He left behind nothing but his razor, a stack of mail, a pile of men's clothing—and the photograph, still gazing down from the wall.

A NEW HOLD ON LIFE

Alberta Lucille Hart, known as Lucille, was born on October 4, 1890, in Halls Summit—a lonesome part of Kansas just west of the Missouri border. The child's father Albert, a hay, grain and hog merchant, died two years later, and his widow Edna moved with Lucille to make a new start in Oregon. They eventually settled there in the pretty town of Albany, where the Calapooia and Willamette Rivers twist together like twine into a single sprawling flow.

When Lucille Hart grew old enough to learn about her father's death, she would comfort her mother: someday, she said, she would grow up to be a man, her mother's caretaker. Hart often secretly fantasized about marrying her female high school teacher—reveries in which she also saw herself as a man.

A talented writer, photographer and mandolinist, Hart graduated high school as salutatorian in 1908. She enrolled at Albany College, transferring to Stanford University in 1910. There Hart entered the premedical department, joined numerous organizations and founded the school's first-ever women's debate club. She enrolled at the University of Oregon Medical School in 1913. Four years later Hart graduated at the head of her class, the first woman to earn the coveted Saylor medal for being the top scholar in each of the school's departments.

"Dr. Hart was a brilliant student," a former classmate said in a 1918 edition of Spokane's *Spokesman-Review* newspaper. "She had the distinction of being the only woman in the class.… She dressed often in a very mannish style, wearing particularly masculine hats and shoes and frequently tight skirts. She walked with a noticeable mannish stride."

Hart, since childhood, had secretly identified as male and been attracted to women. Although she covertly dated several women throughout college, she largely kept her feelings hidden. Then one day, plagued by a phobia that was unrelated to her gender identity or sexual orientation, she sought help from her University of Oregon Medical School professor and doctor J. Allen Gilbert. Suspecting Hart was hiding a deeper secret, Gilbert encouraged her to confide in him. After two weeks of deliberation, Hart returned to the doctor and revealed her entire life story.

At first Hart sought psychiatric help from Gilbert, attempting to convert herself into a conventional woman. Therapy failed. Hypnosis failed. Finally, Hart halted the process—if the conversion worked, she realized, she would no longer think, feel or act like a man. And that thought repulsed her.

"Suicide had been repeatedly considered as an avenue of escape from her dilemma," Gilbert later wrote in his 1920 case study "Homo-Sexuality and Its Treatment," in which he referred to Hart anonymously as "H."

"After treatment … proved itself unavailing, she came with the request that I help her prepare definitely and permanently for the role of the male in conformity with her real nature all these years…," Gilbert continued.

Alberta Lucille Hart in the 1911 edition of Albany College's yearbook *The Takenah.*

"I had to do it. For years I had been unhappy. With all the inclinations and desires of the boy I had to restrain myself to the more conventional ways of the other sex. I have been happier since I made this change than I ever have in my life, and I will continue this way as long as I live. Very few people can understand…, and I have had some of the biggest insults of my career…. I came home to show my friends that I am ashamed of nothing."

—Alan L. Hart

"Hysterectomy was performed, her hair was cut, a complete male outfit was secured and … she made her exit as a female and started as a male with a new hold on life and ambitions worthy of her high degree of intellectuality."

AN UNDAUNTED TRAILBLAZER

After transitioning, Hart was hired as an intern at San Francisco Hospital in November 1917. He lodged with a fellow male intern and hung a photograph of a woman named Inez Stark on his boarding-room wall, describing her to others as his wife. (Hart and Stark, a schoolteacher, were then romantically involved but not officially married.) Three months later, in February 1918, Hart applied for a laboratory position with physician Harry Alderson at the nearby Lane Hospital. Then something awful happened.

"Girl Poses as Male Doctor in Hospital," roared the headline of an article in the February 5, 1918, edition of the *San Francisco Examiner*. "Intern Unmasked as Girl Graduate of Oregon School," reported Portland's *Oregon Daily Journal* on the same day. "Woman Poses as Man Interne in Hospital at Frisco," echoed the *Austin American* on February 6.

It turned out that a former Stanford classmate had recognized Hart while he was applying for the Lane Hospital job and had mentioned his past to someone on San Francisco Hospital's staff. The news eventually made its way to a hospital superintendent—and then into national headlines. Hart abruptly resigned his internship and headed home to Oregon, but he stood by his conviction to transition to a man.

"I had to do it," Hart said in the March 26, 1918, edition of the *Albany Daily Democrat*. "For years I had been unhappy. With all the inclinations and desires of the boy I had to restrain myself to the more conventional ways of the other sex. I have been happier since I made this change than I ever have in my life, and I will continue this way as long as I live. Very few people can understand…, and I have had some of the biggest insults of my career.… I came home to show my friends that I am ashamed of nothing."

But Hart's hardships continued. Later in 1918 he quietly began practicing in the tiny, out-of-the-way coastal town of Gardiner, Ore.—but again, he was recognized and had to move. Hart wrote four medical novels throughout his life. His first, *Dr. Mallory,* is set in Gardiner and features a fictitious "Dr. Gilbert" who sheds light on Hart's real-life hurdles: "She 'made good' in every way, until she was recognized…," Dr. Gilbert says in Dr. Mallory, speaking of a female character. "Then the hounding process began."

Between 1918 and 1927, Hart worked as a doctor in at least seven states, married and divorced Inez Stark, then graduated from the University of Pennsylvania with a master's in radiology in 1928. Hart bounced from state to state—and repeatedly, his fictional characters seemed to offer glimpses of his own struggles.

"When it came to outrunning gossip he found he couldn't do it," Hart wrote of Sandy Farquhar, a gay male character, in his 1936 novel *The Undaunted*. "He went into radiology because he thought it wouldn't matter so much in a laboratory what a man's personality was. But

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wherever he went, scandal followed him sooner or later … His story would get around and then he'd be forced to leave."

In *The Undaunted*, Farquhar commits suicide. But Hart kept going—and saved the lives of countless others.

"Hart was a pioneer in using chest x-rays to detect tuberculosis," says Elliot Fishman, a radiologist at Johns Hopkins University. "At that point, no one was really screening for TB. Sure, if you were coughing up blood, you would get x-rays, but no one was getting ahead of the disease. One in four patients had TB. Many of them were asymptomatic. Because of Hart, doctors were able to treat patients before they had complications. And since TB is an infectious disease, he was able to separate TB patients from others to stop the spread."

"Tuberculosis was a very stigmatizing disease," says Cristina Fuss, a cardiothoracic radiologist and associate professor of diagnostic radiology at Hart's medical alma mater, now known as Oregon Health & Science University. "Because of his own story, I imagine he could really empathize with someone who was struggling with being labeled. Today we still use x-rays to diagnose TB—they remain a hallmark of screening for TB. Hart was certainly a trailblazer."

