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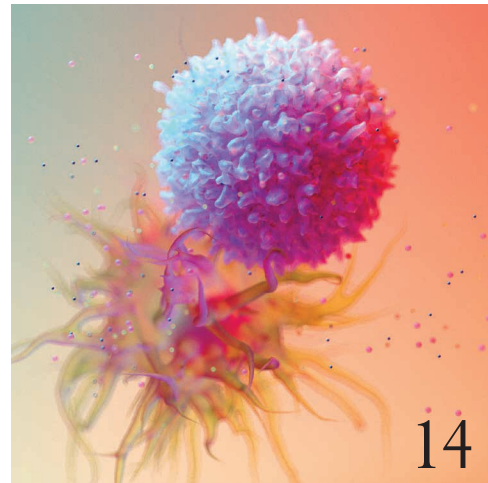
Sleep Science Awakens

Can our genes point the way
toward a better night's sleep?

UCSF

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San Francisco

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28 Why Can't I Sleep?

Too many of us spend our nights tossing and turning, and the resulting lack of sleep could harm our health. Now, researchers are seeing the promise of solutions in our genes.

14 Your Immune System Could Turn COVID-19 Deadly

Some people barely – or don't – survive the disease, while others walk away mostly unscathed. Could hidden autoimmunity help explain why?

34 Uniting the Black Community to Defeat COVID

Health-services researcher Kim Rhoads shares why a “for us, by us” approach is working.

22 Norway's Humane Approach to Prisons Can Work Here Too

Troubled by the health crisis plaguing the American correctional system, physician Brie Williams sought a solution. She found it in an unlikely place.

36 What's Wrong (and Right) with Race in Medicine

Six health care experts grapple with how to address race without being racist.



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8 Can Puzzles and Pills Make Us Sharper?

UCSF scientists share how best to protect the brain – and bust a few myths too.

42 Turns Out, Designing a Vaccine Was Easy

The hard part was everything that came next, says Moderna president and UCSF alum Stephen Hoge.

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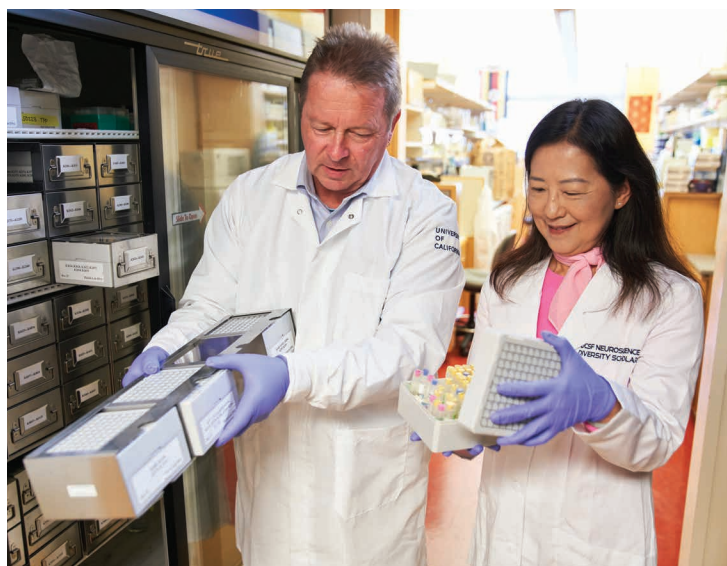
The Great Accelerator

COVID-19 has been called the great accelerator. It is speeding forces that existed before the novel coronavirus emerged, such as deepening economic inequality, and at the same time bringing new urgency, perspectives, and relevance to the work of UCSF scientists.

Take sleep, for example. The worries and upheaval that COVID has inflicted on our lives have disrupted our sleep, something already in short supply in our frenetic culture. UCSF experts say lack of sleep is a major health crisis, given how crucial restorative rest is for our health. This issue's cover story explores their research into the genetic underpinnings of sleep, insights we need more than ever.

COVID has also amplified the national conversation on race and racism, intensifying a long-standing debate in medicine: What is the role of race in clinical research and care? *UCSF Magazine* convened a panel of faculty members to grapple with this complex and challenging question. As you will see from their provocative discussion, there are no easy answers. But the panelists all share the same goal: health equity.

Health equity is also at the heart of a remarkable UCSF program that has gained fresh relevance during the pandemic. When the coronavirus swept through a number of prisons, it opened many eyes to the alarming state of health in America's correctional facilities. Since 2015, UCSF physician Brie Williams and her team have been working to improve the health of incarcerated people and correctional officers. Read about what inspired this work and why it is succeeding.



Pioneering UCSF sleep research collaborators Louis Ptáček, MD, and Ying-Hui Fu, PhD, have discovered several genes that lead to short, hyper-efficient sleep. Their findings are helping decode how sleep is regulated.

COVID is supercharging positive forces as well, like innovation and creativity in basic science. Researchers across UCSF are striving to crack one of COVID's most perplexing mysteries: why it makes some people deathly ill but not others. Their insights are sparking entirely new questions about how the immune system functions, with implications beyond COVID. The story in this issue about their work takes a deep dive into their findings.

I am proud of the tremendous efforts the UCSF community continues to make toward taming COVID and tackling the pandemic's fallout. We will persist with this quest for as long as it takes.

Sam Hawgood, MBBS
Chancellor
Arthur and Toni Rembe Rock Distinguished Professor

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PHOTO: STEVE BABULAK

Five Questions for UC's New President

UCSF-trained Michael Drake – MD '75, residency, and fellowship – became the 21st president of the University of California in August 2020. An ophthalmologist, he also spent 25 years on the faculty of the School of Medicine.

Your top three priorities?

First is focusing on what we can do to keep the University moving forward during COVID. I'm also very concerned about racial equity and social justice in the country and in the world. And then we need to think broadly about the financial viability of the entire enterprise.

What guides your leadership?

When you're a leader, you're out front. You often don't know what path you're supposed to take. And so I've always tried to be clear about my personal values and make values-based decisions. That's the advice I gave to my sons as they were growing up: "When you don't know what to do, step back and ask, 'What's the right thing to do, what matters to me, and why?'"

Favorite piece of advice from a UCSF mentor?

My dear friend Holly Smith, the late UCSF chair of medicine, said to me once, "Remember that the difference between A and A-plus is huge." Doing our very best is always critical.

Is remote learning here to stay?

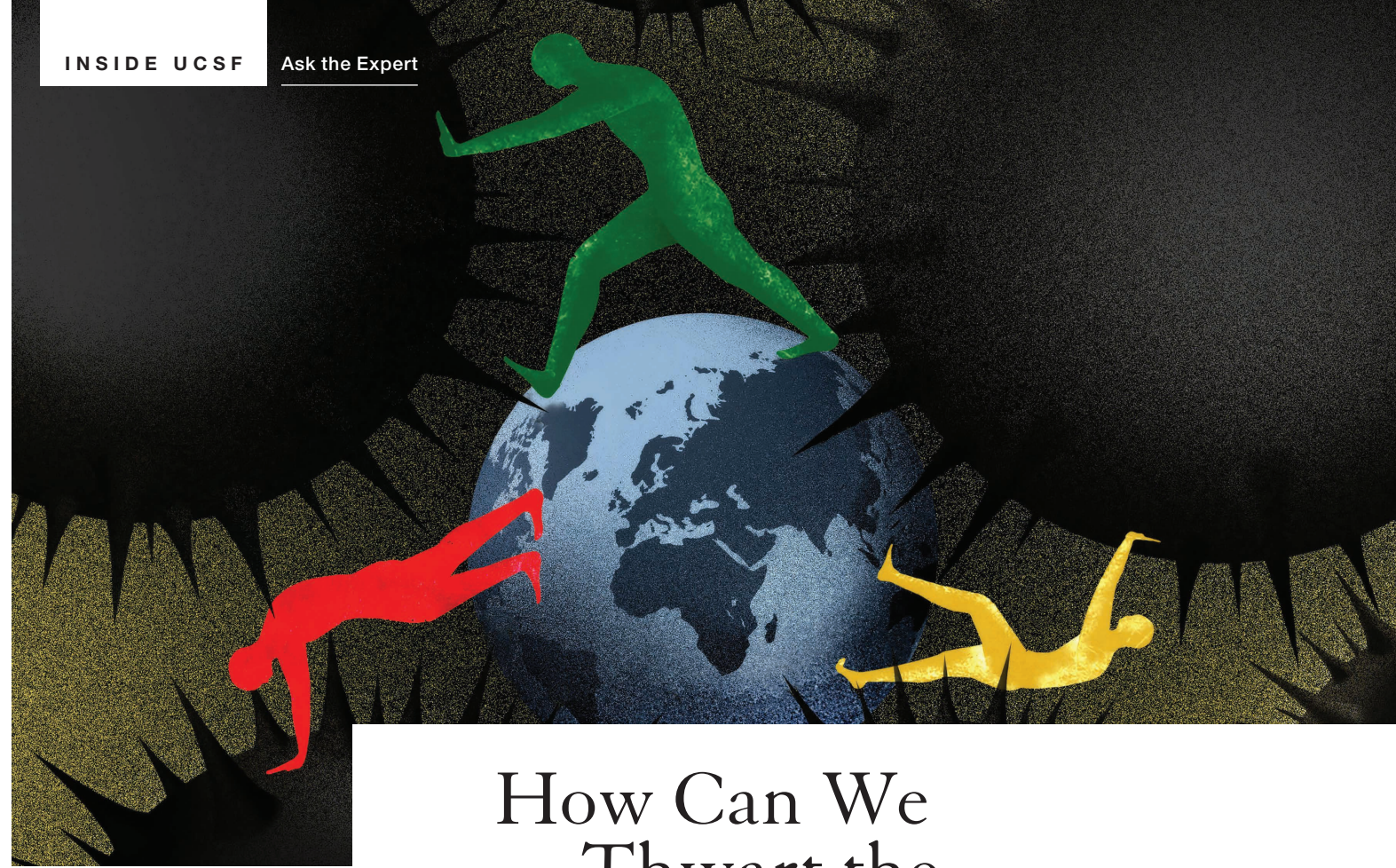
We had to move thousands of courses online on each campus within a week or two. In some areas, tele-education has been as good as, or maybe even better than, in-person learning. From here on, combining traditional methods of instruction with virtual instruction will give students more options to master the curriculum.

You're interested in tele-mental health. Why?

We have a real issue: All our campuses are struggling with providing the appropriate level of mental health services for our students. I hope that tele-mental health will offer additional ways that we can reach out and support people at those particularly important times of need.

Fun fact: Michael Drake is a member of the board of directors of the Rock & Roll Hall of Fame.

PHOTO: ELENA ZHUKOVA



How Can We Thwart the Next Pandemic?

Leading scientists share some of the tools and strategies that could help us better confront and contain future outbreaks.

Harness the gene-editing tool CRISPR to develop rapid, inexpensive testing

One of the interesting things about CRISPR is that in nature, it works as a surveillance system. It's a way that bacteria monitor themselves in their environment for viruses in real time and acquire new immunity. I think using CRISPR in a diagnostic capacity for human viruses is very exciting. We now have three different CRISPR-based chemistries that are supporting viral detection. The goal is to develop a simple saliva test that would allow people to monitor their own health – for example, in their workplace or dormitory. That's likely to happen.

┌ **Jennifer Doudna, PhD**, professor of biochemistry and molecular biology at UC Berkeley, president of the UC Berkeley-UCSF Innovative Genomics Institute, and co-winner of the 2020 Nobel Prize in Chemistry

Keep an eye on coronaviruses

No one has a crystal ball to predict the next big threat, but we need to look back at history. Coronaviruses have been a red flag for some time. I worked on the first SARS pandemic, in 2003. That strongly hinted at the potential of coronaviruses to cause global pandemics, and that bats are a likely source. Then there was MERS, which only reinforced the pandemic potential of this family. Certainly the writing's on the wall for coronaviruses.

┌ **Joe DeRisi, PhD**, Gordon M. Tomkins Professor and co-president of the Chan Zuckerberg Biohub

Create early warnings for new viruses

It will be necessary to establish a network of gene sequencing stations around the world. They would report out on new and emerging viruses in real time, especially in low- and middle-income countries, so they can be analyzed by the scientific community as a whole and shared with global public health officials. This is totally within our grasp and is a concept we were working on at the Biohub even before COVID. The larger philosophical and practical question is whether the global community would be willing to pay for it. ┌ **Joe DeRisi**

ILLUSTRATION: BRIAN STAUFFER

Hone a vaccine strategy

Vaccines and the immune response are pretty specific. We need to develop a vaccine strategy that can be implemented quickly, but probably not too far in advance. It could be tightly coupled with a surveillance system. Let's say we see a signal coming from a gene sequencing station somewhere, and we see there's community spread of this pathogen, probably by respiratory transmission. That should trigger a series of well-planned events so that a vaccine can be designed and implemented even more quickly than it was for SARS-CoV-2.

┌ **Joel Ernst, MD**, professor of medicine and chief of the Division of Experimental Medicine

Expect airborne transmission

We don't know what the next viral outbreak is going to be, but we can predict how it's going to travel: by the airborne route. SARS-CoV-2 is massively successful because it is so readily transmitted. SARS1 and MERS aren't that efficiently transmitted between human beings. An infection that's transmitted by the respiratory route is the best way for a pathogen to get around the world rapidly. ┌ **Joel Ernst**

Consider pandemics a security threat

COVID's threat to society and the economy is on the level of a terrorist or security threat. It's one that goes across the societal touchstones. Security threats also prompt a different management approach in the White House and the State Department. A decision to put pandemics in a security context brings an entirely different group of people to each meeting. You have the ability to have the military understand and be part of your deployment cache. Designating pandemics a security threat also bumps up the budget and the rapid response capability.

┌ **Eric Goosby, MD '78**, professor of medicine, MacArthur Foundation Professor of Global Health Sciences, and UN Special Envoy on Tuberculosis

Ditch a one-size-fits-all approach to treating viruses

We learned from COVID that where people are in the disease stage should inform how we treat them. If you want an antiviral to work best, for example, you've got to give it to patients as soon as possible after infection and diagnosis. Antivirals may help later in disease, but it is clear they are most impactful when given early. We also need oral antivirals that would facilitate rapid treatment and a true test-and-treat approach, potentially breaking the cycle of transmission. On the flip side, when people become more seriously ill from COVID and require oxygen, this is when they benefit from systemic anti-inflammatories like steroids. If we give these to people who don't need oxygen, they may cause harm. We had to recognize this isn't a one-size-fits-all situation.

┌ **Annie Luetkemeyer, MD**, professor of medicine and of infectious diseases

Think beyond vaccines

Instead of targeting the virus, what if we could target the machines in our body that the virus hijacks to cause infections? There's been a large effort both here at UCSF and at many other institutions to map out how SARS-CoV-2 or other viruses commandeer human cells to replicate and cause disease. If there are common systems in our body that many viruses hijack, you could target those systems specifically in an infection. Those would be good solutions for SARS-CoV-2 but also for other viruses. We could have them stockpiled and ready to go for a new pandemic.

One other broad idea is to use laboratory-produced antibodies that neutralize many types of viruses, which we could give to people to target infections. This approach could be effective with the very early stages of infection, or perhaps even as preventives.

┌ **Aashish Manglik, MD, PhD**, assistant professor of pharmaceutical chemistry

PLUS: Five Pandemic Silver Linings

Telehealth can be surprisingly intimate

It's like a home visit, where you can see baby and mom and grandmother, all at the same time. That has helped us build resilience.

┌ **Dayna Long, MD**, co-director of community health and engagement, UCSF Benioff Children's Hospitals

Clinical trials can be launched and run quickly

We've seen barriers fall that we'd been trying to break down for years. I don't think any of it has been shortcutting safety or good science. ┌ **Jennifer Doudna**

Silicon Valley better understands telehealth

Companies now get that we need digital health devices that you don't have to be an internet genius to use.

┌ **Robert Wachter, MD**, Holly Smith Distinguished Professor of Science and Medicine, Lynne and Marc Benioff Professor of Hospital Medicine, and chair of the Department of Medicine

Technology from the past decade is paying off

It took years to figure out that HIV caused AIDS. With today's genomic technology, we can sequence and identify the genomes of viruses, even those that are totally novel, in a matter of days. ┌ **Joe DeRisi**

Some intractable diseases could finally fall

Now may be the time to think about applying new vaccine design technologies, like mRNA, to diseases like malaria, tuberculosis, Chagas, syphilis, and many others that have lacked vaccines for so long. ┌ **Joe DeRisi**

Can Zapping Our Brains Cure Depression?

In June 2020, UCSF researchers implanted a device roughly the size of a pack of gum under the skull of a 36-year-old woman to treat her severe depression. The device, known as a neuromodulator, connects to tiny electrode-studded wires leading to personalized target spots deep inside her brain. The researchers programmed the device to detect patterns of brain activity that induce depression and, in response, to deliver mild, undetectable electric shocks to counteract the activity in real time.