Hart worked with TB patients in Washington State and Idaho before moving to Connecticut, where he earned a master's in public health from Yale University in 1948 at age 57. He continued his TB work in Connecticut. "Hart worked for the department of public health," Fishman says. "TB is a public health problem. He was able to combine his interest in radiology with his interest in public health. I imagine his work helped create other programs across the country."

Albany College Debate Team in 1909. Hart is at the right.

REWRITING HISTORY

Hart lived out the rest of his life in West Hartford, Conn., with his second wife Edna Ruddick, before dying of heart disease at age 71 on July 1, 1962. In his will, Hart instructed an attorney to destroy the personal photographs and records he had stored in two locked boxes. But in 1976 historian Jonathan Katz identified Hart as "H" in Gilbert's 1920 case study and unearthed the doctor's story. Six years later Edna Ruddick Hart died, leaving the majority of her estate to the Medical Research Foundation of Oregon in honor of her late husband.

"When uncovering the story of someone from the past, especially someone from the early 20th century—someone who, today, we would identify as transgender," says Peter Boag, a history professor at Washington State University and an award-winning LGBT historian, "we have to remember that, although the trans identity is recent in history, people often forget that trans people lived in the past. Uncovering the story of any trans person is not just something that affirms trans people's existence today. It rewrites our history." SA

Editor's Note: Up until 1917, Hart publicly identified as Alberta Lucille Hart and used the pronoun "she." After transitioning that year, Hart publicly identified as Alan L. Hart and used the pronoun "he."

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Why Sports Concussions Are Worse for Women

As women's soccer, rugby and other sports gain popularity, scientists are racing to understand how the female brain responds to head injury

By Katharine Sanderson

Soccer players jump for a header at a UEFA women's Champions League match in Décines-Charpieu, France, in March 2019.

Jeff Pachoud *Getty Images*

Katharine Sanderson is a freelance journalist based in Cornwall, England.

LIZ WILLIAMS WAS standing pitchside at a women's rugby match, and she did not like what she was seeing. Williams, who researches forensic biomechanics at Swansea University in Wales, had equipped some of the players with a mouthguard that contained a sensor to measure the speed of head movement. She wanted to understand more about head injuries in the brutal sport. "There were a few instances when my blood went cold," Williams says.

When the women fell in a tackle, their heads would often whiplash into the ground. The sensors showed that the skull was accelerating—indicating an increased risk of brain injury. But medical staff at the match, not trained to look out for this type of head movement as a cause of injury, deemed the women fine to play on. Such whiplash injuries are much rarer when males play.

Williams's observations highlight an increasingly apparent problem. A growing body of data suggests that female athletes are at significantly greater risk of a traumatic brain injury event than male athletes. They also fare worse after a concussion and take longer to recover. As researchers gather more data, the picture becomes steadily more alarming.

Female athletes are speaking out about their own experiences, including Sue Lopez, the U.K.'s first semiprofessional female soccer player in the 1970s, who now has dementia—a diagnosis she has linked to concussions from heading the ball.

Researchers have offered some explanations for the greater risk to women, although the science is at an early stage. Their ideas range from differences in the microstructure of the brain to the influence of hormones, coaching regimes, players' level of experience and the management of injuries.

Given that most, if not all, sports-concussion protocols are based on data from men, female athletes ranging from schoolgirls to this year's Olympic soccer squads are being put at risk of serious injury. "We take all of these data, primarily from studies on men; we apply them to women. That's just got to change," says Michael Grey, who researches rehabilitation neuroscience at the University of East Anglia in England.

Head injuries in sports have had a high profile for many years, with hundreds, if not thousands, of participants in football, rugby, soccer, boxing and other sports experiencing dementia or memory loss thought to be linked to recurrent blows to the head decades earlier. Coaching protocols at all levels are changing to try to prevent injury, but these have generally neglected to include a huge cohort: women.

BIGGER RISK

Studies from U.S. collegiate sports have shown that female athletes are 1.9 times more likely to develop a sports-related concussion than are their male contemporaries in comparable sports. Those female students also missed many more study days as they recovered. Neuropathologist Willie Stewart of the University of Glasgow in Scotland co-authored a study published earlier this year of more than 80,000 secondary-school soccer players in the U.S., with similar results.

It's not just the number of head injuries that differs between women and men but also their nature. A review of 25 studies of sports-related concussion suggests that female athletes are not only more susceptible to concussion than are males but also sustain more severe concussions.

Athletics trainer and sports scientist Tracey Covassin of Michigan State University was one of the first to look at the differences between the sexes, starting in the early 2000s. She was interested in concussion but noticed that all the data were coming from male-dominated sports in the U.S.: ice hockey, boxing and football. In more than 20 papers over almost two decades, Covassin has shown that there are sex differences in concussion rates and recovery times. In 2013, for instance, she published work on concussed soccer players in the U.S. and showed that the female players scored lower in memory tests and experienced more symptoms than did their male contemporaries.

As yet unpublished research by Williams on female rugby players—among the first studies to analyze sex-specific mechanisms of head injury in the sport—showed that more than 50 percent of the 25 female participants experienced injuries caused by their head whiplashing into the ground, whereas only one male

player did. “I didn’t expect that. That’s an important discovery,” says Grey, who has seen Williams’s results.

The actions leading to head injuries in female players might also be different. In Stewart’s soccer study, the girls were most likely to injure themselves when they made contact with an object (such as the ball, when heading it for example), whereas the boys were more likely to make contact with another player. Whether this is a matter of coaching, an individual’s level of playing experience or something else isn’t yet known.

WHY WOMEN FARE WORSE

The damage that causes concussion can be quite subtle. The brain can’t move that much in the skull, Stewart explains. “The brain virtually fills the intercranial cavity, and there’s a little thin film of fluid that fills up what space is left.” But, in the split second after an impact, the head rapidly decelerates, and the resulting forces transmit deep inside the brain. The gelatinous gray matter undergoes significant shear forces when the head stops suddenly, pushing and pulling the brain tissue in a way that can cause structural damage.

Those forces can affect the brains of men and women in profoundly different ways. Doug Smith of the University of Pennsylvania’s Penn Center for Brain Injury and Repair uncovered evidence that could be crucial for explaining some of the different outcomes seen in women versus men: their brain cells are structurally different.

Every neuron has a major fiber called the axon, which is responsible for transmitting electrical signals from cell to cell. Damage to axons, through strong shear forces, is thought to be the main reason that concussions occur. “Your brain literally can break,” says Smith, holding up some silly putty during a video call to demonstrate. When stretched gently, the silly putty deforms and then relaxes back into shape. When yanked violently, it snaps.