The woman reported that while using the device, her symptoms – which had made it

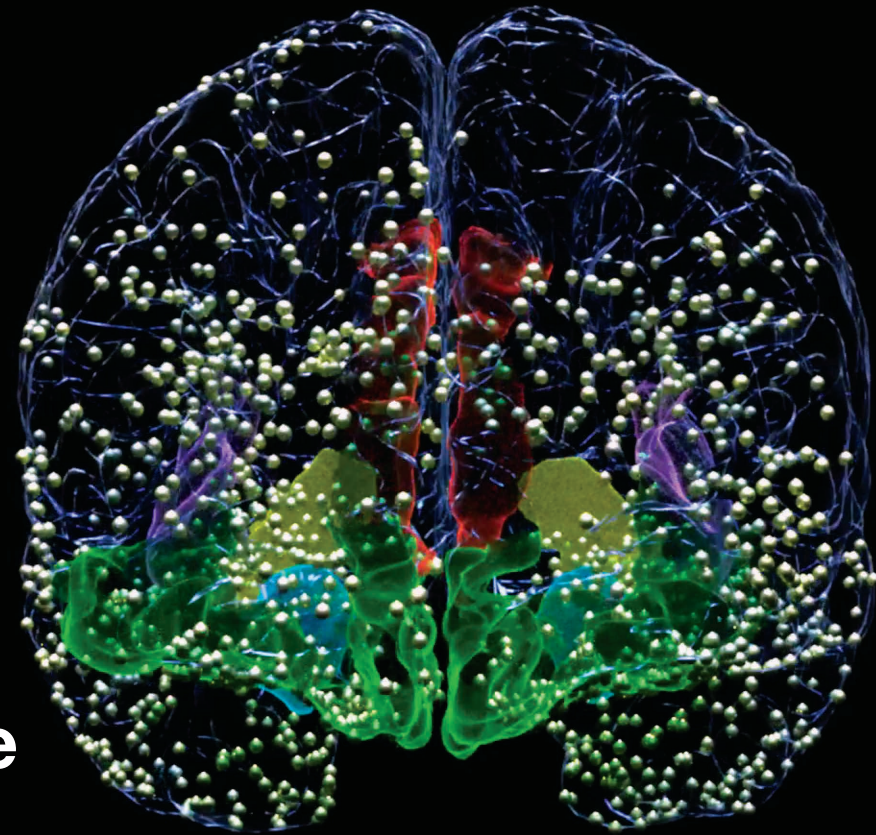
impossible for her to hold a job or even drive – had almost completely vanished. “For the first time in a long time, I feel like I can bob back up again,” she said.

This case study, which was published in January in *Nature Medicine*, lays the groundwork for a five-year clinical trial that will evaluate the effectiveness of personalized neuromodulation in 12 patients with severe treatment-resistant depression. As many as 30% of patients with depression, which afflicts up to 264 million people worldwide, do not respond to standard treatments such as

medication or psychotherapy.

“The brain, like the heart, is an electrical organ,” says Katherine Scangos, MD, PhD, an assistant professor of psychiatry and behavioral sciences, who is leading the trial. “There is a growing acceptance in the field that the faulty brain networks that cause depression could be shifted into a healthier state by targeted stimulation.”

Researchers map neural activity at various electrode-recording sites in the brain to zero in on the regions linked to depression.



Is this One Protein Responsible for Weight Gain?



As obesity has soared worldwide – nearly tripling over the last 50 years – scientists have striven to better understand the condition at the molecular level. Now, new research led by UCSF investigators suggests that a single protein could play an outsized role in weight gain.

Davide Ruggero, PhD, and colleagues studied mice in whom the activity of a protein called eIF4E

is diminished, either genetically or pharmaceutically. They found the modified mice gained only half the weight of unmodified mice, even though they all ate a high-fat diet. “These mice were basically protected from weight gain,” says senior author Ruggero, the Helen Diller Family Professor of Basic Research in Urologic Cancer, “and their livers were more healthy and

not full of fat droplets.”

Obesity is a risk factor for cancer, among other diseases, so the findings provide an intriguing new perspective on this link, Ruggero says. He also wants to study whether this protein can prevent or treat nonalcoholic fatty liver disease, a severe form of liver damage caused by obesity, which may lead to liver cancer.

ANIMATION STILL: CHANG LABBEN SPEIDEL

First Human Trial of CRISPR-based Cure for Sickle Cell Disease

In 2014, two years after her Nobel Prize-winning invention of CRISPR-Cas9 genome editing, Jennifer Doudna, PhD, thought the technology was mature enough to tackle a cure for a devastating hereditary disorder. Sickle cell disease afflicts millions of people around the world, most of them of African descent; some 100,000 Black people in the U.S. suffer from it.

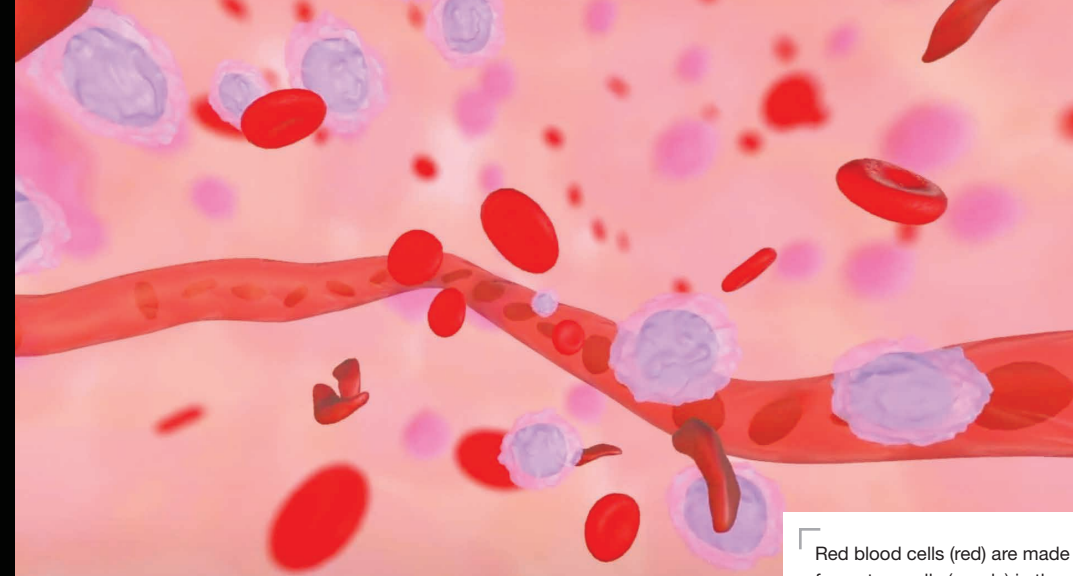
Doudna and her colleagues in the then-new Innovative Genomics Institute (IGI) – a research collaboration between UCSF and UC Berkeley, where Doudna is a professor – sought to repair the single mutation that causes the disease. It makes red blood cells warp and clog arteries, causing excruciating pain and often death. Treatment typically involves regular transfusions, though bone marrow transplants can cure those able to find a matched donor.

After six years of work, the IGI’s experimental treatment was recently approved for a clinical trial by the U.S. Food and Drug Administration. It will be the first test in humans of a CRISPR-based therapy to directly correct the mutation in the beta-globin gene that’s responsible for sickle cell disease. Beta-globin is one of the proteins in the hemoglobin complex responsible for carrying oxygen throughout the body. The goal of the treatment is to create normal, adult red blood cells and cure the disorder.

The trial will be led by physicians at UCSF Benioff Children’s Hospital Oakland and UCLA’s Broad Stem Cell Research Center and will begin this summer.

“This therapy has the potential to transform sickle cell disease care by producing an accessible, curative treatment that is safer than the current therapy of stem cell transplant from a bone marrow donor,” says Mark Walters, MD, a professor of pediatrics at UCSF and principal investigator of the clinical trial and the gene editing project. “If this is successfully applied in young patients, it has the potential to prevent irreversible complications of the disease.”

Red blood cells (red) are made from stem cells (purple) in the bone marrow. Sickle cell disease is caused by a mutation in the beta-globin gene that makes red blood cells warp from a circular into a sickle shape. The sickled cells clog arteries, leading to intense pain and organ damage.



Recommended: Books, Videos, & Podcasts



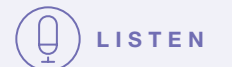
Infiltrating Healthcare: How Marketing Works Underground to Influence Nurses

UCSF School of Nursing alum Quinn Grundy, PhD '15, RN, shines a light on how sales reps from pharmaceutical and other health care companies skirt scrutiny, and get their products used in hospitals and doctors' offices, by forging relationships with nurses.



TED Talk: “Can We Create Vaccines that Mutate and Spread?”

The viruses that cause polio and COVID-19 mutate, but treatments for the diseases don't. For over 20 years, UCSF and Gladstone Institutes scientist Leor Weinberger, PhD, has been thinking of ways to make vaccines work more efficiently by being adaptive, rather than static.



Podcast: “Science is Fun!”

Can dieting help you live longer? Do microbes control your immune system? Can studying snakes help stop the next pandemic? UCSF microbiologist Peter Turnbaugh, PhD, interviews famous scientists and rising stars about research quests that span the spectrum of health.

Brain Boosters: Can Puzzles and Pills Make Us Sharper?

Games and supplements claim to strengthen memory and cognition. Should you buy them?

By Elizabeth Daube

Afraid of Alzheimer's? You're not alone. There's even a name for such anxiety: athazagoraphobia, the fear of forgetting (or of being forgotten).

Arguably, it's an existential problem. But it's also a matter of how well our brains are working. Companies have cashed in on our desire to manipulate the latter, selling online games and pills that claim to reverse cognitive decline or improve focus and memory. Brain-health supplements alone are projected to reach \$5.8 billion in sales by 2023.

But do they work? We asked UCSF researchers to help us understand how best to protect the brain.

MYTH # 1: Puzzles and pills are the best way to stay sharp and avoid Alzheimer's and the like.

Let's start with the bad news! Companies selling over-the-counter solutions for memory and thinking problems don't necessarily have strong scientific data behind their claims.

"Some people will listen to anyone who's giving definitive answers because doctors aren't able to yet," says Joanna Hellmuth, MD, an assistant professor of neurology who's written about the lack of good data behind popular protocols that supposedly delay or stop dementia. "I got into this because of my patients. Some are vulnerable and worried. You see people spend thousands of dollars on interventions that aren't data-driven or effective, which diverts resources from things that could help them."

The good news? Evidence-based ways to reduce your risk of developing dementia do exist, and some are free. Hellmuth's top recommendation is three hours of cardiovascular exercise a week. Anything that benefits your heart can also protect your brain, from eating a healthy diet to keeping your blood pressure under control. And it's not a bad idea to get your B-12 level checked. This vitamin is crucial for your nerves and neurons. Also, get



A FEW TIPS:

- ▶ Exercise three hours per week
- ▶ Eat a healthy diet
- ▶ Get your B-12 levels checked
- ▶ Get enough sleep
- ▶ Stay cognitively active



enough sleep! Read how sleep influences brain health on page 28.

People who stay cognitively active are also less likely to get dementia. This just means trying new activities, whether it's a work-related challenge or a hobby, like learning a new language. Games can fall into this category. In fact, UCSF researchers are investigating whether video games can improve memory in people with mild cognitive impairment. But games are not necessarily better for your brain health than, say, joining a book club. (Social connections can help protect cognition too.)

"You want to use it, or you'll lose it," Hellmuth says. "Forming new connections in your brain provides more resilience over time. If you want to pay to do an online game, great. But free activities are just as good, and it's important that you don't hate the activity."

MYTH # 2: Cognition problems always lead to terrifying outcomes.

It's true that most common causes of changes in thinking and memory, including Alzheimer's, have no cures yet. But there's a broad spectrum of cognitive dysfunction. Having a few symptoms doesn't mean you're doomed to experience your worst-case scenario. And some causes of cognitive impairment, including alcohol and drug abuse, can be treated.

ILLUSTRATION: FARAH HAMADE

That said, if you're worried about yourself or a loved one, that's normal. You don't need to feel bad about feeling bad.

"There's a lot of shame and fear around cognitive disorders," says Hellmuth. "We think of neurodegenerative diseases like Alzheimer's a bit like cancer before cancer had treatments. It was this big scary thing that people didn't want to talk about."

"Our brains allow us to be who we are. And when our brains aren't working well, we think that we are personally failing."

If you have neurological symptoms that are disrupting your life now, Hellmuth recommends getting a medical assessment. If you're fretting over what might happen to your brain in the future, focus on what you can control. Remember those prevention tips? Try some. They can even improve thinking and memory for people who already have cognitive disorders.

MYTH # 3: There's no hope.

False. The brain has been difficult to study, yes. It's complex – it contains some 86 billion neurons – and surrounded by bone. But scientists are making progress.

That includes researchers at the UCSF Weill Institute for Neurosciences, who have created a potential blood test for Alzheimer's, identified a protein that could boost brain function, and much more. For example, UCSF recently shared promising findings about ISRIB, a drug that has restored memory in mice months after a traumatic brain injury (TBI). It's even enhanced cognition in healthy mice.

Neuroscientist Susanna Rosi, PhD, a Lewis and Ruth Cozen Professor at UCSF, says clinical trials of ISRIB for patients with TBI and amyotrophic lateral sclerosis (ALS) could launch in the next year. But until we know more about its safety and efficacy in humans, Rosi urges patience. She's already received hundreds of inquiries from people clamoring for the drug.

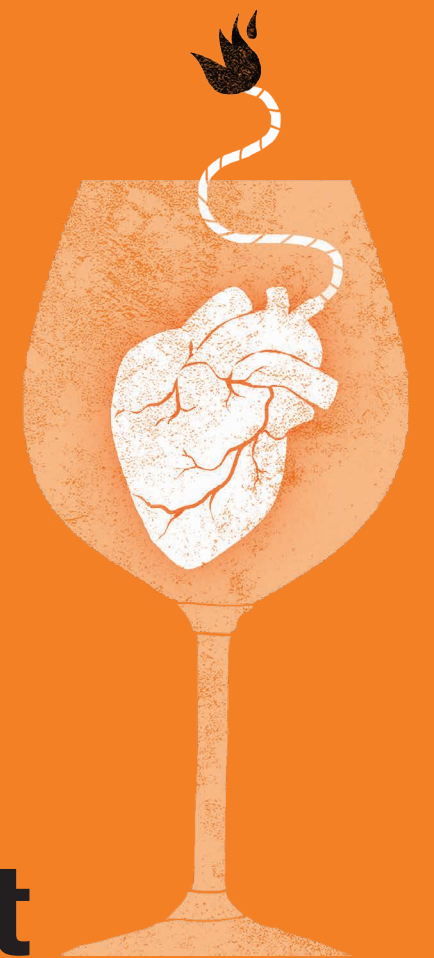
"There was one woman in Italy who said, 'I saw that you can buy ISRIB on the black market,'" Rosi says. "Don't do that. Please."

ISRIB seems to reboot the brain's ability to produce proteins after the brain's integrated stress response has derailed it. A prolonged stress response seems to be a hallmark of aging, and it has been linked to ALS, Alzheimer's, Parkinson's, and other neurological diseases.

"It's a paradigm shift. Each of those conditions has always been historically seen as independent from each other, but they might share a common pathway," says Rosi. "This is the most exciting thing that I have ever seen in my career."

ILLUSTRATION: AGENT ILLUSTRATEUR

Your Heart on Alcohol



If you have atrial fibrillation, alcohol – even a small amount – can immediately trigger an irregular heart rhythm, according to new UCSF research.

In a randomized, double-blinded clinical study, considered the "gold standard" in research, 100 patients diagnosed with atrial fibrillation, the most common life-threatening heart rhythm disorder, received either an infusion of alcohol or a placebo infusion. The patients administered alcohol were given enough to bring their blood alcohol level to .08%, the legal limit for intoxication in the United States. The alcohol appeared to immediately affect the heart's natural recovery period in a way that could trigger an atrial fibrillation episode.

"Ours is the first study to point to a mechanism through which a lifestyle factor can acutely change the electrical properties of the heart to increase the chance of an arrhythmia," says study author Gregory Marcus, MD, UCSF's Professor of Atrial Fibrillation Research and associate chief of cardiology for research.

Breakthroughs and Other Buzz

Rough youth, early aging: Women who experienced childhood trauma are biologically older in adulthood than women of the same age who did not suffer adversity, according to a UCSF study. The trauma appears to age immune cells more rapidly.

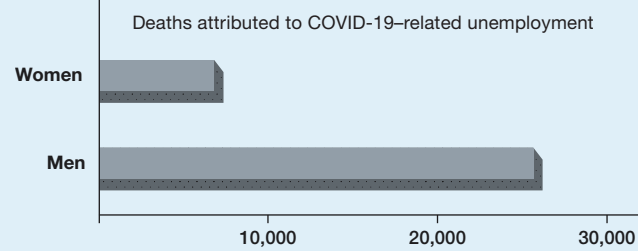
Cancer drug vs. COVID: A drug normally used to treat multiple myeloma, Aplidin, could be a powerful tool for treating patients with COVID-19, report scientists at UCSF and the Icahn School of Medicine at Mount Sinai.



Safer flying: A new computer simulation by UCSF researchers suggests that rapid COVID tests at the airport and shorter quarantines – just five days post-travel – could be enough to stop most infections from spreading. The study offers much-needed data to airlines and states.

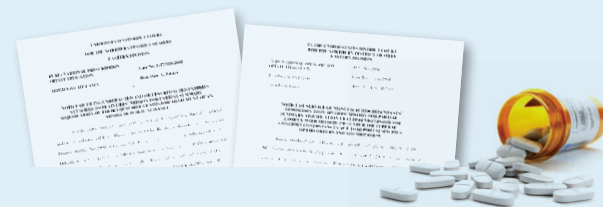
Nurses bolster mental health: The UCSF School of Nursing, in partnership with the UC Davis and UCLA nursing schools, has launched a new initiative to help address the dire shortage of mental health care providers in California.

Game-changer for prostate cancer: UCSF and UCLA obtained approval from the FDA to offer a new imaging technique called prostate-specific membrane antigen PET imaging, which is highly effective in detecting prostate cancer, even if it has spread elsewhere in the body.



COVID's indirect toll: Under any circumstances, job losses can lead to excess deaths from suicide, substance abuse, and the loss of access to medical care. Unemployment has soared during the pandemic, and UCSF researchers estimate that over 30,000 people in the U.S. may have died as a result – adding to the nearly 600,000 deaths directly attributed to the virus. Such deaths took a disproportionate toll on Black people, men, and older people and especially on those with the least education, their study indicates.