Inside each axon, tiny protein tunnels, called microtubules, that give cells their structure behave similarly, Smith says. These microtubules, only 25 nanometers wide, carry proteins in the axons and help them to function. If a microtubule is damaged, its protein cargo builds up, causing inflammation and ultimately a breakage, Smith explains: “And if you disconnect an axon, it’s gone forever.”

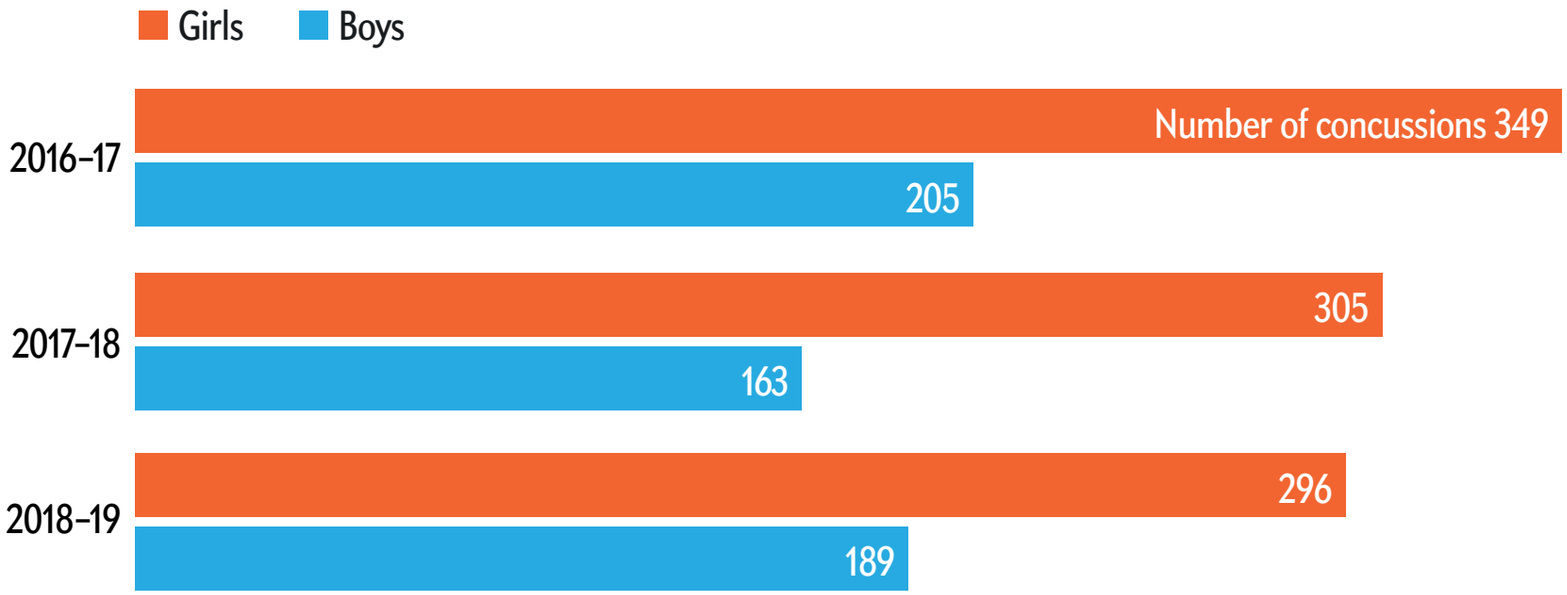
Smith’s team knew from imaging and brain-tissue studies that axon fibers from the brains of female rats and humans are slimmer than those from males. They wanted to know more about the differences and what effect they might have on brain injury, so they cultured rat neurons and then damaged them by exposing them to a rapid air blast. In the neurons from female rats, the axons were smaller and the microtubules narrower and more susceptible to damage than in the cells from males. The same was true for cultured human neurons.

Knowing the extent of axonal damage could be an indicator of how well someone could recover from a concussion. In a sports setting, this could be used to determine when an athlete is safe to return to the field, perhaps in the form of a blood test. Smith is now trying to find biomarkers of axonal damage in the blood—for instance, proteins that leak from axons when they are harmed. He is doing studies on professional ice hockey players and measuring axonal protein levels in blood before and after injury. “We did find out that some of these proteins and protein fragments, at a certain level, will actually predict who’s going to have a poor outcome,” Smith says.

Grey urges caution in extrapolating too much from Smith’s work on neurons in culture, which is mainly in rats. “Now that’s not to say that I disagree,” he adds. “It’s just that we need to be cautious. This is one study. I personally think there are other issues that are

Concussion Risk

A survey of more than 80,000 secondary-school soccer players in Michigan found that girls are nearly twice as likely as boys to experience concussions.



Nature; Source: *Bretzin et al. 2021*

more important."

One of those might be differences in neck strength, which some researchers think could have a considerable role in mitigating the damage wrought by concussion. Williams's mouthguard study also measured neck strength to see what sex differences there are. She found that female players' necks were 47 percent weaker than men's. Williams is working on improving neck strength in female rugby players to understand whether specific training could lessen the likelihood of concussion.

Not everyone agrees, however, that neck strength is the problem or the answer. Stewart isn't convinced by any of the studies showing that neck strength is a factor in increasing the risk of a concussion or a factor in improving the outcome of concussions.

Some researchers, including Grey, favor the idea that concussion is aggravated by the hormones that govern the menstrual cycle.

In 2014 Jeff Bazarian, a physician specializing in brain injury at the University of Rochester Medical Center, published a paper that showed a clear correlation between the menstrual cycle and how women recover from a traumatic brain injury. His team found that women who arrived at the emergency department with a head injury sustained while they were in the luteal phase of the menstrual cycle, which begins after ovulation and is when progesterone levels are highest, fared worse a month later than did women who hit their heads during the follicular stage, which marks the start of a new cycle and ends at ovulation. Women who were taking oral contraceptives, which balance out hormone levels, also fared better.

A doctor examines an athlete for injuries during a boxing match at the Tokyo Olympics in July 2021.

Ueslei Marcelino *Getty Images*

Initially this seems counterintuitive because progesterone has been shown to have a neuroprotective effect, and the luteal phase is when that hormone peaks. But other studies have reported an association between progesterone and concussion. Martina Anto-Ocrah, a reproductive epidemiologist at the University of Rochester, who has continued Bazarian's work, says this is because the brain injury causes progesterone levels to abruptly plummet.