Can a mouthwash help contain COVID? Dentistry faculty from UCSF are leading a clinical trial to determine whether using an oral rinse can reduce coronavirus levels in saliva. The research holds promise for helping infected individuals potentially reduce their risk of spreading the virus.



Big opioid reveal: UCSF and Johns Hopkins recently released a trove of documents culled from legal rulings, settlements, and ongoing lawsuits related to the nation's opioid crisis, which has resulted in nearly 500,000 deaths. The archive is free and open to the public.

Where there's (not) smoke: Most parents suspect when their kid smokes, but they are much more likely to be in the dark when their child vapes or uses other tobacco products, according to a national UCSF-led study. The researchers also found that when parents set strict household rules against using tobacco, their children are less likely to start tobacco use.

Operation opera: UCSF and the San Francisco Opera have teamed up to make a mask designed to keep singers safe when they belt out arias on the live stage. UCSF's Sanziana Roman, MD, a classically trained soprano turned thyroid surgeon, created the prototype.

What are these chemicals in our blood? A UCSF study of the blood of pregnant women detected 109 chemicals, including 55 never before reported in people and 42 "mystery chemicals." The chemical industry should be required to standardize its reporting of chemical compounds and uses, say the researchers.

Strong heart, sharp mind: A healthy lifestyle in your 20s could protect your brain decades later. UCSF researchers found that high body mass index, high blood glucose levels, and hypertension – risk factors linked to an unhealthy diet, smoking, and a sedentary lifestyle – in early adulthood were associated with a doubling of the incidence of cognitive decline that individuals experienced later in life.

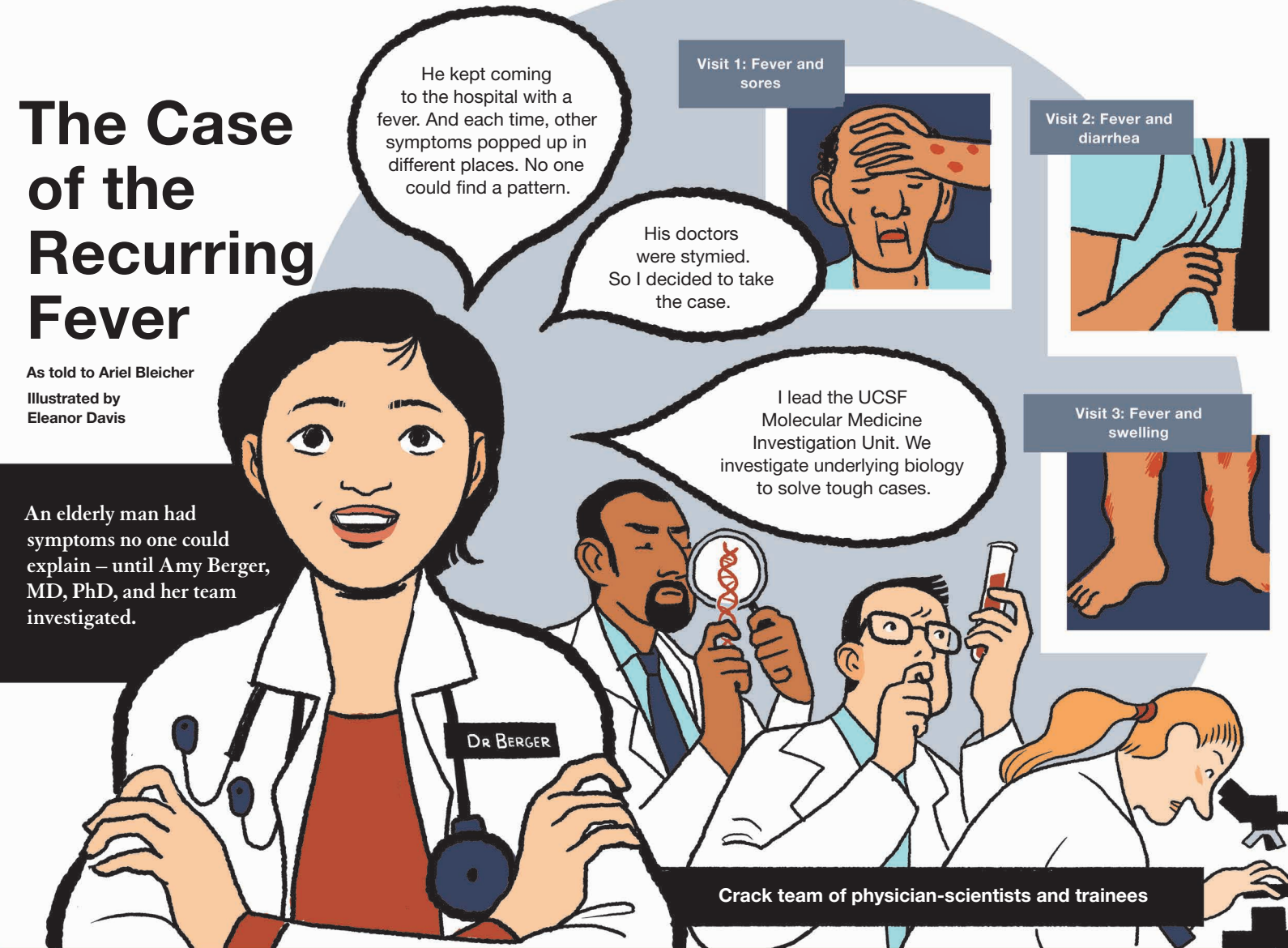
Alzheimer's breakthrough: A UCSF team of molecular biologists and neuropathologists identified the neurons that are among the first victims of Alzheimer's, as they accumulate toxic "tangles" and die off earlier than neighboring cells. The findings could lead to targeted treatments to boost the brain's resilience.

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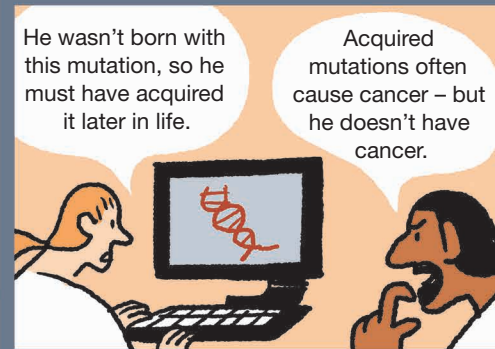
The Case of the Recurring Fever

As told to Ariel Bleicher
Illustrated by Eleanor Davis

An elderly man had symptoms no one could explain – until Amy Berger, MD, PhD, and her team investigated.



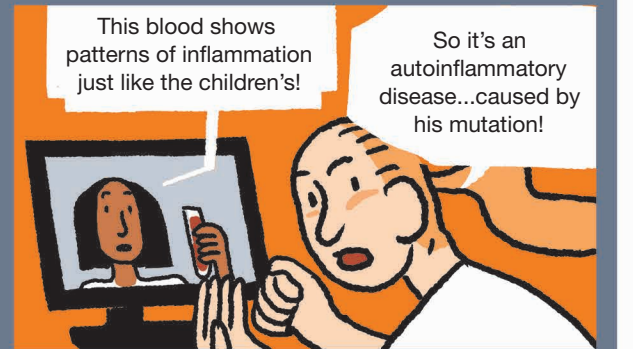
Clue #1: Testing had revealed a blood-cell mutation.



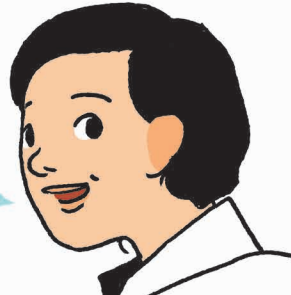
We dove into the scientific literature and found clue #2.



We sent the researcher who wrote the report some of the man's blood.



Now we're studying the man's cells to better understand what went wrong. There may be more patients like him who are searching for answers.





By fall 2020, Cronutt was one very sick sea lion.

The 7-year-old pinniped was disoriented, experiencing increasingly severe seizures (similar to those of a human with epilepsy), and rapidly losing weight because he had stopped eating. Scores of marine mammals along the West Coast suffer this way every year, poisoned by toxins from algae blooms. More than half of them die as a result.

With Cronutt facing “humane euthanasia,” veterinarians Claire Simeone and Shawn Johnson at Six Flags Discovery Kingdom in Vallejo, Calif. – who had adopted him after he was rescued by the Marine Mammal Center in Sausalito – turned to Scott Baraban, PhD, UCSF’s William K. Bowes Jr. Professor of Neuroscience Research. Baraban had pioneered the transplantation of embryonic brain cells

PHOTO: SHAWN JOHNSON



PHOTO: DIANNE CAMERON

into epileptic mice, inhibiting seizures in the rodents and restoring their diminished cognitive and physical capabilities.

Baraban didn’t know if Cronutt could survive such a procedure – the world’s first interneuron cell transplant treatment in a higher mammal – much less whether it would be successful.

Survive he did, and more: The weekend before the Oct. 6, 2020, procedure, Cronutt had close to a dozen seizures. Since the transplant? None. And he’s now back to a healthy weight.

Baraban is hoping to help other stricken sea lions in the near future and will continue to advance cell transplant science. “Cellular therapies for humans with epilepsy won’t be available next year,” he says, “but we’re very excited about the long-term clinical potential of this work.”

– Janet Wells

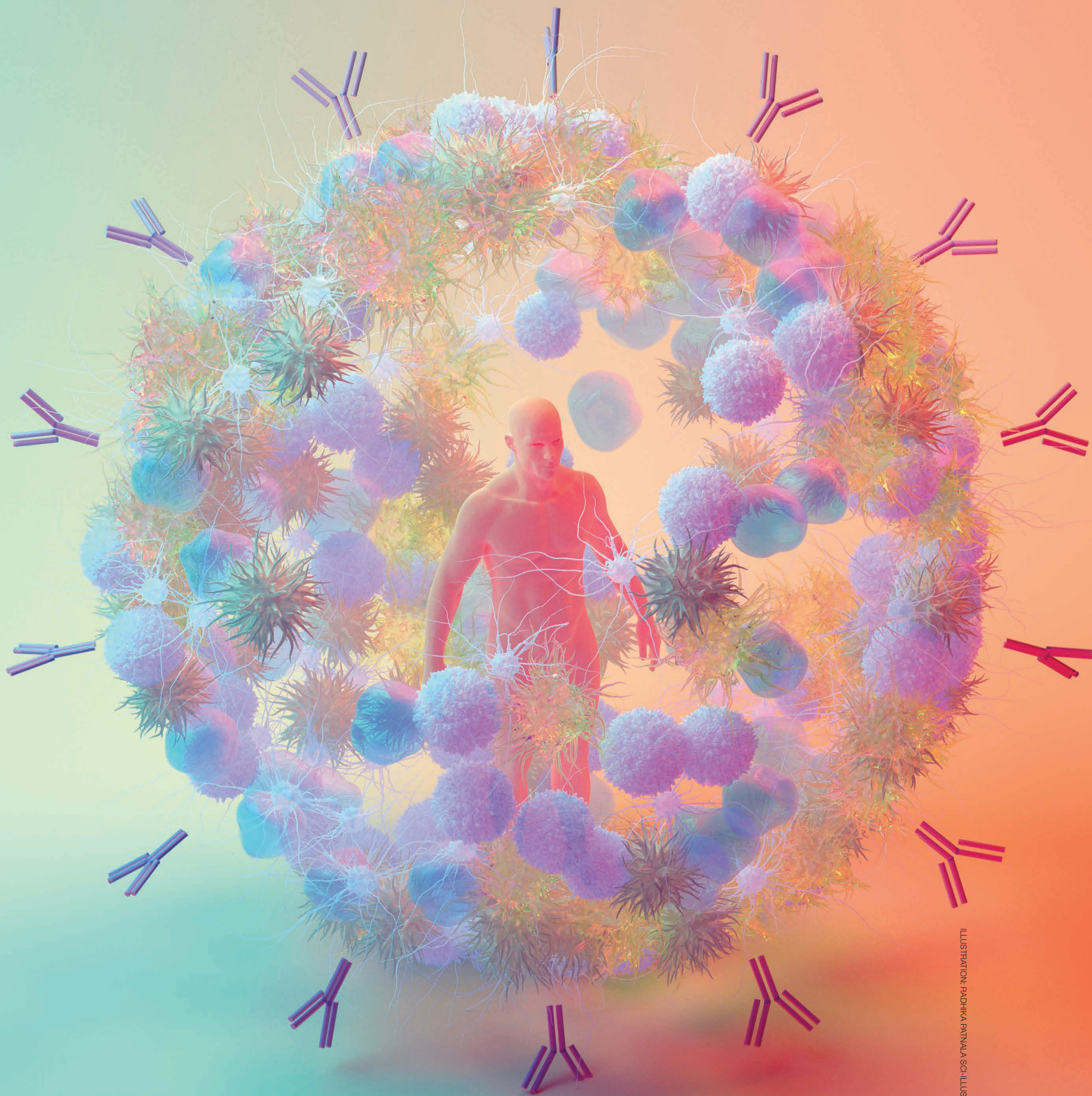


ILLUSTRATION: RADHIKA PATNALA SCHILLUSTRATE

YOUR
IMMUNE
SYSTEM
COULD
TURN
COVID-19
DEADLY

Hidden autoimmunity may explain how the coronavirus wrecks such widespread and unpredictable harm.

By Ariel Bleicher

ONE

of the enduring

mysteries of COVID-19 is why it makes some people deathly sick but gives others only mild symptoms or none at all. We know that age matters, as do race; gender; and pre-existing medical conditions like high blood pressure, heart problems, and obesity. We also know that most people who succumb to the disease die because they develop severe pneumonia, also known as acute respiratory distress syndrome, or ARDS.

What we still don't know, however, is what tips one COVID-19 victim toward ARDS but not another. Early in the pandemic, doctors noticed that, compared to forms of ARDS caused by other respiratory infections like flu, some features of COVID ARDS were peculiar. Patients were not only slower to develop the syndrome but also slower to recover, in some cases spending weeks on a ventilator. Often, their immune systems continued a ruinous battle against their own bodies – ravaging their lungs and choking them of oxygen – even after SARS-CoV-2, the virus that causes COVID-19, had been cleared from their systems.

“It was very strange,” says UC San Francisco’s Carolyn Calfee, MD, MAS ’09, a critical care physician and one of the world’s leading experts on ARDS. “I thought, ‘What kind of ARDS does this?’” she recalls. “‘This is not normal.’”

It turns out that a lot about COVID-19 is not normal. Experts have learned that in addition to infecting the respiratory tract, SARS-CoV-2 can infect the heart, gut, and blood vessels. As in the lungs, however, the damage that the virus inflicts on these tissues often appears to pale in comparison to the destruction caused by patients’ own immune response. Inflammation is rampant and widespread – turning up even in the brain and the toes – and causes myriad debilitating symptoms that sometimes persist for months. In rare cases, children (and some adults) who have recovered from COVID-19 develop a mysterious inflammatory syndrome, in which many organs throughout the body become inflamed.

All of this has piqued scientists’ curiosity: What is going wrong with people’s immune systems?

In searching for answers, Calfee and other researchers are finding that COVID-19 unhinges the immune system in ways no one expected, going so far as to turn the body against itself. Some people who get especially bad or unusual symptoms, for instance, harbor rogue antibodies – similar to those seen in autoimmune diseases – that disrupt the body’s normal immune response or attack its own tissues. These discoveries could explain how the virus wreaks such extensive and variable harm; they could also help predict who, if infected, will fall dangerously ill and identify effective treatments. More profoundly still, they could change scientists’ fundamental understanding of human immunity and how it can go awry.

A BROKEN ALARM

Alexis Combes, PhD, couldn’t sleep. An early-career scientist at UCSF, he had grown up in Marseille, France, where a childhood illness had sparked a reverence for medical science. He arrived in San Francisco in 2017 to train in clinical immunology and, less than two years later, was hired to direct a new, state-of-the-art laboratory for UCSF Bakar ImmunoX, an initiative that is exploring the immune system’s role in cancer and other diseases in hopes of inspiring treatments.

In April 2020, members of ImmunoX teamed up with Calfee and other clinical researchers to launch a study examining how people’s immune systems respond to the new coronavirus. The study, called COMET (COVID-19 Multi-Phenotyping for Effective Therapies), required collecting blood and other bodily substances from hospitalized patients and then processing the samples – extracting fragile immune cells, genes, and other molecules – so that researchers could analyze them. Combes, whose lab specializes in this kind of deep investigation, jumped at the chance to help.

Still, he felt anxious. He lay awake, picturing himself pipetting tiny drops of blood from people dying of COVID-19, and hoped that nothing would go horribly wrong. “Later on, we learned there is almost no virus in the blood because it stays in the lungs,” Combes says, “but back then, we didn’t really know how dangerous these samples were.”

Around 4 a.m., he rose and dressed. The light-rail train he normally took into the lab had stopped running, so he rented an electric Lyft bicycle and pedaled the 15-minute commute on dark, abandoned streets. He arrived early so that he could get samples from the hospital’s morning blood draw while the specimens were still fresh. He had to work fast. Within hours, many important but short-lived immune cells would already be dead.

Combes ran the blood through a series of assays designed to pluck out immune cells and decode the genetic material in each cell, one by one – a process called single-cell sequencing. He wore two pairs of gloves, two lab coats, and an N95 mask. He focused on sequencing RNA, a marker of which genes (DNA) a cell has turned on. Like a computer’s task manager, which shows the software programs currently in use, the decoded RNA would reveal which genetic programs a patient’s immune cells were running in response to the coronavirus infection.