Anto-Ocrah became interested in concussion and female sexual health after seeing evidence from the National Football League that some 30 years after sustaining concussions, male athletes were experiencing low testosterone levels and erectile dysfunction. "But there was nothing in the literature for women. I started thinking, Why are we not looking at how concussion affects female reproduction, female menstruation, female sexual health?" she says.

Anto-Ocrah is discovering signs that not only does the menstrual cycle have an impact on concussion but, conversely, head injuries can affect the menstrual cycle and other aspects of reproductive function by interfering with the brain regions that, in tandem with other glands in the body, help to control levels of estrogen and progesterone.

TREATING WOMEN DIFFERENTLY

One thing scientists agree on is the need for more research about women who sustain head injuries. In sports, this could transform the concussion treatment protocols, recovery experiences and the return to play. In July, World Rugby, rugby union's global governing body, made a statement committing to conduct research into injury-prevention programs specific to women and stressing the need for such initiatives. Grey says he knows of no sports bodies that have actually implemented woman-specific concussion measures or protocols.

Research funders are beginning to recognize the need to study sports concussions separately in men and women. The U.S. National Institute of Neurological Disorders and Stroke has allotted a total of $6.8 million over five years to two large projects studying sex differences in concussion and its assessment.

As part of this push for more data, in 2019 Stewart and his collaborator Katherine Snedaker, who runs PINK Concussions, an advocacy group for women's head injury, put out a call for more female athletes to pledge their brains to the Glasgow traumatic brain-injury archive he curates. Stewart's team plans to use the archive to investigate further how traumatic brain injury harms brain tissue and alters gene expression and how it might go on to cause degenerative brain disease. Of the 1,800 or so donated brains in the archive, 75 percent are from men; fewer than 200 are from athletes, and none of those is from a woman, although a number of high-profile U.K.-based female athletes have pledged their brains, including Scottish soccer player Rose Reilly, judo international Connie Ramsay and Scottish rugby star Lee Cockburn.

Prompted by what she saw on the pitch and facing some enforced downtime during the COVID-19 pandemic, Williams put together a survey of almost 2,000 female rugby players from 56 countries, who answered questions about their experiences of concussion. Early results suggest that players vary hugely in their knowledge of how to recognize and deal with brain injuries.

Williams says that her work, and that of others, is slowly gaining traction. In April, the University of Otago in New Zealand announced the start of a study in collaboration with World Rugby that will use a mouthguard to quantify aspects of head injuries in both male and female rugby players.

There are bright spots, but at the moment, Grey says, sports bodies mostly ignore the steadily building knowledge about sex differences in concussion. The male game is still the priority, Stewart says. "There's this general focus on male sport, male injury and male outcomes and less on female. It's terrible neglect." SA

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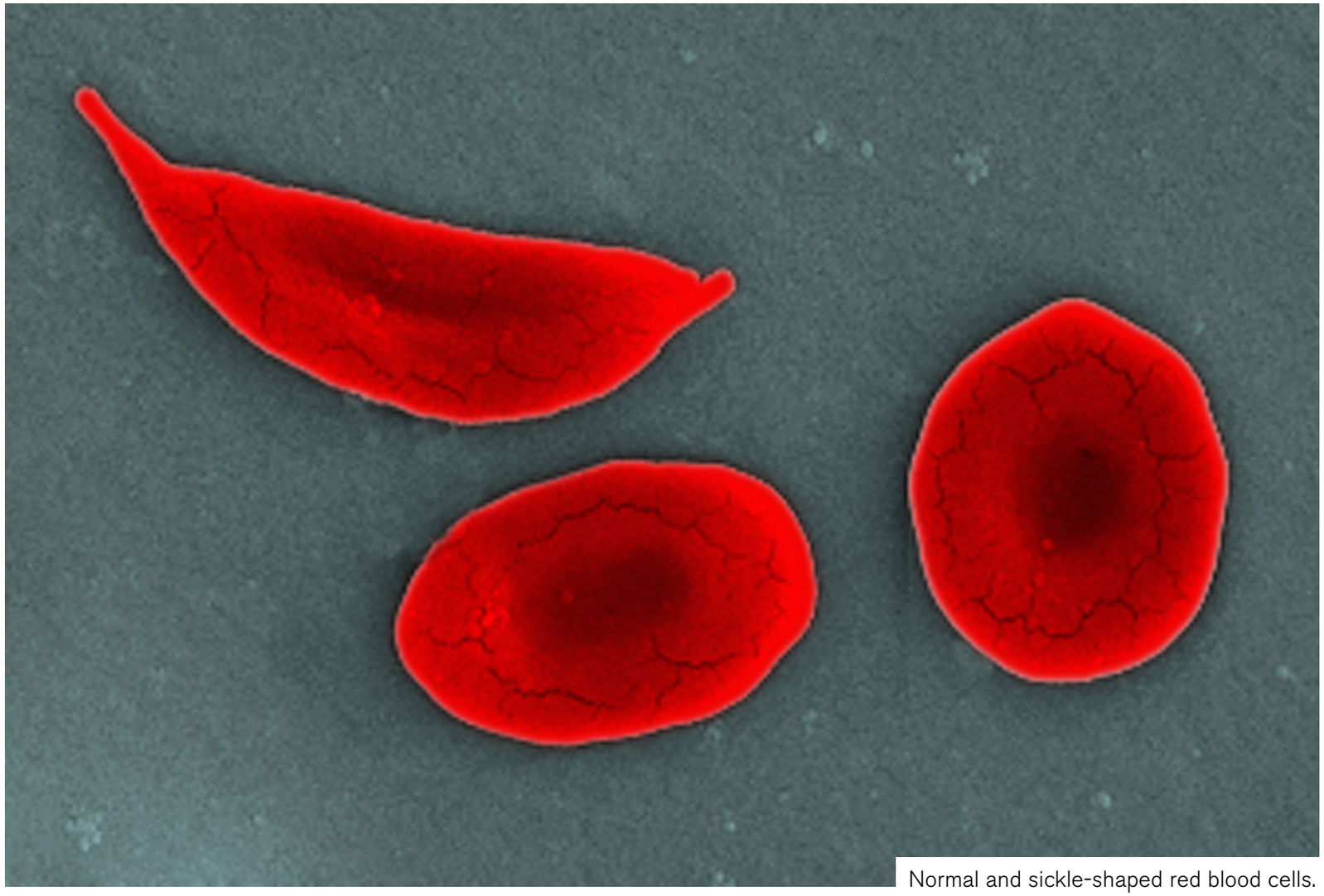
Carolyn Barber has been an emergency department physician for 25 years. She is co-founder of the homeless work program Wheels of Change and author of many articles and a new book, *Runaway Medicine: What You Don't Know May Kill You*, which was recently named an Amazon #1 Hot New Release in Health Care Administration.

GENETIC ENGINEERING

How Designer DNA Is Changing Medicine

A genomic revolution is poised to cure sickle cell and other genetic diseases



Normal and sickle-shaped red blood cells. Getty Images

For as long as he could remember, Razel Colón had known pain. It ripped down his neck and back, shot through his legs and traveled on to his feet, often leaving him writhing and incapacitated. He suffered occasional attacks of "acute chest," in which breathing suddenly becomes difficult. "It felt like an elephant was sitting on my chest, with tight, tight pain," Colón tells me. Trips to the emergency department and the hospital were commonplace. "If I was lucky," he says, "I could stay away for a month."

Colón, from Hoboken, N.J., is just 19, but the sickle cell disease that produced these effects had been a constant, if unwelcome, companion. But he tells his story now from the perspective of one who has gone a year and a half without that pain. He can do things that previously were out of the question: play basketball, lift weights, swim in cold water. His treatment, says his long-time physician Stacey Rifkin-Zenenberg, a pediatric hematologist-oncologist at Hackensack University Medical Center, "changed him from having the disease to being a carrier."

Colón's case represents a point on the curve of an emerging technology that may forever alter our approach to treating diseases like sickle cell. That world, the cutting-edge world of innovative genomic therapies, is once again in the midst of explosive change—and designer DNA lies at the heart of the conversation.

This is daring new territory. Some strategies, such as gene therapy, have been available for some time, including the ability to genetically modi-

fy cells to produce a therapeutic effect—that is, to add a corrected gene into the genome to try to treat disease. Traditionally viruses have been used to deliver healthy genes into cells, but the past decade has been witness to profound change. Multiple gene therapies have been approved to treat a variety of conditions: squamous cell skin cancer, a rare form of inherited blindness, melanoma, blood disorders, and so on.

It was this type of treatment, as part of the largest lentivirus ongoing gene therapy trial led by Bluebird Bio, that effectively arrested Colón's sickle cell condition. Unpublished interim data from 19 participants in the trial followed for at least six months, with a history of severe vaso-occlusive events (VOEs), or sickle cell crises similar to Colón's, demonstrated complete resolution of severe VOEs in all patients, according to a company spokesperson. The trial is ongoing, and data are not yet complete, so caution is prudent, but "the promise is tremendous," the spokesperson says.

The next-generation technology, gene editing, is another level altogether. Gene editing enables scientists to precisely target abnormal genes of many organisms (bacteria, plants, animals), snip the DNA, then remove, replace or add new DNA at the incision site. "Imagine you have a car with a flat tire," says Fyodor Urnov, a gene-editing expert at the University of California, Berkeley, and the Innovative Genomics Institute. "Gene therapy is taking a fifth wheel and putting it somewhere on the car and hoping it runs. Gene editing is repairing the flat."

The technology received a huge boost with the arrival in 2012 of a gene-editing tool called CRISPR, an acronym for clustered regularly interspaced short palindromic repeats. The CRISPR technology is easier to use, cheaper and more efficient than older genome-editing methods, enabling scientists to quickly alter DNA sequences to modify gene function. That could positively affect the health of the organism or even reverse disease symptoms.

"It is often described as 'molecular scissors,'" says Jennifer Doudna, its co-inventor and Nobel laureate in chemistry. "Scientists can harness CRISPR to not just cut specific locations in DNA of any organism but also to provide a template to repair the DNA."

In sickle cell disease, or SCD, a single mutation in the beta-hemoglobin gene leads to red blood cells that become crescent-shaped, or sickled. These sickled cells are sticky, and they clog arteries, preventing adequate oxygen delivery to tissues in the body. This can cause acute debilitating pain episodes, such as the kinds that Colón experienced, and may result in any number of complications: anemia, strokes and organ damage involving the lungs, heart, kidney or spleen.

Patients often have a poor quality of life because of repeated hospitalizations and transfusions and face the prospect of early deaths. In region ssuch as Africa and the Middle East where health-care resources are much more limited, many children die of SCD before their fifth year of life.

CRISPR is accelerating the pace at which treating such disease via genetic engineering is moving. Matthew Porteus, a gene-editing pioneer, founder of CRISPR Therapeutics and professor of pediatrics at the Stanford University School of Medicine, says researchers currently employ two primary gene-editing strategies in their attempt to cure sickle cell patients. One type uses CRISPR to essentially flip a genomic switch, turning on healthy fetal hemoglobin production again, which was shut down early in life. The advantage? The fetal hemoglobin doesn't sickle.

A second gene-editing strategy, gene correction, directly fixes the mutation in a faulty gene that has caused disease. In the case of sickle cell, the correction allows the body simply to produce normal hemoglobin. Researchers have logged a staggering amount of work trying to get to this point.

While progress has been made with the approval of several new drugs to help alleviate the symptoms of SCD, they are not curative. Bone marrow (stem cell) transplants are the only option for cure, but finding healthy donor matches can be challenging. Enter the genomic therapies, which Theodore Friedmann of the University of California, San Diego, first proposed for genetic disease in 1972, and which took a step toward reality the same year with the production of recombinant DNA by Paul Berg of Stanford. In the 1980s scientists showed how DNA could be delivered into cells, and by 2003 the entire human genome had been deciphered.

There were setbacks, and even when gene-editing systems came to be as the new century opened, using them remained challenging and time-consuming. Then came CRISPR, slicing and dicing its way into the clinical arena, poised to potentially change not only treatment but preven-

tion of disease. The technology is already being employed by scientists researching cancer, lymphoma, AIDS, cystic fibrosis, and more, for diagnostics, including SARS-CoV-2 detection, and even in agricultural efforts to engineer larger tomatoes, nonbrowning apples and longer-lasting mushrooms.

In real time, the hope is that genetic editing will provide a cure for a very common and debilitating inherited disease, sickle cell. Several experts with whom I spoke suggested, for the first time, that a cure for SCD may be in the offing.

That is an astounding thought. In practice, the ability to excise nonworking genes and replace them with normally functioning ones may help blunt the worst effects of a wide variety of diseases. When the 2020 Nobel Prize in Chemistry was awarded to Doudna and Emmanuelle Charpentier for their invention of this technology, the secretary-general of the Royal Swedish Academy of Sciences, Goran K. Hansson, put it plainly: "This year's prize is about rewriting the code of life."

And scientists are already working on next-gen CRISPR technology that's more precise. "Base editors," which correct single-letter DNA mutations without cutting the DNA double helix, have been shown recently to treat sickle cell disease in mice. And then there are "prime editors" which can replace even larger DNA snafus.