Together with a couple dozen technicians and trainees, Combes repeated this process of extracting and sequencing immune cells every morning for nearly two months. Then he and other COMET scientists began to dig into the resulting data.

The emerging insights into the immunology of COVID-19 could change scientists’ fundamental understanding of human immunity and how

it can go awry.

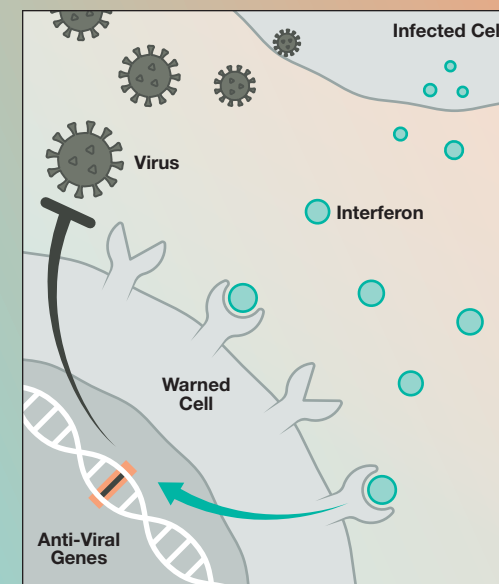
Immune cells deploy a variety of programs for fighting viruses. One of the most powerful is known as the interferon response. Some immune cells are stationed along the body’s borders, such as in the skin or a nasal membrane. When one of these sentinel cells detects a virus attack, the cell emits warning proteins called interferons – the biochemical equivalent of an air raid siren. Nearby cells respond to the interferons by turning on antiviral genes, which slow the reproduction of the virus and induce any cells that do become infected to commit suicide.

Parsing the sequencing data, Combes’s team noticed that the immune cells from patients with mild COVID-19 (those discharged from the hospital within a few days) were running this crucial virus-defense program without a hitch. But that was not the case in the immune cells from patients with severe COVID-19 (those admitted to the ICU, often with ARDS). Alarming, *none* of their cells had deployed the interferon response.

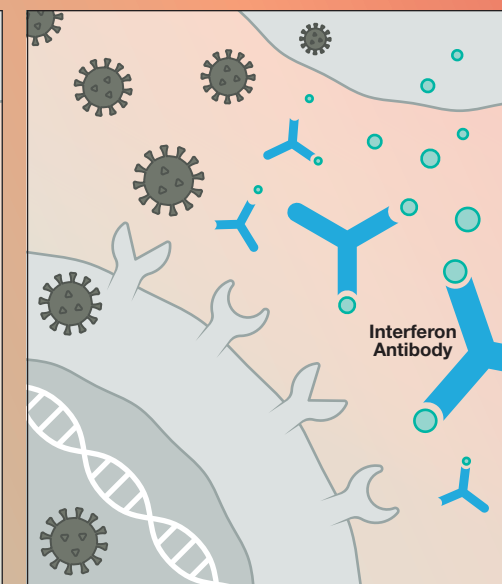
“What’s concerning is this is something we see across the entire

immune system,” says Matthew “Max” Krummel, PhD, the chair of ImmunoX, UCSF’s Smith Professor of Experimental Pathology, and co-lead of the COMET study. Without an interferon response to keep a virus contained, he explains, an invader is free to spread rapidly and widely. Increasing numbers of ambushed cells would call for reinforcements by flooding the bloodstream with inflammatory proteins called cytokines, setting off what’s known as a cytokine storm. Fresh troops arriving from the blood, such as white cells and antibodies, would then attempt to flush out the virus through biological carpet-bombing, resulting in extensive inflammation and tissue damage – much like that seen in COVID ARDS.

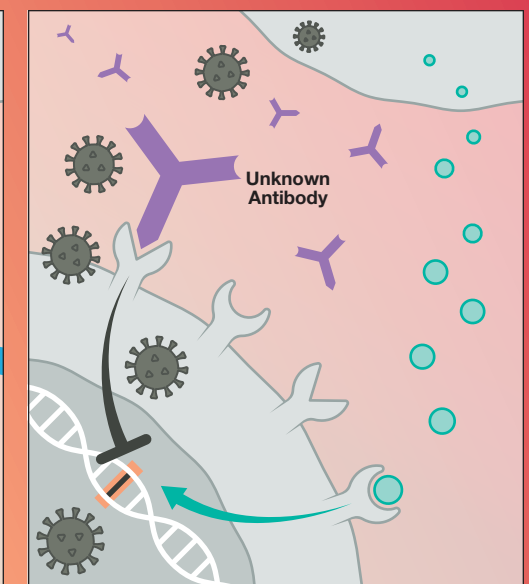
HOW ANTIBODIES THWART THE BODY’S VIRUS ALARM



A functional alarm: During a viral attack, infected cells emit warning proteins, called interferons, that cause nearby cells to turn on anti-viral genes. This interferon response prevents an infection from rapidly spreading.



Antibody attacks: About 10% of patients with severe COVID-19 have antibodies in their blood that attack interferons and thus prevent an interferon response.



Antibody interference: In other patients with severe COVID-19, a variety of (currently unknown) antibodies may bind to a cellular receptor called CD32B, which overrides the interferon signal.

By fall 2020, scientists around the world had amassed similar evidence pointing to the same conclusion: In the sickest COVID-19 patients, something was shutting down their interferon response. But what?

THE AUTOIMMUNE CONNECTION

One day in February 2020, a 32-year-old woman checked into a hospital in Lombardy, Italy. She was struggling to breathe and had a fever and a cough. Her symptoms, no surprise, were caused by COVID-19. Because she was young, her doctors thought she would recover quickly. But her condition worsened. She remained in the hospital for 37 days, including a week on a ventilator. By the time she was discharged, the burgeoning coronavirus outbreak had sickened more than 85,000 people in Italy. Her case might have been lost in the wave, save for one odd detail: She happened to have a rare autoimmune disease called autoimmune polyglandular syndrome type 1, or APS1.

APS1 is unusual in that it's linked to heritable mutations in a single gene; these mutations cause an astonishing array of autoimmune conditions, including type 1 diabetes, endocrine dysfunction, and chronic fungal infections. Mark Anderson, MD, PhD, a co-founder of ImmunoX and UCSF's Friend Professor of Diabetes Research, has studied APS1 for more than 20 years. The miscreant gene, he and others have learned, plays a role in teaching the immune system to ignore, or tolerate, the body's own cells and molecules. In APS1, self-tolerance breaks down, permitting the immune system to generate renegade warrior cells and antibodies that make civilians and allies the targets of war. One of these ally targets is the immune system's virus alarm protein, interferon.

Antibodies that target interferons capture these proteins the way a glove traps a baseball – stopping them from delivering their warning and tagging them for destruction by immune cells. These antibodies are so abundant in APS1 patients that their presence is often used to diagnose the disease. Weirdly, though, they had never seemed to do much harm, Anderson notes, since patients had tended not to get bad cases of the flu and other viral infections. “Then, lo and behold, COVID comes along, and word gets out on the street that a few APS1 patients who got the virus had a very poor clinical course,” he says. After the Italian case, two more popped up in Maryland.

Then, in early August, Anderson got a call from Jean-Laurent Casanova, MD, PhD, an immunologist at Rockefeller University in New York City. Upon examining blood from nearly 1,000 people hospitalized with life-threatening COVID-19, Casanova told Anderson, his team had been shocked to find that more than 100 of them (about 1 in 10 people) had antibodies against interferons, just like the APS1 patients. None of these COVID patients, however, had any known autoimmune diseases.

In laboratory experiments, Casanova's team showed that these antibodies block the inter-

feron response in cells exposed to SARS-CoV-2, thus preventing the cells from resisting the virus and controlling its spread. The team had found no such antibodies in people with mild or asymptomatic COVID-19. They appeared to be a feature – a cause, likely – of some of the worst outcomes.

The implication – that hidden autoimmunity could turn an otherwise benign infection deadly – was almost too crazy to believe. “When I heard about it, I was like ‘Oh, my goodness, I have to see if it's true because this is totally paradigm-shifting,’” says Sara Vazquez, an MD-PhD student who works with Anderson and Joe DeRisi, PhD, UCSF's Gordon Tomkins Professor and an infectious-disease expert.

Immunologists, Vazquez points out, have long recognized a relationship between autoimmunity and infectious disease. Autoimmune diseases frequently follow microbial attacks, which can trigger these diseases in people with genetic and other predispositions. *Streptococcus pyogenes*, the species of bacterium behind strep throat, for example, is thought to cause rheumatic heart disease when antibodies generated to fight the bacterium attack tissues in the heart. However, hints that rogue antibodies could change the course of a viral infection were few and far between.

Intrigued, Vazquez decided to repeat the Rockefeller experiment in blood samples from COMET patients and others at Zuckerberg San Francisco General Hospital. “I'm still amazed we were able to replicate it,” she says. The Rockefeller data, which the journal *Science* published in October, hadn't been a fluke: In San Francisco, as in New York, antibodies against interferons lurked in the blood of roughly 10% of patients brought to the brink of death or killed by COVID-19. Working with UCSF systems biologist Jimmie Ye, PhD, Vazquez and her team showed that immune cells from these patients had failed to run the interferon-response program, implying that the antibodies were directly responsible for the patients' bad COVID outcomes. (For unknown reasons, almost everyone who had interferon antibodies was male, perhaps providing a clue as to why more men than women have died from COVID-19.)

What had caused these antibodies to appear is a mystery. One possibility is the coronavirus itself, but Vazquez and her colleagues doubt that's the culprit. Patients with interferon antibodies showed consistently high levels of them throughout their hospital stays, she explains, “meaning those people probably had the antibodies before they ever got COVID.” She also tested blood from more than 4,000 people living in San Francisco's Mission District who had never been infected with SARS-CoV-2 and found that 13 of them nevertheless had interferon antibodies.

The implication – that hidden autoimmunity could turn an otherwise benign infection deadly – was almost too crazy to believe.

If the ratio revealed by the Mission study holds up, something on the order of 10 million people worldwide could have these antibodies. They may be more likely to become very sick if they get COVID-19. “We're dealing with an unusual pathogen,” Anderson says. “It's now so rampant, it's plucking people out of the general population who don't even know they have this susceptibility,” which he speculates may result from a combination of genetics and previous viral infections. “Their ability to respond against the virus is slowed down, and the virus starts winning.”

ANTIBODIES GONE AWRY

Interferon antibodies may be just the tip of the iceberg. Their discovery raised an obvious question: If these antibodies are responsible for around 10% of severe COVID-19 cases, what accounts for the other 90%?

Combes's and Krummel's research points to one plausibility. In January, their team published findings in *Nature* showing that a variety of other, unknown antibodies from severe COVID-19 patients can also quash the interferon response without directly capturing interferons. To grasp how this works, it's helpful to understand the relationship between antibodies and immune cells.

An antibody, which is shaped like a Y, has essentially two parts. The “arms” of the Y grab a specific target, such as a piece of a virus or, in unfortunate cases, an interferon. The “stem” of the Y, meanwhile, con-

nects to a protein receptor on the surface of immune cells, like a plug in a socket. In this way, an antibody delivers instructions to an immune cell according to the type of receptor its stem plugs into. A typical message is: “I found the enemy – attack!” The *Nature* study revealed that antibodies from severely ill COVID-19 patients deliver to cells almost the opposite refrain: “Ignore the air-raid sirens.”

The receptor that receives this command goes by the name CD32B. Among other functions, Krummel thinks, it serves as a brake on the immune system once an infection is under control. Normally, this is a good thing. During a virus attack, he explains, cells running the interferon-response program shut down their operating machinery in order to keep the virus from hijacking it. “If your cells did that forever, you'd

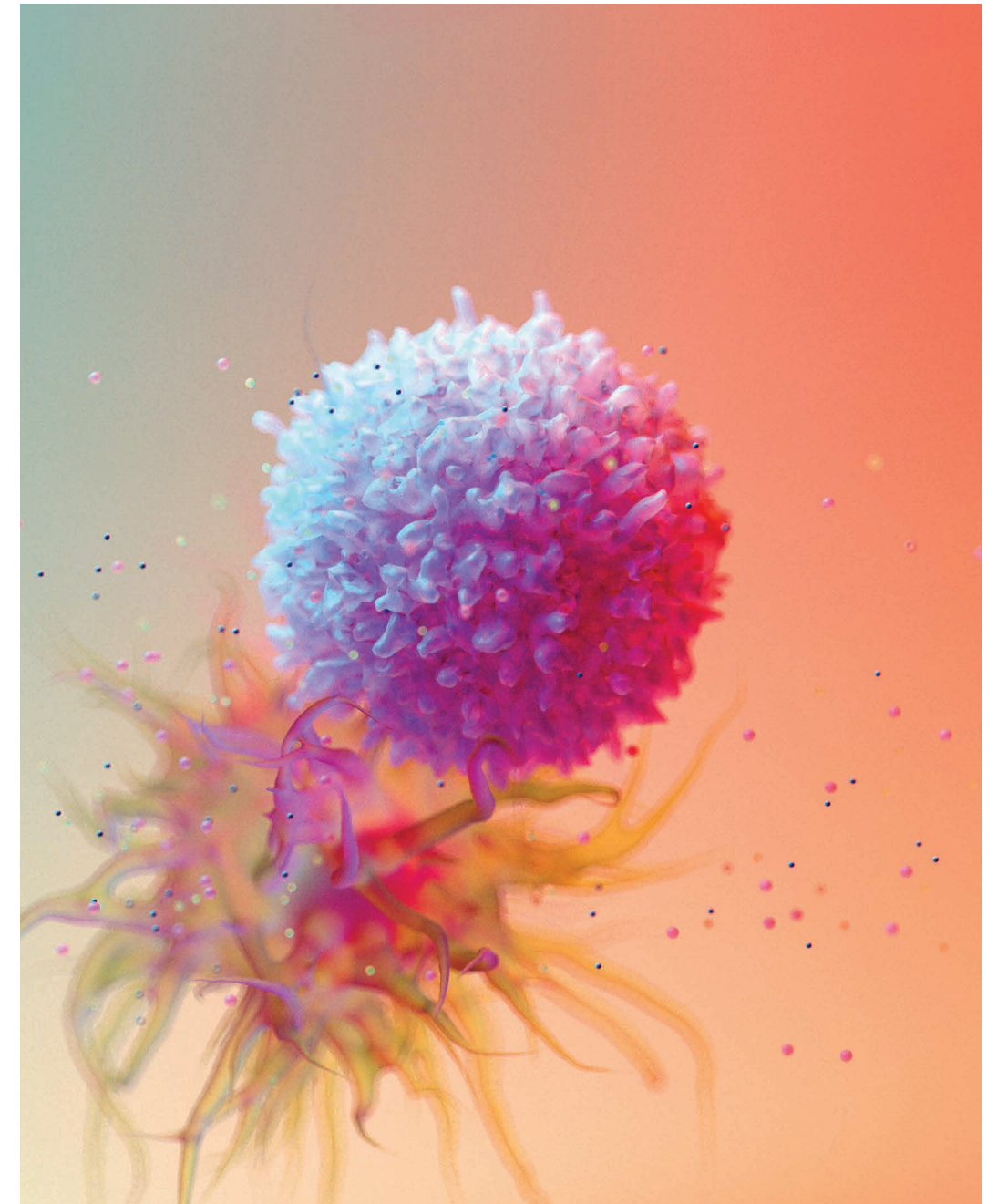


ILLUSTRATION: PADHIKA PATNALA SCHILLUSTRATE

die,” he says. “CD32B is a way for antibodies to say to a cell, ‘We’re here. We’ve come to the rescue. Go ahead and get back to business because you’ve got to live.’” But in severe COVID-19, antibodies may deliver this message erroneously, perhaps communicating it too soon or too strongly. As a result, the antibodies turn off the interferon response while it’s still needed – in effect, pitting the immune system against itself.

Scientists are still exploring what these signal-jamming antibodies are and why they’re made. Krummel suspects that many of them are autoimmune, meaning that their “arms” attack the body’s own molecules – and not just interferons. He points to a study from Yale in which researchers engineered yeast cells to display some 3,000 human proteins. In exposing the cells to antibodies from COVID-19 patients, the researchers found that these antibodies targeted a wide variety of proteins. These included signaling proteins like interferons as well as proteins commonly expressed in cells and tissues throughout the human body. The worse a patient’s infection, the more kinds of human proteins their antibodies targeted.

“That’s super weird, because you’d think antibodies are supposed to be the good guys, right?” Krummel asks. “They’re supposed to protect you, not make you sicker.”

Immunologists have a theory, called the “danger model,” that could explain how a coronavirus infection might induce the immune system to churn out self-attacking antibodies, also known as autoantibodies. According to this theory, the immune system does not distinguish between self and non-self but rather between things that are dangerous and things that are not. Such an approach would seem to enable the immune system to root out not just viruses and other pathogens but also diseased cells, such as cancers.

A novel virus that the body has never seen before, Krummel speculates, might evoke a cacophony of danger signals that beckon and mobilize immune cells over many days. Caught up in the enduring commotion, some human proteins might get mistakenly labeled as “dangerous,” causing the immune system to make antibodies against them. Inflammation at the site of the infection or in other tissues might then recruit these autoantibodies while also prompting the immune system to generate more of them, resulting in a runaway autoimmune reaction. The inflammation that sets off this reaction could be caused by the invading virus itself or an unrelated infection or trauma.

Inflammation is also a hallmark of aging. “As people get older, they get more inflammatory cues in their blood, as if they’re responding to something all the time,” Krummel says. The same is true with obesity, he points out. A link between inflammation and autoantibodies might explain why COVID-19 disproportionately sickens both the elderly and the overweight.