It's all pretty remarkable—and it's still early. "The field of genomic therapies for the hemoglobinopathies is not a zero-sum game," Urnov says. "I am convinced ultimately that there will be multiple approved medicines. There will be multiple gene therapy approvals, and there will be multiple gene-editing approvals."

Many questions remain, including the moral implications of how far a concept like gene editing might be taken, as well as cost, safety and accessibility (experts say current treatments can run to $2 million). Says Doudna, "A true cure means a treatment for everyone who needs it, which is why we're hard at work on the next generation of therapies to bring down the cost and make it more accessible." And because gene editing is not perfect, "the long-term safety of all the genetic modification therapies will have to be studied carefully," Porteus says.

In the coming months, a University of California Consortium (U.C. San Francisco, U.C. Berkeley and U.C.L.A.) will conduct the first human open label phase I–II trial using nonvirally delivered CRISPR technology developed at the Innovative Genomics Institute. Scientists hope to alleviate the suffering of sickle cell trial participants by substituting their faulty beta-globin gene—the one that causes the disease—with a corrected one, directly fixing the mutation in their blood stem cells.

"The more of the mutations that are corrected and propagated in healthy red blood cells, the more likely a cure is to follow," says Mark Walters, the trial's principal investigator and a professor of pediatrics at U.C. San Francisco. "Sickle cell disease will be cured using genomic therapies." That is the highest use of the technology, after all—and it may become a reality even as we continue to learn about the field.

Virginia Chang is a certified end-of-life doula and founder of Till The Last.

BEHAVIOR

How End-of-Life Doulas Help Ease the Final Transition

We are your personal advocate, cheerleader, companion, guide, ear, rock

Getty Images

Birth and death are the bookends of life, yet we welcome one and dread the other. Why is it that birth is celebrated, but death is taboo?

When a friend was expecting her first child, she needed additional support through her pregnancy, so she hired a birth doula. The idea of women helping other women during childbirth is not new. Since the beginning of time, women have labored and birthed at home, attended by a midwife and their female friends and kin. This camaraderie of women, once universal, was a way to provide birth support and also to pass on knowledge about pregnancy, childbirth and parenting.

The natural birth movement of the 1960s begged a return to this approach with women demanding unmedicated, less interventional births. Hence, the inception of the birth doula—a nonmedical caregiver who assisted pregnant women in the transition to motherhood.

Can the same idea apply to death? The evolution of death care has followed a similar trajectory to that of childbirth care. For most of human history, people were cared for and died at home, with corpses even displayed on the dining room table for mourning. This began to change in the mid-20th century as society saw great advancements in medical technology for diagno-

sis and treatment of illnesses. These developments moved health care away from the local doctor, who made house calls, to inpatient stays at hospitals. When people fell ill, they went to the hospital and eventually died there. In 1980 60.5 percent of people died in hospitals. This number peaked in the mid-1980s but has since steadily decreased in response to a growing movement for death to be less medicalized, less institutionalized and more natural. By 2016 half as many people (29.4 percent) were dying in hospitals, roughly equaling the number of people dying at home (30.5 percent). While this trend is encouraging, these numbers still do not reflect the fact that 71 percent of people would prefer to die at home.

I am a death doula or what is now more commonly termed an end-of-life doula. This role grew out of the increasing awareness of and desire for more humane and compassionate ways to die. Similar to birth doulas, end-of-life doulas are nonmedical professionals offering emotional, spiritual, informational and physical support—not at birth but at the other end of the spectrum of life—at death.

An elderly man with a terminal illness is afraid to die. He fears for the family he will leave behind—his wife, children and grandchildren—and how they will cope after he is gone. He has not expressed this fear to his doctors or to his wife, who is already handling so much. I listen. I hold space for his despair and angst. He realizes the fear is based on his immense love for his family. He drinks champagne with them on his deathbed. Reconciliation with the things that are important can allow one the peace to let go.

End-of-life doulas work with those with serious illnesses who are facing death—and also for those who are healthy and just want to prepare for death. On practical matters, doulas can advise on advance care directives, vigil planning and postdeath options, and assist with life review and legacy. On more emotional matters, doulas can facilitate conversations about unresolved issues or complex family dynamics and offer space for the fears and uncertainties around death and dying. When we are prepared for death, we are better able to face it when the time comes.

Despite her wish to die at home, an elderly woman is taken to the hospital by her son, who can no longer bear to watch his mother die in excruciating pain. The hospital wants to discharge her, finding nothing wrong, and, at her age, what can be done anyhow? The family is distressed by the hospital's response and calls me. I suggest that they ask for a palliative care consultation. Eventually the mother is placed on a proper pain management plan and discharged to hospice care. How do you know what to ask for, if you don't know the choices?

Palliative and hospice care are philosophies of care that focus on comfort and symptom management to alleviate pain and suffering. Both are available to persons with serious illnesses. While palliative care can be given concurrently with curative care, hospice is typically for those who no longer seek curative treatments.

End-of-life doulas advocate for the wishes and needs of the dying person. We work with the health-care team in ongoing care and coordinate with the support network of family and friends in place or help to establish a needed support system. We fill gaps in care and tackle tasks that are difficult to do or face. All the while, we can be a calming presence for loved ones and the dying person, especially for those who are facing death all alone.

A middle-aged man lies actively dying, completely nonresponsive, in his bed. He displays "death rattle" breathing, and his body has occasional violent spasms. At his bedside, a petite woman sits, his aunt, pained to watch her nephew die this way. After creating rapport with the aunt, I seek to allay her distress and encourage her to speak to him. The aunt responds gratefully, awakened to the possibility of making a difference for her nephew. He dies peacefully, immersed in soft light, music and love. Sometimes all a loved one needs is permission to be an active participant in the process, to turn helplessness into empowerment.

While death brings sadness and loss, there can also be positive emotions of love, honor and pride. It is possible to feel seemingly contradictory emotions all at the same time—because death is loss, and grief is the natural expression of love.

On the end-of-life journey, we doulas are your personal advocate, cheerleader, companion, guide, ear, rock—whatever you need us to be to face a difficult, intense and emotional time because no one who wants support at the end of life should have to go without.

Carolyn Barber has been an emergency department physician for 25 years. She is co-founder of the homeless work program Wheels of Change and author of many articles and a new book, *Runaway Medicine: What You Don't Know May Kill You*, which was recently named an Amazon #1 Hot New Release in Health Care Administration.

MENTAL HEALTH

Critical Care Doctors Are in Crisis

Who's caring for the ICU physicians?

Pitchayanan Kongkaew *Getty Images*

As a critical care physician, Kelli Mathew knew her days were spinning in the wrong direction. For one thing, her well of empathy was dry. When unvaccinated people came to her, suffering the effects of COVID, Mathew began snapping back. She had run out of comforting or even neutral things to say.