ATTACKS ON THE BRAIN

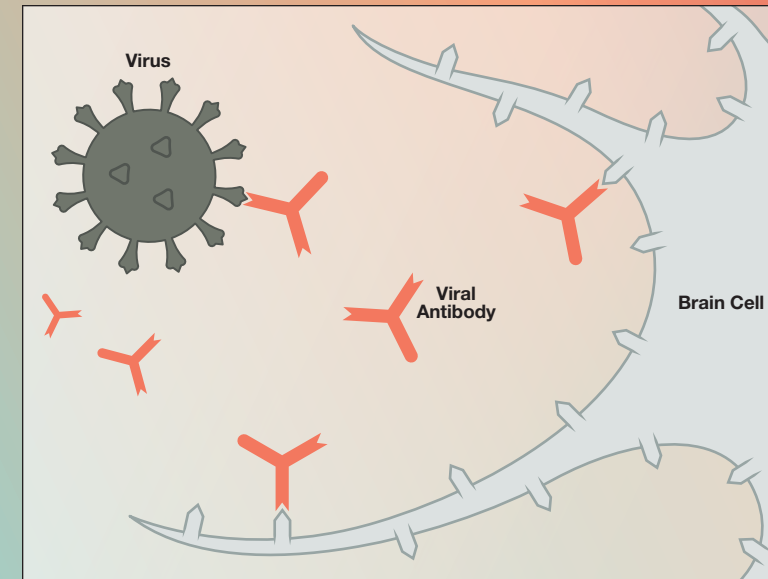
Researchers at UCSF’s Weill Institute for Neurosciences have begun to suspect that autoantibodies might also have a hand in COVID-19’s strange smorgasbord of neurological symptoms. About a third of people hospitalized for the disease exhibit these symptoms, including headaches, muscle fatigue, impaired cognition (or “brain fog”), and loss of the senses of smell and taste. For some people, including those who experience only mild respiratory symptoms, brain and behavior problems can persist or develop even after they recover. For instance, patients are more likely to receive a new psychiatric diagnosis, such as anxiety disorder or dementia, after a bout with COVID-19 than after some other health event.

A few months into the pandemic, experts started to wonder if SARS-CoV-2 was infecting some people’s brains. Would researchers find traces of the virus in their cerebrospinal fluid, which bathes the brain and spinal cord? “Almost universally, the answer was ‘no,’” says Michael Wilson, MD ’07, MAS ’16, an associate professor of neurology at UCSF’s Weill Institute. He knew, however, that brain-infecting viruses, such as West Nile, often show up in cerebrospinal fluid fleetingly – for just a day or two – even when patients are sick for months, making these viruses easy to miss. Consequently, physicians diagnose West Nile by testing for viral antibodies, which persist in cerebrospinal fluid much longer.

So Wilson, who is also the University’s Rachleff Distinguished Professor, teamed up with other scientists at UCSF and Yale to look for antibodies in samples of cerebrospinal fluid from hospitalized COVID-19 patients with neurological symptoms. “That we would find anything seemed very far-fetched,” says psychiatrist Christopher Bartley, MD, PhD, a postdoctoral fellow in immunopsychiatry at the Weill Institute, who co-led the experiments in the labs of Wilson and of Samuel Pleasure, MD, PhD, UCSF’s Johnson Professor of Neurology. But to the team’s surprise, the first seven fluid samples they tested all contained antibodies against SARS-CoV-2.

“That’s very unusual,” says team member Colin Zamecnik, PhD, a UCSF bio-engineer who is building new tools to screen for antibodies, including previously unknown ones. “The brain is compartmentalized from the rest of your immune system,” he explains. “The antibodies that you have circulating in your blood” – to fight an infection in the lungs, say – “don’t just passively show up in cerebrospinal fluid.”

Even more curious was the fact that five of the seven fluid samples also contained autoantibodies. These antibodies bind to brain tissue in mice, Bartley says, “which means they probably bind to brain tissue in humans.” The team found some brain-targeting antibodies in cerebrospinal fluid from uninfected people, too, but they appeared less frequently and proved to latch onto mouse brain tissue less capably than did those in the fluid from the hospitalized COVID-19 patients.



Mimicry trickery: In rare cases, some people might produce antibodies against a coronavirus protein that resembles a protein in brain tissue, thereby triggering an immune attack on the brain. UCSF scientists are investigating whether this theory, known as molecular mimicry, could help explain COVID-19’s strange array of neurological symptoms.

ILLUSTRATION: CHRIS PHILPOT

Intriguingly, Bartley and his colleagues also discovered brain autoantibodies in three patients who developed acute psychiatric symptoms after having otherwise mild or asymptomatic COVID-19. One patient, a 30-year-old man with no history of mental illness, became suddenly violent and developed delusions that he was speaking to the dead and being experimented on “like a guinea pig.” He recovered after being treated with immunotherapy. When Bartley’s team analyzed the autoantibodies in his cerebrospinal fluid, they found that some of them targeted brain cells thought to be involved in schizophrenia.

Precisely how autoantibodies relate to COVID-19 and sufferers’ symptoms is unclear, although Pleasure’s lab is developing a mouse model to try to unpack this relationship. “The clinical story is still murky,” Wilson says. “Could antibody attacks be behind some of this weird neuro stuff? That’s a definite possibility, but we don’t have enough data yet to know.”

He suspects that, ironically, some patients might produce brain autoantibodies to battle the coronavirus itself. These antibodies may target a part of the virus that, by chance, resembles a part of a protein in brain tissue. This phenomenon is known as molecular mimicry. “It’s guilt by association,” Wilson explains.

His team is now taking a closer look at the coronavirus antibodies from COVID-19 patients to see if some of those same antibodies also target brain proteins – evidence of molecular mimicry at play. So far, they have identified two antibodies in one patient that seem to fit the bill. “It might just be some weird fluke,” Wilson says. “But if it turns out to have legs, it could be an interesting wrinkle.”

CURES FOR COVID AND BEYOND

The more we learn about antibodies and their effect on COVID-19, the better we may be able to identify who is likely to fall badly ill and how to treat them. Anderson, the APS1 specialist, is now working with colleagues in the UCSF Department of Laboratory Medicine to develop a clinical test for interferon antibodies. “If it were up to me and money was no expense, anybody who comes into the hospital would get this test,” he says. “Probably only like one in 1,000 patients would test positive, but it could make a huge difference in outcomes because then we could intervene.”

For instance, patients with interferon or other immune-dysregulating antibodies might benefit from treatment with experimental antiviral or immune-based therapies early in their infection, says Calfee, the ARDS expert. “If we knew who those people are who are at risk for progression to serious disease, we could focus on getting them into clinical trials,” she says. Krummel, meanwhile, has co-founded a startup aimed at developing drugs that can restore the interferon response

by barring antibodies from plugging into the immune-cell receptor that turns it off.

Emerging insights into the immunology of COVID-19 likely will have an impact beyond the current pandemic as well. “What we’re finding probably is not unique to COVID,” says ImmunoX’s Combes. In recent experiments not yet published, his team found that antibodies also appear to shut down the interferon response in many patients with bad cases of flu. If current or newly developed immunotherapies prove effective in preventing severe COVID-19, these therapies might help curb suffering and deaths from other viral diseases, including future outbreaks. (COVID-19 cases aside, ARDS kills more than 70,000 people in the U.S. every year.)

Likewise, knowledge of antibodies’ role in COVID-19’s neurological symptoms could have profound implications for psychiatry. Bartley points out that about 1 in 100 people have a psychotic disorder for which the cause is unknown. He suspects that brain autoantibodies triggered by viruses might be culpable in a small percentage of those cases. “COVID gave us the opportunity to ask: Is there an association between a viral infection and the onset of psychiatric symptoms?” he says. “We think the answer is yes.” If that’s also true for viruses other than SARS-CoV-2, he speculates, “the impact could be enormous.” Many patients who don’t respond to antipsychotics, for example, might be cured by immunotherapy.

“Suddenly there are so many new questions scientists are beginning to ask about autoimmunity and its relationship to infectious disease,” says Vazquez, the MD-PhD student. “It has opened up this whole new field that didn’t exist before.”

Norway's Humane Approach to Prisons Can Work Here Too

The Scandinavian nation strives to rehabilitate instead of punish. UCSF's Amend program is showing that this model can help solve the public health crisis plaguing the American correctional system.

By Ariel Bleicher



PHOTO: GABRIELA HASELUN

Amend director Brie Williams, MD (center), with San Quentin State Prison medical chief Alison Pachynski, MD '02 (left), and Amend team members Fernando Murillo, Michele Casadei, and Daryl Norcott, JD.

ALL PHOTOGRAPHY FOR THIS ARTICLE FOLLOWED COVID-19 SAFETY PROTOCOLS.

In August 1997, on her first day of clinical rotations as a medical student in New York City, Brie Williams, MD, sat down at the bedside of a young woman. The patient lay on her back, a blanket pulled up to her neck. Staring at the ceiling, she answered Williams's questions with curt, one-word replies. Finally, Williams asked the woman to sit up so she could examine her.

"No."

Williams froze. Had she done something wrong? She fidgeted silently, at a loss for words, until at last the woman said, "Why don't you ask me why I can't sit up?"

"OK. Why can't you sit up?"

"Take the blanket off me, and you'll see."

Williams lifted the blanket. The woman, who Williams later learned was incarcerated at the nearby Rikers Island jail, was handcuffed to the bed frame.

"In that moment, she taught me that the most important factor in her health care was something so invisible to me that I didn't even think to ask about it," Williams says. It was a lesson she brought with her to UC San Francisco, where, as a medical resident and geriatrics fellow, she began studying the often-unseen health effects of imprisonment. By the time she joined the faculty, in 2007, she was one of the nation's few authorities on the subject. In her expert opinion, the U.S. correctional system – with its overcrowded wards, rapidly aging population, stark racial disparities, and excessive use of force and isolation – has created a public health crisis.

The crisis, as Williams and her colleagues describe it, began in the 1970s, when rising crime rates and ensuing tough-on-crime policies ushered in an era of mass incarceration. American prisons and jails – which in previous decades had focused more on rehabilitation – became harsh, punitive milieus. Guards (now called correctional officers) increasingly responded to behavioral health problems with discipline and separation, including solitary

confinement. But instead of becoming safer, many correctional facilities became plagued by violence, sexual assault, and suicide.

This evolution has taken an enormous physical and psychological toll. Today, about 2.3 million people – over 1 in 100 American adults – are behind bars, more than in any other nation. They are disproportionately

"Everyone in Norway will tell you: People go to court to be punished; they go to prison to become better neighbors."

– Brie Williams, MD

afflicted with chronic disease, mental illness, and a history of trauma and substance use disorders. The food they're served is typically unhealthy, leading to obesity and poor nutrition. They are at risk of exposure to toxins like lead and mold and are especially vulnerable to infectious diseases, as COVID-19 has tragically spotlighted. Depression is rampant, as are anxiety, insomnia, and suicidal ideation. Even after someone is released from prison, they're more likely to die during their first two weeks of freedom than someone in the community of similar age and gender.

And it's not only incarcerated people who suffer. Around a decade ago, evidence began mounting that the punitive settings were also undermining the health of staff. Officers reported witnessing violence almost daily and worrying constantly about being attacked. They experienced high rates of diabetes, heart disease, mental health problems, and symptoms of post-traumatic stress disorder (PTSD). On average, they die by age 60.

"That got people's attention," says Cyrus Ahalt, MPP, a UCSF public health researcher who has worked with Williams since 2010. "We realized these environments are so corrosive that even stepping foot in them as a worker is elevating your risk of stress-related illness

and the social outcomes of that, like divorce, addiction, and suicide."

With Ahalt's help, Williams, who is now a professor in the Division of Geriatrics, searched for a way to reverse these trends. Her quest led her to found a program called Amend – the name a nod to the Eighth Amendment's decree against "cruel and unusual punishment." For

the past six years, Amend has worked with legislators and correctional staff in seven states, including California, to turn prison cultures away from retribution and toward health and healing. The program has begun, slowly but surely, to improve the well-being of those who live and work in American prisons.

Williams's quest started with a simple but radical idea. "I said, 'Surely there must be a place where public health is the centerpiece of criminal justice,'" she recalls. "We found that place in Norway."

"In Norway, we have a saying: If you pee your pants on a cold winter day, it will feel very warm, and then it will freeze like hell," says Tom Eberhardt, who has worked in the Norwegian Correctional Service for 26 years and joined Amend as a consultant last year. The proverb warns against doing something that fixes a problem momentarily but makes it worse in the long run. For Eberhardt, it's the perfect metaphor for a revenge-driven approach to corrections.

"If a horrible criminal act has been done, it's only natural to say, 'Lock them up! Throw away the key! Treat them really bad!'" he says. "That's revenge – it feels good for a while, but eventually you start to hurt everybody in the prison and in the general society because you are just creating more violence and more revenge."

Norway, whose prisons are extolled today as some of the most humane in the world, came to this insight the hard way. Until fairly recently,

Norwegian correctional facilities were run much like their American counterparts. Officers were quick to punish incarcerated individuals for even minor infractions and typically kept them locked in cells. As one formerly incarcerated Norwegian put it, "they just wanted to catch you or punch you down." Those who were imprisoned reacted in kind, with verbal and physical assaults, riots, and Hollywood-esque escapes. As many as 70% of Norwegians released from prison reoffended within two years – a recidivism rate now mirrored in the U.S.

That changed in the 1990s, when Norway overhauled its prison system to prioritize rehabilitation and reintegration into society. This shift, which has slashed recidivism to about 20%, followed three basic principles. The first is "normality," which prescribes that life inside prisons resemble life outside as closely as possible. Nowadays, people incarcerated in Norway often wear their own clothes, cook in communal kitchens, and move about unaccompanied by officers. They might work, take classes, play sports, or shop for groceries. Their cells tend to look like dorm rooms, with throw rugs, curtains, and mini-fridges.

If such amenities sound indulgent, they make sense in the context of the second principle – "progression," or preparing people in prison for when they get out. "What is done wrong in a lot of prison systems is that they keep people behind bars in high-security environments almost to the day they are released," Eberhardt says. "Then those people, who are considered too dangerous even to leave a cell, become your neighbors or your friends' neighbors." People imprisoned in Norway, by contrast, gradually earn more freedoms by taking on responsibilities or accomplishing goals; as they near the end of their sentences, they can apply to transfer to lower-security facilities or to live or work in the community.

"Everyone in Norway – your taxicab drivers, your waiters – will tell you: People go to court to be punished; they go to prison to become better neighbors," Williams says.

"You can treat incarcerated people with humanity. That is universal."

– Cyrus Ahalt, MPP



Amend partners with incarcerated people, community leaders, and advocates to reduce the debilitating health effects of U.S. prisons. "Mass incarceration is a public health crisis," says Amend director Brie Williams, MD (left).

PHOTO: GABRIELA HASBUN



Since 2019, Amend has worked closely with correctional officers in the California Department of Corrections and Rehabilitation to improve the health and well-being of people who live and work in the state's prisons.

"This is a deeply public-health vision. Every policy, every procedure, every interaction in a prison is scrutinized for its capacity to help people and the community heal."

It is the third principle of Norwegian corrections that makes this healing possible. Known as "dynamic security," it focuses on the role of prison workers. Norway's correctional officers routinely socialize with residents, joining them for meals and card games and talking through problems. Officers are trained to use force when absolutely necessary but also study law, ethics, human rights, and the science of behavior change. They learn that building positive relationships with incarcerated people helps them get their lives on track and reduces the risk of violence. Even in maximum-security prisons – where most people are in custody for violent crimes like murder or rape – assaults against officers are rare, Eberhardt says.

That may sound counterintuitive if you've been taught to think of security in terms of barriers, weapons, oppressive rules, and threats of added punishment. But a Norwe-

gian officer will explain that getting to know incarcerated people on a personal level better alerts you to potential conflict and earns you their respect. "A lot of my colleagues, they will say, 'If you meet an ex-inmate in a pub, there's a much bigger chance he will buy you a beer than knock you down,'" Eberhardt says. "It's true. Whenever I've met formerly incarcerated people on the outside, they are often thanking me. It's always a very rewarding experience."

When Williams first visited Norwegian prisons, in 2014, she was surprised to hear so many officers say they loved their jobs. They weren't overly stressed and hypervigilant. They didn't perpetually fear for their safety. They didn't think about killing themselves or take out their frustrations on their families. Williams knew she'd found the model system she'd been searching for – the basis for Amend. It gave prison residents a chance at a healthy, meaningful life and made the lives of staff healthier and more meaningful, too.

If Norway could pull that off, she thought, why not the U.S.?

Since its inception in 2015, Amend has arranged for U.S. policymakers and correctional leaders to travel to Norway to see for themselves how its prisons operate. Williams calls these "hearts and minds tours."

Beforehand, the travelers are almost unanimously skeptical. Norway's approach to corrections would never work in the U.S., they insist; the two countries simply are too different – different values, different politics, different demographics. "We hear 'Norway's so socialist' or 'Norway's all white,' which is actually not true," says Ahalt, who is now Amend's chief program officer. About two-fifths of those incarcerated in Norway are from Africa, Eastern Europe, and the Middle East, making Norway's prisons more racially and ethnically diverse than is often assumed.

But once Amend participants visit Norwegian prisons, Ahalt says, "the skepticism and resistance evaporate." The visitors realize, from observing and talking with prison workers and residents, that the key to their relative well-being is not some quirk of Norwegian society or even the comforts in some prisons.

PHOTO: GABRIELA HASSEIN

"The message is 'You can treat incarcerated people with humanity; you can be invested in their success; you can play a positive role in ending the cycle of incarceration and violence,'" Ahalt says. "That is universal."

Still, Norway's system has some advantages. For one, the country does not share the U.S.'s legacy of systemic racism, born of chattel slavery, which has led to disproportionate imprisonment of non-white men. Norwegians also are far less likely than Americans to be sent to prison for minor criminal offenses, and the longest sentence they face is 30 years – compared to U.S. sentences of over 10,000 years. As a result, Norway's prisons are far less crowded, with as few as one staff member for each incarcerated person.

It would thus be hard to precisely replicate Norway's model in the U.S. But, says Williams, that's not Amend's goal. "We're not trying to create mini-Norways," she says. Rather, with Amend's guidance, Norway gives American prisons inspiration for making their own reforms.

These reforms are happening as much from the bottom up as from the top down. In 2018, Amend launched a culture-change program, which offers job-shadowing and hands-on training with Norwegian officers for American correctional staff. To date, over 400 officers in California, North Dakota, Minnesota, Oregon, and Washington have enrolled.

David Jantz, now a captain at Oregon's Snake River Correctional Institution, was one of the first. For most of his career, he found corrections work pretty miserable. "Eight hours a day of doing tier checks and a couple shakedowns – there's not a lot of job satisfaction in that," he says. Just putting on his uniform made his heartbeat rise. He believed his sole duty was keeping incarcerated people in line. "If you would've asked me back then what was wrong with our population, I would have said, 'They think they're human, and we need to dial them back in.'"

Jantz remembers the moment his mind began to change. It was the first day of his Amend training, and the class was role-playing an officer trying to get an uncooperative person out of a cell. "I announce who I am, and I

pound on the door," he recalls. Two more officers stand behind him, ready to back him up in case things get rough. Jantz tells the person in the cell, "Hey, I need you to move your leg or something, so I know you're OK." Silence. Jantz pounds harder. "Then I start kicking the door," he says, and the Norwe-

"Officers can proudly tell their kids about somebody's life they helped change."

– Brie Williams, MD

gian instructor "looks at me horrified."

"Why would you do that?" he asks Jantz.

"That's the way I was trained," Jantz replies.

Then they switch roles, and Jantz gets in the cell. From inside, he sees three officers peering in at him intimidatingly. "When they start yelling and kicking the door, I can literally feel my irritation starting to rise – like, at any split second, the scenario could become confrontational." At this point the instructor steps in and takes a different tack. He tells the back-up officers to stand off to the side, still close but out of Jantz's view. He speaks calmly, asks if Jantz is OK, says he just wants to talk. Jantz feels his body relax, and he opens the door – no confrontation necessary.

"That's when the value of the training started to sink in," Jantz recalls, "because it simply made sense: 'Be human.' It's not really that complex. Me and the other officers, we just didn't know it. Prior to Amend, we thought if you had an opportunity to take care of business and go home safe, that was a pretty good day. Boy, how wrong were we?"

Amend has inspired prisons to rethink dehumanizing practices like the use of force and solitary confinement, with measurable impact. North Dakota's department of corrections, for instance, has decreased its use of solitary confinement by 80%. And Jantz's unit at Snake River has helped six men get out of long-term isolation, including one man who'd been confined alone for over a decade.

"I was pulled out [of my cell] one day

and brought into a conference room where 10 [correctional] staff members told me they all had a vested interest in my success," the man later wrote to Amend's staff. Before that, he confessed, he saw himself as fundamentally broken. But the Amend-trained officers gave him a new lease on life. "These people treated me like anyone in society would treat me, rather than [as] a burden," he wrote. "This ultimately has made me feel like I'm equally worthy of returning back into society, and for this I am truly grateful."

"One of the biggest skills you get from Amend is just listening," says Daniel Moyer, a sergeant at Salinas Valley State Prison, who started Amend training last fall. (During the pandemic, Amend shifted its culture-change program to a virtual platform.) "A lot of guys in custody know you're not going to be able to solve all their problems, but as long as they feel like you care, that usually does a pretty good job of de-escalating the situation."

The benefits extend to prison staff. Officers at one prison who enrolled in Amend's culture-change program were 60% less likely to have been assaulted six months later. They also reported fewer PTSD symptoms, less concern about their own drinking and overall health, and better relationships with family and friends. "We have officers who say they can look at themselves in the mirror for the first time in 10 years because they can finally feel good about what they do," Williams says. "They can sit down at the dinner table and proudly tell their kids about somebody's life they helped change."

Considering the vastness of the U.S. correctional system, it might be tempting to dismiss such progress as a drop in the bucket. There is, to be sure, much more that needs to be done to mitigate the harm that incarceration inflicts on American communities, and Amend is only part of the solution. But a true revolutionary will remind you that the seeds of change often start small and grow. "When you give people a vision and skills for a different approach, they start to demand more from themselves and from their profession," Williams says. "It becomes almost like a social movement – you can't stop it."



Insomnia is miserable, and lost sleep can harm our health. Now, researchers are seeing the promise of solutions in our genes.

By Cyril Manning



Why can't I sleep?



For as long as she can remember, Joanne Osmond has gone to bed at midnight and awakened around 3:30 a.m.

Not restless. Not groggy. Wide awake, ready for a new day.

Like others in her family, Osmond is a super-sleeper. For seven decades, she's packed her prolonged days full of activity: as an adviser to small businesses, a member of her local school board, a state-level education leader, a Boy Scout volunteer, a church volunteer, a marathoner, a mountain climber, and a mother.

"I'm not brilliant, I'm not a genius," she says. "But I've had more hours in the day, so I could work harder than most people."

History is full of productive and powerful people, from Mozart to Thomas Edison, who claimed to sleep just four hours per night. But anyone trying to sleep-hack their way to greatness should be warned: The rare ability to succeed on so little sleep is a genetic trait, not a feat of will or skill. Sleep scientists at UC San Francisco are working to decode the relevant genes and find answers. By improving sleep, they hope to not only help you sleep better but also resolve a hidden public health crisis.

That may sound dramatic, but sleep deprivation can literally take years off your life. It is directly linked to obesity, insulin resistance, diabetes, increased cancer risk, cardiovascular disease, premature birth, and neurodegenerative diseases like Alzheimer's. In addition, insomnia often triggers depression, and depression can lead to insomnia – a true cycle of misery.

Lack of sleep is also a killer for your immune system: In a gross but convincing study that involved giving a live cold virus to volunteers and then measuring the mucus and congestion among those who became infected, UCSF sleep expert Aric Prather, PhD, showed conclusively that the less people sleep, the more likely they are to get sick. (He has also shown that lack of sleep prior to receiving a vaccination can reduce its protective effect; he is currently studying this link among COVID vaccine recipients.)

Sleep deprivation hurts us in other ways, too. Driving while drowsy is nearly as deadly as driving drunk. Without sleep, our minds are muddled and we are worse employees, worse students, worse friends, worse partners. How many marriages have crumbled, at least in part, due to how awful we are to the people we love when we are constantly exhausted?

Considering the stakes, pioneering UCSF sleep research collaborators Ying-Hui Fu, PhD, and Louis Ptáček, MD, see sleep as the ultimate target for human wellness. "If we understand how our sleep is regulated – what makes us or keeps us from sleeping soundly – we can have better therapies for sleep disorders like insomnia," says Ptáček, the University's Coleman Professor of Neurodegenerative Diseases.

Fu puts it simply: "Sleep is essential for our survival. It allows us to be happier, healthier, and smarter. So it's time to give our sleep the respect and attention it deserves."

The mystery of sleep



There's no question that the brain is doing astounding and essential work while we're unconscious each night. It is processing memories, emotions, and new knowledge; recharging the immune system; flushing away toxins; and restoring our mental and physical energy. But no one is quite clear how it all works.

Many people imagine that in a sleep clinic, doctors can attach electrodes to the brains of sleeping subjects and peer into the inner workings of their insomnia. But the truth, explains Prather, an associate professor of psychiatry, is that when sleep is measured using polysomnography (a study with those electrodes), "they only provide a proxy

for what's going on in the brain. We're trying to infer what's happening throughout the brain, but we're likely only scratching the surface."

How does sleep create physical restoration? What role does it have in energy? What is the difference in brain activity for someone who reports getting a "good" sleep as opposed to a "poor" one?

Sleep researchers and clinicians from across the UCSF Weill Institute for Neurosciences are pushing for answers. "Our team is drilling down on this question of how much sleep people need in ways that are pushing the envelope forward and are ahead of most other places," says Andrew Krystal, MD, vice chair of research in the Department of Psychiatry and Behavioral Sciences, the Dolby Professor of Psychiatry, and a leader of a cross-departmental initiative on the neuroscience of sleep.

"Sleep is essential for our survival. It allows us to be happier, healthier, and smarter. So it's time to give our sleep the respect and attention it deserves."

Ying-Hui Fu, PhD



Here's some of what we *do* know:

The process of falling and staying asleep is guided by two separate biological mechanisms: sleep pressure and circadian rhythms. These work in concert, vary significantly from person to person, and are exceptionally easy to throw out of whack.

Sleep pressure is the inevitable accumulation of sleepiness each day, caused by a gradual buildup of the molecule adenosine in your brain. (Adenosine is a byproduct of expending energy; it's freed up from the energy-carrying molecule ATP, or adenosine triphosphate, which fuels all living cells.) The most commonly used drug in the world, caffeine, can fend off sleep pressure by temporarily blocking the brain's adenosine receptors. But caffeine doesn't stop adenosine from accumulating, which is why once caffeine clears your system, built-up sleep pressure can hit you like a tsunami.

Your circadian rhythms are much more nuanced. A 24-hour biological clock keeps time for your every cellular function, allowing your body to reliably anticipate and respond to its physiological needs – including sleep. The inner workings of this elegant clock are proteins that build up each night and degrade each day, and the whole system is reliant on environmental cues, most notably natural light.

ICONS (AND PREVIOUS SPREAD): FLATIRON.COM



So what's keeping you awake?

With all this complexity, it's not a surprise that there's no one-size-fits-all answer to the question.



You literally can't breathe. The first possible cause to consider is sleep apnea: You are choking on your own collapsing airway, awakening over and over again, just enough to gasp for air, sometimes as often as once every minute. Although sleep apnea affects 22 million Americans, most people don't recognize it in themselves and only seek treatment at the ultimatum of their miserable bed partner, whose endurance of nightly snoring, gasping, and choking sounds ensures their own variety of sleep deprivation. (No bed partner? Other warning signs include excessive daytime sleepiness and morning headaches.)

The good news: Once sleep apnea is diagnosed, treatments for it – lifestyle changes, oral appliances, and airway pressure devices – are very effective.

PHOTO (AND PREVIOUS SPREAD): ELENA ZHUKOVA

You are anxious or distressed. Almost everyone has at least occasionally experienced the maddening exhaustion of wanting, needing, *begging* to fall asleep, but being stuck wide awake instead, mind racing. This is insomnia – which can show up as an inability to fall asleep or to stay asleep, or both – and it is often triggered by anxiety or psychological distress.

What's going on? Basically, your nervous system is stuck in fight-or-flight mode, and the hormones cortisol, adrenaline, and noradrenaline keep your brain alert and ruminating. About 25% of Americans will suffer a short-term bout of insomnia in any given year, but it usually resolves on its own. For about a quarter of this group, however, the problem becomes chronic, lasting three months or longer. At that point, it's definitely time to see a sleep specialist.

Your body's clock is out of sync.



There are countless ways to confuse your circadian rhythms. Hop a flight halfway around the world and you'll wake up before sunrise and be a staggering zombie by midafternoon. Stay up night after night, doom-scrolling or playing email catch-up, and you'll find your regular bedtime is hard to get back to. Switch between day and night shifts, and you may find yourself snapping at loved ones, blanking out while driving, or rereading a sentence several times over, unable to focus.

Many of the sleep disorder patients Krystal sees have an out-of-sync rhythm called delayed sleep phase syndrome; they tend to stay up late and sleep late. There's nothing inherently wrong with a late bedtime, but since the world doesn't stop for late sleepers, this pattern generally leads to the terrible outcomes associated with too little sleep. "The goal in these cases is to fix the circadian rhythm problem," Krystal says, "because you can't drag a person to go to sleep at a time that their biology is not aligned with."

We live in an always-on culture. Even those of us who don't suffer from sleep apnea, insomnia, or sleep-phase disorders often don't get the sleep we need. As UC Berkeley neuroscientist Matthew Walker, PhD, puts it in his *New York Times* bestseller, *Why We Sleep*, "Humans are not sleeping the way nature intended. The number of sleep bouts, the duration of sleep, and when sleep occurs [have] all been comprehensively distorted by modernity."

Louis Ptáček puts it in these stark terms: "Right now, awareness of the impact of sleep deprivation is where we were with smoking 40 years ago. Back then, the tobacco industry fought to obscure the risks of cigarettes. Today, our entire society is fighting against sleep health, through this 24/7 culture we live in."

Sleep Hygiene

Common tips you can count on – and myths to watch out for

Healthy sleep habits are pretty straightforward: Keep a consistent wake-up time. Exercise. Avoid caffeine, alcohol, and big meals right before bed. Cultivate a cool, dark bedroom and banish devices. Make time to wind down before bed.

It's easy to find these and other good habits online, but UCSF's sleep experts warn that you may also find some common tips that you should take with a grain of salt:



Don't: Force yourself into a consistent bedtime

A regular bedtime is great if you're sleeping well. But if you can't fall asleep, trying to force it will only make things worse. Instead, get up and do something relaxing until you're sleepy. Lying awake perpetuates insomnia by stoking your anxiety and weakening your mind's association that *bed* means *sleep*.



Don't: Obsess over sleep data from your smart devices

Aric Prather says today's sleep trackers can't accurately estimate sleep stages, but the analyses they generate may cause sleep anxiety. There's actually a term for this: *orthosomnia*. Most people are better off just listening to their bodies and waking at a consistent time. "You know when you wake up and don't feel refreshed," says Prather. "You don't need a device to tell you that."



Don't: Focus too much on blue light

Worried about the effect of your smartphone's blue light on your sleep? Some evidence suggests that blue light exposure can impair sleep, but Prather says the hype may be stronger than the science. Likely more harmful to slumber are some kinds of content. Reading a relaxing book on your phone is probably fine. But the stimulation of emailing, texting, tweeting, or doom-scrolling the news could trigger insomnia. Even so, it wouldn't hurt to turn on your phone's blue-light filter.



Your genes play a role. Super-sleepers like Joanne Osmond inherited a preternatural ability to thrive on only a few hours of sleep. But this genetic trait is very, very rare, so if you regularly sleep less than 7½ hours a night and suspect you might fall into this category, think again; chances are much higher that you are not only sleep deprived but also so used to living this way you can't even see the problem. It's true, however, that there's much more variation in individuals' sleep needs than we generally recognize. "A lot of people say everyone must sleep 7½ to 8½ hours or you're not going to be healthy. That's not true," says Ptáček. "There are some people who require less, and some who require more."

What's more, genetics can account for extreme night owls (who might naturally sleep, for example, from 2 to 10 a.m.) and extreme morning larks (who might sleep from 8 p.m. to 4 a.m.). But unlike treatable circadian rhythm disorders, these patterns are inherited and lifelong. For anyone with these atypical sleep traits, obligations as simple as helping kids with after-dinner homework or showing up for morning classes or meetings can be serious problems.

Finding the missing puzzle pieces

No one has done more to understand the relationship between our genes and the mechanisms of sleep than Fu and Ptáček.

In 2009, Fu identified the first gene known to be responsible for "familial natural short sleep," as Joanne Osmond's extreme sleep efficiency is officially known. Fu discovered a tiny mutation in a gene called *DEC2* and found that individuals with the mutation sleep significantly less than people without it. (To conclusively prove the matter, her team genetically engineered mice to express this same mutation; as predicted, the rodents slept less without decreasing their performance on physical or cognitive tests.)

Since that initial discovery, Fu and Ptáček have worked together tirelessly to find additional short-sleep genes, sequencing whole exomes of more than 30 families with this inherited trait, including Osmond's family. The massive effort paid off in 2019 when they discovered mutations in three more genes that also lead to short, hyper-efficient sleep. They expect to publish several more such discoveries in the near future, and Ptáček speculates that, all told, there may be 10, 20, or more as-yet-undiscovered genes associated with familial natural short sleep.

As they find these additional pieces of the genetic puzzle, they are working with Krystal and another colleague, Liza Ashbrook, MD '11, to decode how the underlying blueprints of sleep regulation work, why sleep benefits human wellness so dramatically, and what specific molecules and processes should be the targets of next-generation sleep medications and therapies. They believe that understanding these genes could provide all of us with more restorative sleep.

"When I hear the National Academy of Medicine talking about healthy aging," says Fu, "they are talking about drugs and equipment to help old people. For me, I want to help everybody sleep efficiently to achieve long, healthy lives. That would be such a much bigger impact for humanity."

For Osmond, however, the value of learning that her unusual sleep pattern is a genetic trait has been far more personal. For all the advantages the trait may confer, she has spent a lifetime being told that her minimal sleep pattern is unhealthy; a sister who shares the trait was even prescribed sleeping pills to "normalize" her nights. "I think it's a very lonely type of life," Osmond reflects. "When I finally learned that I'm this way because of my genes, I was like, 'Oh, I'm not broken. I am OK.'"

ICONS: FLATIRON.COM



"This was a sleep intervention, but it suggested benefits for psychological functioning and well-being." Jennifer Felder, PhD



The Best Treatment for Insomnia Usually Isn't a Pill

If you're having trouble sleeping, you're not alone. The fear, loss, isolation, and exhaustion of living through a pandemic – alongside a fire hose of economic, political, and racial traumas – have upended the peaceful slumber of millions of Americans. That's worrisome because insomnia goes hand in hand with anxiety and is often associated with depression.

Clinical psychologist Jennifer Felder, PhD, whose research has focused on new and expectant mothers, has shown promising results in addressing depression by helping patients improve their sleep.