"In my mind, it was like, 'This is your doing. You chose not to get vaccinated and here you are,'" says Mathew, who works at Deaconess Henderson Hospital in Henderson, Ky. "I would say, 'You're probably going to die, and this could have been preventable—how sad is that?' I would walk away. And that's not who I am."

In the end, Mathew reached out for help, entering counseling to try to understand what had happened. Her doctor-patient relationships were crumbling in front of her, and she knew she was the reason why. "I've always been the most empathetic, compassionate person to a fault," she says. Clearly, something had changed.

For more than 18 months, critical care workers have been on the front lines of one of the worst medical crises in American history. The intensive care unit (ICU) death toll for COVID-19 patients is almost unimaginable: a mortality rate of approximately 35 percent, according to one meta-analysis. Nurses in the ICU have served, suffered devastating loss and ultimately left the profession in droves. We have read their stories of grief and pain.

Only now, in the long tail of COVID's run, are we beginning to understand the depth of the toll the pandemic has taken on the physicians on the front lines. Though hardly

surprising, the news is not good.

"ICU doctors are experiencing among the highest levels of stress, burnout and fatigue from COVID-19," says Greg Martin, president of the Society of Critical Care Medicine. "Perhaps more than any other specialty, they continue to experience the full brunt of COVID-19."

Over the course of recent weeks I've had conversations with many intensivists, mental health counselors and other health experts. The agreement is nearly unanimous: COVID is devastating some of our critical care physicians.

In a national survey of roughly 12,000 doctors, more than half of critical care physicians reported burnout. Staffing and personal protective equipment (PPE) shortages, the death toll, personal safety concerns, a feeling of inadequacy in providing emotional support to patients and their families—all contribute to a wave of difficulty that, deep into the summer of 2021, continues to build. The current surge in cases across the U.S. and the emergence of the Delta variant virtually assure that these scenarios will repeat, as ICUs again fill and, in some places, push beyond their normal capacities. "It really is a retraumatization," says James Jackson, a leading authority on depression and post-traumatic stress disorder at Vanderbilt University Medical Center.

"I have seen many ICU physicians with somewhat uncharacteristic outbursts, apathy and sloppiness in patient care that I haven't seen before," says Gabe Wardi, a critical care specialist at the University of California, San Diego, and two smaller facilities. "I think as doctors, and ICU doctors in particular, we pride ourselves on being able to handle any task or patient load. COVID was a reminder that we need to lean on others for our own mental health and patient care." Wardi struggled with the fear of carrying infection home to his pregnant wife and young child, and he felt guilt over the amount of time he was spending at the hospital. His medical school roommate, he says, only recently returned to work after a year away, driven from his job by the trauma of seeing so many COVID patients die in his ICU.

Neil Greenberg, lead author of a U.K. study and professor at King's College London, says that among those surveyed, ICU physicians confirmed "very high levels of post-traumatic stress symptoms, depression [and] anxiety, and some were also at risk of alcohol misuse." More than one in seven ICU staff reported thoughts of suicide or self-harm. (In the U.S., an estimated 300 to 400 physicians commit suicide every year, roughly double the rate of the general population.)

Experts say that from the outset of the pandemic, physicians have had to deal with vast amounts of uncertainty, which pierces their normal sense of control and level of assuredness about their practice. As a 25-year emergency department physician, I can attest to that craving for control of medical outcomes, along with a tendency toward perfectionism. We want to do our best by our patients. COVID, though, has resisted such certainty. "It's hit or miss," Mathew says. "Some people live and some people die, and you can't pick and choose."

For some professionals in critical care, part of the frustration is the notion that the worst of the damage is largely avoidable. In Kentucky's Henderson County, where Mathew works, only 36 percent of residents are fully vaccinated, along with about half the nurses at Deaconess (although the hospital will soon be requiring vaccinations of employees). "We're in the red zone," she says. "It's awful. I have a full ICU with only one code bed available."

Mona Masood runs the Physician Support Line; since the spring of 2020, volunteer psychiatrists have fielded more than 3,000 calls from physicians anonymously requesting mental health support. In the pandemic's early months, Masood says, ICU doctors were "up a creek without a paddle—that is, just doing whatever they could in order to survive." Among other things, the line's psychiatrists received calls about unprocessed grief, with some doctors saying they hadn't had time to work through losing, say, 20 patients in the course of a single week.

"The psychological toll has been immense and is ongoing," says Venktesh Ramnath, an ICU physician with U.C. San Diego Health. "Many health-care workers are still trying to process and heal from the experiences of the last year, and there are harbingers of a fourth wave in which there is fear that earlier experiences and mistakes may be repeated."

Physicians, especially intensivists, are trained to react in the moment and to push off emotional considerations for later. In the age of COVID, with its seemingly relentless waves of illness and death, that has proved impossible, in part be-

cause "later" never seems to arrive.

Erin Hall, a clinical health psychologist who has worked closely with the ICU teams at Geisinger Medical Center in Danville, Pa., has witnessed the trauma experienced by providers, often because obstacles beyond their control prevent them from delivering what they deem to be appropriate care. "Watching people die without family, with a stranger (usually a nurse) in the room just so the person was not alone—over time, this stuff does affect you," Hall says. "You can be the most resilient person and still struggle with taking some of this stuff home."

Mental health professionals are quick to separate terms. Burnout is certainly common, but for ICU clinicians and other health-care staff it is now increasingly being joined by moral injury, a sense that they are not able to provide the care they normally expect to.

Morally challenging decisions, like rationing care because of resource shortages, have placed mental and emotional strain on ICU physicians. "There were a number of young patients who died that would have had at least a fighting chance with ECMO [an oxygenation machine]," Wardi says. But that was not possible at some smaller, community-based facilities, and patient transfers were impeded by overcrowding at hospitals.

Physicians also are asked to deliver bad news to families, systemic barriers notwithstanding. They carry the sadness, blame and grief that is often directed at them from patients. Masood says the resulting thought for some doctors is, "'Maybe I am the one who messed this up. Maybe I am the one at fault." She describes this process as "death by a thousand paper cuts" for physicians' psyches.

There is a practical health-care aspect to this trauma. America faced a shortage of intensivists before the pandemic, especially in remote areas. Patricia Pittman, who runs the County Workforce Estimator, which tracks hospital labor deficits, says 198 counties in the U.S. are experiencing such shortfalls, requiring "crisis" levels of staffing. The pandemic "has exacerbated the issue," Martin says. In an international survey of 2,700 ICU providers worldwide, the reported shortage of intensivists in the U.S. was put at 12 percent.