"In my work with patients and in my research, a lot of pregnant and postpartum women have told me their depression was triggered by sleep deprivation," Felder says. She decided to evaluate whether cognitive behavioral therapy for insomnia (CBT-I) could improve her patients' sleep. Although CBT-I has been shown to help three-quarters of people with insomnia, there was reason to be skeptical: There are many practical reasons beyond true insomnia why pregnant women often have trouble sleeping, from physical discomfort to the frequent need to pee.

Nevertheless, in a randomized clinical trial of more than 200 pregnant women, Felder found that those who received CBT-I experienced significantly greater improvements in their insomnia symptoms than the other study subjects. "But what was also super exciting," she says, "is that they also had improvements in their depression and anxiety symptoms. This is important because we were not targeting those symptoms. This was a sleep intervention, but it suggested broader benefits for these women's psychological functioning and well-being."

Another promising aspect of Felder's study was its validation of using digital CBT-I apps such as Sleepio and SHUTi in place of one-on-one sessions with a therapist. The fact that these digital interventions work so well is important, Felder says, "because frankly there aren't enough trained clinicians to get this effective intervention into the hands of people who need it."

So, what exactly is cognitive behavioral therapy for insomnia? The intervention can include several components, including breathing and visualization techniques, mindfulness, and bio-feedback, but "the biggest hammer of CBT-I,"

says UCSF sleep psychologist Aric Prather, "is time-in-bed restriction." That means you don't lie in bed waiting to fall asleep, but instead stay up until sleepiness finally has its way with you. The long-term goal is *more* sleep, but the near-term path to getting there is often *less* – but better and uninterrupted – sleep.

"There's something powerful about when you restrict someone's time in bed – it leads to more sleep consolidation," says Prather. "Subjectively, a big bolus of sleep feels better than that same amount of sleep, broken up."

UCSF sleep specialists recognize that medications can be appropriate for certain patients who can't sleep, but point out that many primary care physicians are too quick to prescribe them and don't realize that CBT-I is the gold standard, first-line treatment for insomnia. Sleep specialist Andrew Krystal often sees patients who are either skeptical of or impatient with the idea of therapy. "Many of them become the most ardent supporters once they experience it," he says. "'I'm amazed,' they tell me. 'I'm sleeping better. I'm not taking any medication. I didn't believe it was going to work, but it did.'"

PHOTO: ELENA ZHUKOVA

Uniting the **Black Community** to Defeat COVID

Health-services researcher **Kim Rhoads, MD, MPH**, founded Umoja Health Partners to unite about 30 community organizations combating COVID-19 in Black communities in the Bay Area. She shares why the Umoja approach (the organization's name comes from the Swahili word for "unity" or "oneness") is working.

By Ann Brody Guy



PHOTO: ANASTASIA SARON

What's behind Umoja's community-driven approach?

Something one of our community leaders said really captures it: "You can't teach what you don't know, and you can't lead where you won't go."

You point to sources for Black distrust of the medical establishment beyond the often-cited Tuskegee experiment – for example, the so-called "chest pain while Black" 2010 study documenting disparate cardiology interventions and your own research exposing differential cancer treatments.

Yes. Also, pulse oximeters, which measure oxygen levels, were recently found to give unreliable readings for people with darker skin.

How are these issues connected?

They seem disparate, but they all come under one umbrella, which is that our agenda – as health care institutions, as academic institutions, as public health organizations – does not align with the agenda of Black people, and it never really has. That underpins why Tuskegee was allowed to go on and on: because that agenda is the preservation of the health of white people.

That agenda *sort of* includes Black people: "Whatever we build, it's generic, it's for you." It's not, though, because it doesn't take into account the history of Black people in this country, the ways in which we've been dispersed and displaced and othered.

We need to go further and understand that the Centers for Disease Control was formed in 1946, as a new branch of the U.S. Public Health Service, to manage three diseases, and syphilis was one of them. So the problem with the Tuskegee experiment goes beyond the fact that a government study tricked Black people and allowed them to remain sick; it's actually that our federal-level public health institution is founded, in part, on that study. That part of the Tuskegee story doesn't get told. That's in the soil from which everything else grows in public health.

So lack of trust should be thought of as an expected response to historically untrustworthy behavior.

How does Umoja address this deep history?

We're very intentional about going to places where our partners say Black people will come. Everything is for us, by us – our materials are created by community members; our mobilizers are local or from partner churches. Our tents are red, green, and black. We are signaling so loudly: *This is for Black people*. Yes, other people can come, but, Black people, this was actually created for you.

We also emphasize an ongoing relationship. Every week we share our data in real time, and we give the community an opportunity to comment on it. We post the data publicly – we don't embargo it while waiting for publication. Our agenda isn't necessarily the academic agenda; it's the public health agenda – for the African American community.

Why is it important to have separate efforts targeting Black and Latinx people?

"Black" and "brown" are often conflated, but the epidemiology of COVID is different in these two communities. The Latinx story is about infection. The African American story is about death. Yes, Latinx people are dying, but if you look at Alameda County's case fatality rates for Black people who get COVID, their risk of dying is up to four times higher than it is for Latinx people who get COVID.

Umoja started with testing and added vaccination. How's it going?

It's going gangbusters. At our first big vaccine pop-up, our turnout was amazing – and over 60% African American; the line was around the corner.

As of late April, about 51% of the folks coming for our vaccines are African American, with the rest split among multiple groups. That's better than, for example, the pop-ups with FEMA trailers that went to the Black churches – they're getting about 25%. The Oakland Coliseum, a Deep East Oakland zip code, was 4% African American.

How did you get your numbers so high?

When we saw that the Deep East Oakland census tracts were about half Latino, I said, "OK, to reach African American people we've got to go smaller." That's how we started doing the pop-ups.

That fall, 57% of people who were tested at our sites were African American. In January, we were well above 70% Black people, which is way over-represented, because they're only 30% of the population of those census tracts. It speaks to this idea that if you want to engage African Americans, you have to take it to the people.

Now, everybody talks about "the Umoja model" because we showed them who we could reach with testing. The Alameda County Department of Public Health said, "We're going let you have your own vaccine allocation." We're not partnering with a clinic – these are *our* vaccines.

What happens when lots of white people start showing up at your clinics?

Our percentage of Black people, which we're watching all the time, could be driven down and defeat the purpose of even being Umoja. The county gave us these vaccines because they know we can reach Black people. So I'm finding myself as the gatekeeper.

When white people ask for favors – like when they're out-of-tier – or clearly only volunteered with us in order to get vaccinated themselves, I give them the shot, but I make sure they understand that Umoja isn't really meant for them.

It's hard to do something for Black people. Other people will feel excluded. And yet, that is the experience of being Black in America all the time. And so there's this piece about privilege and entitlement that needs to bubble into our dialogue when we talk about anti-racist environments, and making UCSF anti-racist, for example. Instead of just talking about disparities and microaggressions, we need to start talking about privilege, because if we can tear that down, there really is no inequity or disparity.

Kim Rhoads is also director of the Office of Community Engagement at UCSF's Helen Diller Family Comprehensive Cancer Center.



Wrong
~~*Right*~~
 What's ~~Wrong~~ With
 Race in Medicine

Six health care experts grapple with how to address race without being racist.

By Megha Garg, MD, MPH

When *UCSF Magazine* asked me to moderate a panel discussion about race in medicine, I reflected on how far our field has come. Physicians didn't talk much about this topic when I was in medical school.

Thankfully, that's no longer the case. Race is now at the forefront of conversations at academic health centers across the country. Faculty members, staff, and students alike are wrestling with difficult questions about the role that racial categories play in biomedical science and the delivery of care. Is our knowledge about human illness and how to treat it based on biased studies or assumptions? Should race factor into our clinical decisions and the tools we use to guide our care? How can we ensure that the disparities exposed by the COVID-19 pandemic, which has disproportionately harmed and killed people of color, do not continue?

The following discussion (which has been edited for length and clarity) offers a window into this complex – and sometimes contentious – debate. I learned a lot, and I hope that you will too.

ILLUSTRATION: MARK HARRIS

Should Doctors Ignore Race?

MEGHA GARG: Do you believe that racial categories should be used in clinical practice and research?

JENNIFER JAMES: This question, to me, feels overly simplistic. There's a straw-man idea out there that the word "race" should never be uttered within 50 feet of a hospital, but I know of very few people who actually think that.

However, I do think that the way we're using race now is essentialist: We often assume that differences in disease incidence or outcomes between racial groups boil down to inherent biological differences, which is scientifically untrue – and often harms people of color. Historically, medicine and science have advanced racism and systemic oppression through the identification of these supposed biological "differences." And the legacies of this are still seen in our clinical care.

PHUOC LE: When I was in medical school in the early 2000s, we were taught to put race in the one-liner.¹ We couldn't just say the patient was a 55-year-old person coming in with chest pain. We were taught to put "55-year-old African American male." The way I train medical students now, and the way I think about race in my own practice, is I ask myself: "What is the purpose of using race?" When you put race in the one-liner, all you're doing is – excuse me for the pun – coloring somebody else's thoughts about the patient. You're perpetuating implicit bias. In that case, let's not use race.

At the same time, I absolutely do not believe in a "color-blind" approach to medicine. In law, decades of so-called color-blind policies have clearly failed to achieve racial equity. It's the same in medicine: If we simply ignore race, we will fail to call out inequities in our health care system.

GARG: I, too, learned to write the patient's race in the one-liner. And that was some years after you, Dr. Le. So things are slow-changing in medicine.

NEIL POWE: In a perfect world, we would not use race. But we don't have a perfect world. Therefore, we have used race as a proxy, or what clinical researchers sometimes call a surrogate marker, for biologic and social factors that we may not completely understand or have good data for. It's not unusual that we use surrogates in research and medicine. Cholesterol is a surrogate marker for heart disease. Education or occupation is a surrogate for socioeconomic status.

KATHERINE POSSIN: When it comes to brain health, neuropsychologists like myself consider race or ethnicity to be a crude proxy for lifelong social experience. If you look at the history of cognitive testing, for example, what we've seen is that it's the most socially disadvantaged

PANELISTS



MODERATOR:

Megha Garg, MD, MPH, is an assistant professor and course director for the curriculum covering social justice and racism at the UCSF School of Medicine. She is also the associate chief of hospital medicine at the San Francisco VA Medical Center.



Akinyemi Oni-Orisan, PharmD, PhD, is a geneticist at the UCSF Institute for Human Genetics and an assistant professor of clinical pharmacy. His research illuminates how genetic variation affects medication response in diverse populations.



Jennifer James, PhD '16, MSW, MSSP, is a medical sociologist and bioethicist at the UCSF Institute for Health and Aging in the UCSF School of Nursing and an assistant professor of social and behavioral sciences. She studies the relationship between patients and health care providers and how people make decisions about their care.



Katherine Possin, PhD, is a neuropsychologist and associate professor of neurology at the UCSF Weill Institute for Neurosciences. She focuses on Alzheimer's disease and related disorders and holds the John Douglas French Alzheimer's Foundation Professorship.



Phuoc Le, MD, MPH, is an associate professor of medicine and pediatrics. He co-founded the Health, Equity, Action, and Leadership (HEAL) initiative, a fellowship program that trains health professionals to serve low-resource communities around the world.



Neil Powe, MD, MPH, MBA, is a clinical epidemiologist and outcomes researcher, the Constance B. Wofsy Distinguished Professor, and chief of the Department of Medicine at Zuckerberg San Francisco General Hospital. He also co-chairs a joint task force of the National Kidney Foundation and the American Society of Nephrology assessing the use of race in diagnosing kidney disease.

ILLUSTRATIONS: STEPHANIE KOCH

groups² that get the lowest scores. These disparities are *not* inherent. They are caused by inequalities – in income, education, stress, etc. – that can advantage some groups over others, starting in early childhood. So what we need to do is unpack that social experience and measure it systematically so that we can understand the true factors that predict somebody's baseline cognitive function.

AKINYEMI ONI-ORISAN: I agree that there is a strong social component to race, but there is also a genetic component. And genetic variants have biological consequences. So, in addition to social factors, our research studies need to account for as much genetic variation as possible. One way we do this is making sure our studies include participants from diverse genetic ancestries, and we often use race to approximate ancestry.

POWE: I'm sure that Dr. Oni-Orisan knows the work that [UCSF professor] Neil Risch has done with the GERA³ study, where researchers asked people for their self-identified race and then determined their ancestry through genetic testing. And they found there is a good correlation between race and genetic ancestry. Somebody recently gave me a 23andMe kit. When I got my results back, I knew what they were going to show, and that's what they showed. I didn't need to pay somebody to tell me that.

ONI-ORISAN: Right. I think many geneticists ultimately want to replace race with genetic ancestry, which is a more precise estimation of genetic variation, plus the social determinants that Dr. Possin described. But we're not yet at a point where ancestry data are readily available. The solution for that is simply more research, particularly in underrepresented populations, which for now requires taking race into account.

Can Using Race Solve Inequities?

GARG: What counts as a "good" use of race versus a "bad" one?

ONI-ORISAN: When I go to my favorite barbershop in Oakland, I know people are there not just to get their hair cut. I know there's going to be a long line, but no one is in a hurry. I know I'm going to be entertained with animated conversation. This is how Black barbershops are.

Recently, clinicians and researchers at UCSF have taken advantage of this cultural aspect of Black-owned barber-shops to provide health counseling and care to Black men with hypertension. The evidence shows that this intervention greatly improves outcomes for these men. This is an example

If we simply ignore race, we will fail to call out inequities in our health care system.

→ On the other hand, using race too often creates inequities by directing more attention or resources to whites.

¹ **One-liner:** the summary of a patient and their illness in their medical chart

² **Socially disadvantaged groups:** A century ago, such groups included Eastern Europeans and Italians; today, they include Blacks and other people of color.

³ **GERA:** Genetic Epidemiology Research on Adult Health and Aging

⁴ **2013 concussion settlement:** the resolution of a high-profile lawsuit in which the NFL agreed to pay retirees up to \$5 million each if they have certain neurological conditions

of how race can be used – not to stereotype, but to provide more effective care – because a one-size-fits-all approach is often not the best way to care for a patient.

LE: For me, as a pediatrician working at UCSF Benioff Children's Hospital San Francisco, I often see diseases that predominantly impact the privileged class. Cystic fibrosis is a classic example. One out of about every 3,000 white children is afflicted by this awful disease. Meanwhile, 1 out of every 300 Black children is afflicted with sickle cell disease. That's a *10 times* greater rate than for cystic fibrosis.

And yet the National Institutes of Health provides three times as much funding for the disease that afflicts mostly white children. Similarly, the amount of philanthropic dollars raised for cystic fibrosis is an order of magnitude more than for sickle cell disease, even though the amount of suffering is disproportionate in the opposite direction. This is where I think race can be used to identify and address inequity.

POSSIN: On the other hand, using race too often *creates* inequities by directing more attention or resources to whites. I recently wrote about a class action lawsuit against the National Football League filed by retired Black players. These are people who played for many years in the NFL and then later in life developed dementia. Research suggests such a diagnosis is linked to the head impacts they sustained during games. If retired players can prove they have dementia, they're entitled to substantial monetary awards under the landmark 2013 concussion settlement.⁴

The current lawsuit accuses the NFL of requiring that clinicians use race as a factor in determining dementia. If you're Black, you need to score lower on the same tests to be considered impaired enough for a dementia diagnosis. This is called race norming. It's meant to "correct" for the average statistical difference in test scores between Blacks and whites. But I think it's a very concerning practice because it makes it harder for a Black player than for a white player to qualify for a settlement award.

POWE: But suppose you didn't use race norming. If you just take at face value the fact that African Americans, on average, score less well on cognitive tests – which, by the way, are developed mostly from data on white Americans – you might conclude, “A lot of African Americans have some cognitive dysfunction.” That is the danger of just removing race.

I'm currently embroiled in a similar issue with how race is used in eGFR,⁵ an estimate of kidney function based on a patient's age, gender, race, and level of creatinine⁶ in their blood. There is a well-intentioned movement to eliminate race from this calculation, but I think what's lacking in the debate is an appreciation of the history. There's this myth that race was brought into the eGFR calculation because of the racist idea that African Americans have more muscle mass. But that's not quite true.

What happened was the original equation for estimating kidney function was developed in 1976 from 249 Caucasian men and extrapolated to other groups. A couple decades later, investigators began noticing that African Americans in the U.S. had higher creatinine levels than whites. We don't know why that is, but the increase doesn't always reflect a kidney problem. So, in 1999, the equation was updated with new study data that included African Americans (and women) and confirmed the racial differences in creatinine levels. That's when race was factored into eGFR to account for those differences.

Critics say this race adjustment overestimates kidney function in African Americans. But what's the alternative? If we get rid of race, then we're just giving Black people the “white” value, which may be an *underestimate*.⁷ In my mind, that kind of normalizing can be *more* racist.

Is Studying Genetics by Race Inherently Problematic?

GARG: Historically, scientists often looked for biological differences between racial groups to justify white supremacy.

⁵ **eGFR:** *estimated glomerular filtration rate*

⁶ **Creatinine:** *a waste product from muscle that gets filtered by the kidneys*

⁷ **Underestimating kidney function:** *Potential consequences of this include prescribing an ineffective dose of medication or disqualifying a patient for life insurance or certain treatments or clinical trials.*

⁸ **NIH's five racial categories:** *American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White (plus two categories for ethnicity: Hispanic or Latino and Not Hispanic or Latino)*

Now we know how unfounded – and incredibly harmful and racist – that research was. Some researchers today, particularly geneticists, still study biological differences along racial lines, but with an intention to understand how these differences affect health and improve patient care. Are there concerns with using race in this way, even though the intention is good?