We had a dysfunctional health-care system in the U.S. well before the pandemic, but with COVID the dike has broken wide open. The problems have been laid bare: inadequate staffing, inefficiencies, rising expenditures and the corporatization of medicine (with its ever escalating productivity asks, documentation requirements and relative value unit, or RVU, and metric expectations). All these factors are combining to depersonalize medicine and suck the soul out of many providers.

Change is needed now, not later, and my conversations produced several suggestions from experts. Making mental health resources more openly available to physicians is a must. Efforts to eliminate the stigma associated with doctors seeking help or admitting they are hurting—and, particularly, to remove mental health questions from state and hospital licensure applications—will open doors for all physicians to access much needed care.

We need health-care leaders willing to be vulnerable and open up about their own struggles—affirming that they are indeed anxious, taking antidepressants, seeing a therapist, and so on. These actions will help normalize the experience, giving other providers permission to be vulnerable. "Suddenly, we have all taken off our masks and communicated at a deeper level," Jackson says.

And dealing with the structural problems—hospital dysfunction, staffing shortages and failed leadership, to name a few—is critical. A Mayo Clinic study determined that the most effective strategies for alleviating physician burnout "will target organization-directed changes rather than the level of the individual," and that suggests the kind of broad-scale change the health industry often resists.

"It may be the question of the year for health care," Martin says. "How do we really support providers? Because it gets to the question of why are people leaving the profession—and clearly they are."

IF YOU NEED HELP

If you or someone you know is struggling or having thoughts of suicide, help is available. Call the National Suicide Prevention Lifeline at 1-800-273-8255 (TALK), use the online Lifeline Chat or contact the Crisis Text Line by texting TALK to 741741.

The Physician Support Line is a free and confidential service, staffed by volunteer psychiatrists, that offers support for physicians and U.S. medical students. For help, call 1-888-409-0141 between the hours of 8 A.M. and 1 A.M. ET.

Claire Pomeroy is an infectious disease physician and researcher and president of the Lasker Foundation, which is dedicated to advancing medical research. During her academic career, her research focused on HIV/AIDS.

PUBLIC HEALTH

A Tsunami of Disability Is Coming as a Result of "Long COVID"

We need to plan for a future where millions of survivors are chronically ill

Getty Images

Even as U.S. policy makers and business leaders seek to put the COVID pandemic in the rearview mirror with the help of highly effective vaccines, a fundamental policy and planning gap is looming. Many who survive the initial viral illness suffer debilitating long-term sequelae. Unlike the common cold or even influenza, this virus causes a bewildering array of symptoms that persist long after the acute illness is resolved and can render some affected unable to resume their usual activities. As scientists and clinicians continue to delineate the "long-haul" course of COVID, policy makers and planners must anticipate and prepare for the impact of this new cause of disability, including its implications for federal and private worker's compensation and disability insurance programs and support services.

Consider the numbers we know. At least 120 million Americans (and probably many more) have already contracted COVID. An increasing number of studies find that greater than one fourth of patients have developed some form of long COVID. (In one study from China, three quarters of patients had at least one ongoing symptom six months after hospital discharge, and in another report more than half of infected health-care workers had symptoms seven to eight months later.) Initial indications suggest that the likelihood of developing persistent symptoms may not be related to the severity of the initial illness; it is even conceivable that infections that were initially asymptomatic could later cause persistent problems.

Common long-term symptoms include fatigue; respiratory problems; "brain fog"; cardiac, renal and gastrointestinal issues; and loss of smell and

taste. Surprising manifestations continue to emerge, such as the recent realization that infection may precipitate diabetes.

For some, symptoms have now continued for many months with no apparent end in sight, with many survivors fearing that they will simply have to adjust to a "new normal." More and more sufferers have not been able to return to work, even months after their initial illness. While the number of patients with persistent illness remains undetermined this early in the pandemic, estimates suggest that millions of Americans may enter the ranks of the permanently disabled.

The related health-care and disability costs are also still unknowable. How many "long haulers" will never be able to return to work? How many will need short-term disability payments? How many will be permanently disabled and become dependent on disability programs? As increasing numbers of younger people become infected, will we see an entire generation of chronically ill? We must actively work to better understand the size and scope of the problem and begin planning now.

In addition to the personal suffering, long-term disability comes with a staggering price tag—including increased health-care costs; reduction or loss of employment; and economic strain on worker's compensation and disability support programs. It's been estimated that as much as 30 percent of the COVID health burden could arise from COVID-induced disability. As physician and University of Massachusetts medical professor Steven Martin recently told NPR, "If we end up with a million people with ongoing symptoms that are debilitating, that is a tremendous burden for each of these individuals but also for our healthcare system and our society."

Current U.S. disability programs appear ill-equipped to deal with this new stream of patients with chronic disability. Patients and employers alike can be overwhelmed by the inherent bureaucracy of the system, including worker's compensation, Social Security disability, and private disability insurance. For example, it is extremely difficult to pinpoint if workers contracted infection at their place of employment or in the community; limited access to testing means that many sufferers are unable to document their initial infection; and the Social Security Administration (SSA) requirements that the impairments must last or be expected to last at least 12 months and prevent "substantial, gainful" activity are daunting. But we cannot be short-sighted; barriers to disability support can exacerbate the severity of the medical problems and prolong the time in which patients are unable to return to their normal activities.

Here's what we need now:

Research to better understand disability inflicted by long COVID. Scientists are partnering with patient groups such as Survivor Corps to better define these syndromes. The National Institutes of Health has called for proposals supported by the $1.15 billion in funding provided by Congress. We need to prioritize health economics studies to determine the financial implications of disability associated with the virus.

Clinical services to manage long COVID. Clinics to care for "long haulers" are being opened but must be adequately staffed and funded. Both the CDC and AMA recently released guidelines for care. Coordinated collection of data on a national (and global) level will accelerate insights.

Worker's compensation programs and private disability insurance. A national consensus on criteria for qualifying for payments is key. Insurance plan administrators should use health economics research to prepare for future costs.

Federal disability programs. Analysis of the likely number of patients who will require short- and long-term disability payments and services should be at the front of the SSA's agenda, followed by modeling of the funding needed to support them. Requirements (including types of medical documentation and waiting periods) to qualify for aid also need to be reexamined.

It's understandable that we don't yet have all the issues related to COVID-associated disability figured out; we haven't fully grasped all the implications of this pernicious (and still somewhat mysterious) malady. After all, since early 2020, we've been struggling to address the immediate crisis and how to deal with the new problems that arise day by day. But the time has come to proactively plan for what will certainly be the enormous new impact that long-haul COVID will have on our disability programs.

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