JAMES: COVID is a great example. I felt frustration seeing studies looking for genetic or biological differences between racial groups to explain COVID disparities, instead of focusing on solutions to the racism that led to these disparities. For example, people of color are more likely to be infected with COVID because they are more likely to be exposed to the coronavirus due to things like the kinds of jobs they hold and the kinds of housing they can afford. This is clearly due to racism, not race. People of color are also more likely to die of COVID because of a higher burden of chronic disease – which, again, is due to environmental exposures, lack of access to health care, and other forms of structural racism.

ONI-ORISAN: If you look at the literature on COVID-19, there are many more papers on the social determinants of these disparities than on genetic factors, and deservedly so. But why is it so offensive for people to study genetic variation in populations and look for factors that may be associated with susceptibility to or severity of COVID-19? I don't look at data on the social determinants of health disparities and say, “Why are people publishing that?” Why can't we do both?

POWE: It's not either/or. We need to study both and understand the interrelationship between them. Some social variables are more imprecise or just as imprecise as biological variables, in my opinion.

ONI-ORISAN: I'm one of only a few Black geneticists in this country. I worry that when nongeneticists discredit the entire field of population genetics as not important – or, even worse, as racist – then minority students and trainees will be less likely to go into this field.

JAMES: Absolutely, and I certainly didn't intend to imply that your work is racist. In fact, I think the work you and other geneticists are doing to look at differences across diverse populations and identify genetic risks for disease is critically important. My point is that genetic diversity across populations is not the same as racial categorizations, and I get concerned when I see studies conflating the two.

We often take too narrow a view in medicine, thinking about health as being just biology and not thinking about health as being the entire social structure. For many people, the five racial categories⁸ that the National Institutes of Health uses don't make sense. I identify as Black, but I've also identified as mixed. So do I count as Black, or do I count as not-Black? My children – who are half me and half white – are they Black? Where's the line? These groups don't have an inherent biological meaning.

ONI-ORISAN: I would argue that racism is also not the same as racial categorizations. Race is complex and captures multiple components, including genetic ones. We have to acknowledge that genetic differences between racial groups *do* exist and *can* have clinical significance. So even though social factors play the largest role in racial health disparities, we also need to address other factors, including genetics. As a geneticist, I consider myself a health disparities researcher.

Where Do We Go From Here?

GARG: How do we use race appropriately – not to discriminate but to deliver equitable care?

POSSIN: We have to keep measuring race because that's how we can identify disparities. We have to make sure that our care clinics are serving a diverse population that represents our region. If they're not, then we need to do outreach to the communities that are not coming into our clinics. Because if we just wait for who makes it in our door, we're going to get an advantaged slice of the population. We need to go out and find the patients who need our care.

JAMES: We also need to be more consistent and transparent with how we talk about race in our studies. What do we mean by race? Is it patient-reported? Is it provider-reported? Is it whatever ended up in the electronic health record? Or is it something like ancestry?

And we need to have more nuanced conversations about race with our patients. If I'm asked to check a race box, no one's saying, “This is what we're going to do with this information; this is what it might mean for you.”

For instance, let's say having darker skin puts you at greater risk for a certain disease. It would be useful for a

Every single institution in this country is reckoning with their own racist history, including UCSF.

Read More:

“Beyond Seeing Race: Centering Racism and Acknowledging Agency Within Bioethics,” by Jennifer E. James et al., in the American Journal of Bioethics

“Black Kidney Function Matters,” by Neil R. Powe, in JAMA

“Embracing Genetic Diversity to Improve Black Health,” by Akinyemi Oni-Orisan et al., in NEJM

“Perils of Race-Based Norms in Cognitive Testing,” by Katherine Possin et al., in JAMA

“Race-Based Medicine Can Blind Doctors from Social Injustice,” by Phuoc Le et al., in The Health Care Blog

Ariel Bleicher and Elizabeth Daube produced and edited this article.

patient from the Dominican Republic to know that and realize, “Oh, it's important for me to articulate that I have dark skin in this answer.” Or maybe it's ancestry, not skin color, that a clinician or researcher really needs to know. So if this patient has three white grandparents, they might decide it's important to indicate the white part of their background even though they might identify as Black.

ONI-ORISAN: One of the key issues, historically speaking, is the idea of hierarchy – that there's one race that's superior to others. This idea is unscientific; it's not appropriate. What I'm advocating for is to celebrate and study differences between populations *without* the idea of hierarchy. I think that's how we can make progress.

LE: Right now, every single institution in this country is reckoning with their own racist history, including UCSF. It's an amazing time, but it's also a tense time. I sense that tension even in this Zoom call.

My prescription for using race is to first acknowledge that in medical research and practice, we've had actions and policies that have been informed by structural racism. Then we need to ask ourselves, “What is the preferential option?” In the case of disproportionately low funding for sickle cell disease, the preferential option would be to dramatically increase it. Some people will call this a form of reparations. For me, it's simply prioritizing the group that has been oppressed and has suffered the most.

JAMES: In some ways, I feel like we're arguing the same thing from different perspectives. Many of us think the way we're using race now is inappropriate, and the ultimate goal is to do something different.

POWE: It's health equity that we want, right? That's what we're all aiming for, no matter what it takes to get there.

We often take too narrow a view in medicine, thinking about health as being just biology.

BUT: We have to acknowledge that genetic differences between racial groups do exist and can have clinical significance.

ALUMNI HUB

When the pandemic hit, UCSF alumni across the globe drew on their training, skills, and savvy to combat the coronavirus. Here are five who stand out.

SCHOOL OF MEDICINE

Stephen Hoge, MD '03

Turns Out, Designing a Vaccine Was Easy

The hard part was everything that came next

It took a team of Moderna biologists exactly one hour over a weekend in January 2020 to design an extraordinarily effective vaccine against a deadly virus about to bring the world to its knees.

COVID-19 was still two months shy of being declared a global pandemic, but Stephen Hoge, president of the biotech firm, had heard about a pneumonia-like virus sickening people in Wuhan, China. He and his company were eager to test Moderna's vaccine technology, employing messenger RNA (mRNA), against the novel pathogen.

Using the SARS-CoV-2 virus's genetic sequence, which had been publicly released just days earlier by Chinese scientist Yong-Zhen Zhang, PhD, Hoge and his team inserted two mutations from MERS (the Middle East Respiratory Syndrome, caused by a cousin of SARS-CoV-2), into the novel coronavirus's sequence. This created a tiny piece of SARS-CoV-2's spike protein to alert the immune system to kill any invading viruses armed with that protein.

"We did it in an hour, and it worked brilliantly," says Hoge, who joined Moderna as head of drug invention in 2012 and was named president in 2015.

The speed with which Moderna whipped up the vaccine belies the decades of experimentation and painstaking research that led to that moment – a fact Hoge is well aware of.

"Science is a collective effort with different groups playing different roles at different times," he says. "Basic mRNA research was happening in academia 15, 20 years ago at the University of Pennsylvania with Katalin Karikó. When it was introduced, most thought it would never amount to anything because it was too difficult to work with. But that early research was insightful for us."

Indeed, Moderna, now a juggernaut of the biotech industry, was founded in 2010 to prove that mRNA could deliver a new way to make medicines and possibly vaccines. The company spent a decade and a couple of billion dollars perfecting the mRNA biological process and fixing the way mRNA-based medicines enter the body's cells, using lipid nanoparticles – a sort of soap bubble – to stabilize the mRNA.

"It all came together on January 13, 2020," Hoge recalls. "But it was not accomplished in that hour. It was accomplished over the two to three decades of work leading up to that moment, not only at Moderna but across the scientific community. You want to be circumspect as a scientist or clinician and recognize that you're just running your leg of the race."

Still, Moderna's "leg" is a significant victory for the human race. Hoge says he will never forget his reaction when the U.S. Food and Drug Administration (FDA) announced in mid-November that Moderna's vaccine was 94% effective against the virus and 100% effective against severe disease and death.

"It was the most intense feeling of relief that I had ever felt," he recalls. "It was this wave of hope and the relief that goes with hope. Then I got back to work, because it wasn't done."

Not even close. Hoge says he still feels like he spends "almost every hour of every day, every day of the week, including weekends" working to ensure that Moderna fulfills its obligations to help end the pandemic. "I've not had much time to reflect because it still feels like we're only halfway up the mountain. None of us are safe until all of us are safe, because this virus will mutate until we control it – so this still feels very much like a grind."

Given that the vaccine was available before 2 million people lost their lives to the virus, many have asked whether it should have been approved sooner. Hoge has fielded that question many times. First, he notes that no one knew in January 2020 whether Moderna's vaccine was effective or even safe. Then, as the vaccine moved to clinical trials, many reasonable people, including scientists and clinicians, were concerned about the speed of the process. Hoge remembers hearing over and over: "Where's the data? We haven't seen everything we need to have

“ A passion for curiosity, a passion for the 'why' question, a passion for the public health mission. I've never seen it come together in quite the same way anywhere else as it does at UCSF. Weaving those threads together is something that I've thought about through the last year. ”

confidence.” The more scientists questioned the process, the more Americans wondered whether to take the vaccine, creating a crisis of confidence last summer that threatened to derail the public health response.

Only now can we look back and wonder if we could have deployed the vaccines sooner and maybe saved a lot of lives, Hoge says. “But maybe nobody would have accepted it. Maybe physicians wouldn't have recommended it. And maybe they wouldn't have been wrong because, in truth, at that point, there was just not enough data.”

That didn't come along until November, and the rest, as they say, is history.

Hoge calls the story of Moderna's vaccine development an illustration of what is best about American culture, namely its embrace of entrepreneurship. “Entrepreneurs like to take risks to push in new directions,” he notes. “In biotech, we often build upon research coming out of academia and try to translate it into something that impacts human health.”

What is often forgotten by free market moguls, however, is the crucial role played by strong regulatory institutions like the FDA and National Institutes of Health, which provide independent, scientific oversight and were essential to the development of Moderna's vaccine, Hoge notes.

“That's what gives everyone confidence to take big steps like vaccinating tens of millions of people,” he says, noting the skepticism plaguing vaccines developed in countries like Russia and China – countries that don't have strong regulatory agencies or public review processes. “There's confidence here because of the rigor, transparency, and independence of the process.”

It's been almost two decades since Hoge walked the hallways of Parnassus, the VA medical center, and Zuckerberg San Francisco General Hospital while earning his MD. But those years at UCSF taught him that public health, patient care, and innovative scientific research could coexist in the same space and time. That lesson shaped his career and is helping him shape Moderna.

“UCSF is an incredibly special institution. When I was there, I saw that intersection of public health, basic science, and clinical practice,” he says. “I try to build on that at Moderna – understanding how basic science can be used to make everyone's lives better. I'm very much a product of the UCSF community in that way.”

■ Katherine Conrad

SCHOOL OF PHARMACY

Lisa Kroon, PharmD, Resident Alum

Mission: Vaccinating UCSF

Just four hours after UCSF secured its first shipment of Pfizer's COVID vaccine on Dec. 16, eager pharmacists-in-training were delivering doses into the arms of frontliners just as eager to receive the lifesaving substance.

"This is history – it's very emotional – and our students wanted to be part of it," explains Lisa Kroon, chair of clinical pharmacy and the T.A. Oliver Professor, who despite the significance of the event was surprised by the speed with which volunteers signed up.

Speed. Efficiency. Precision. Safety. That's how Kroon describes UCSF's all-hands-on-deck effort to vaccinate frontline workers, patients, clinicians, scientists – in short, every eligible and willing arm. UCSF poured resources into the effort – primarily people – and administered more than 100% of the doses it received. (Pfizer's five-dose vials actually contained enough for six or even seven doses.) That was a feat few other institutions achieved, especially in the early days of vaccine availability.

The successful rollout meant working around the clock, seven days a week. But Kroon says people simply stepped up, ready to do whatever was needed. They were aided by a COVID-19 vaccine standard operating procedure manual created by UCSF Health's Pharmacy Department – a guide that outlines every facet of the logistically challenging enterprise. The 100-plus-page document describes how to open and run mini pharmacies at Parnassus (those are now closed), Mission Bay, San Francisco City College, and UCSF Benioff Children's Hospital Oakland.

"We carefully prepare each dose, labeling every syringe so we know exactly when the vaccine came out of the freezer to ensure we don't waste any," Kroon says, "because that would just be tragic."

In a pandemic defined by tragedy, Kroon is determined not to add to the misery.

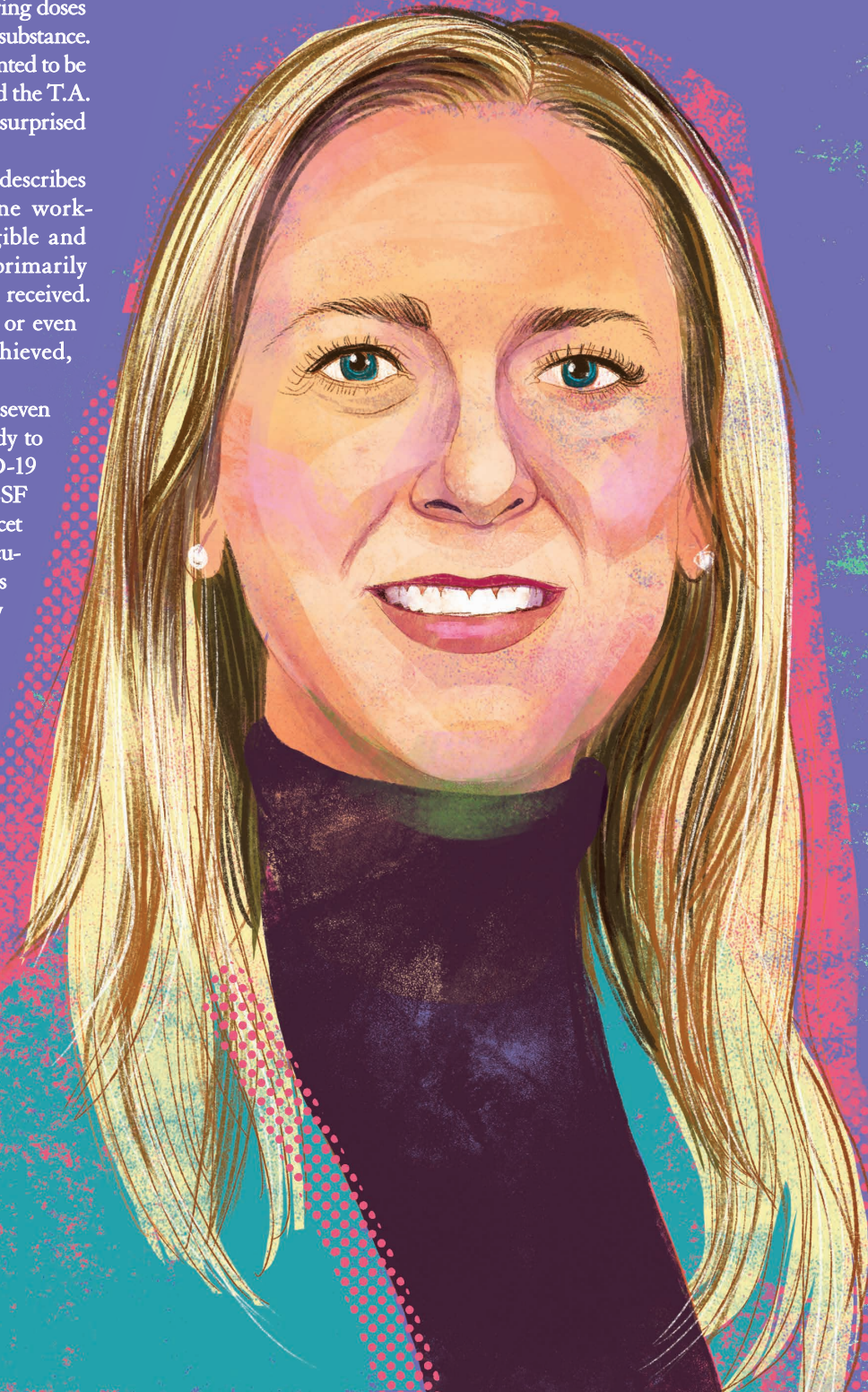
At the beginning, those managing the rollout huddled many times a day to discuss what went right and what went wrong. Most wrinkles were easy to iron out. One was not.

"Appointments are scheduled based on the anticipated supply, but this has been in flux," she says. "Unfortunately, vaccine schedules have had to be adjusted last-minute."

As the rollout continues, supply has become more dependable. In the meantime, some patience and a can-do attitude go a long way.

"It's not a 'We can't.' It's just 'How are we going to do this?'" Kroon says. "That's UCSF."

■ Katherine Conrad



SCHOOL OF NURSING

Francisco Alvarez, MS '19, RN

Caring for Kids with COVID Complications

The patients arriving in Francisco Alvarez's emergency department at Valley Children's Hospital in Fresno have changed: fewer sniffles and scrapes, far more serious symptoms.

"We had to actually shift the way we were practicing because of COVID," Alvarez says. "The kids are coming in sicker than before because there's that delay – that fear of coming into an ER now."

Some have a condition called multisystem inflammatory syndrome in children (MIS-C), which can affect children with COVID. Symptoms of MIS-C include fevers, rashes, gastrointestinal issues, and even heart damage. MIS-C is rare, but Fresno has one of the highest per-capita case counts of the condition in the country. Alvarez, who works to improve care for acutely ill children, has already identified several with MIS-C.

"It's scary," he says. "Before, a kid could come in with one to two days of fever and look pretty sick. You could give them medication. They could look a lot better. You could send them home. Now, if they have a COVID history, we really have to discern whether this is MIS-C. If it is, we need to get them treated because it can be fatal."

In December, the coronavirus spread faster in Fresno County than in any other metro area in the nation. To take pressure off other medical centers, Valley Children's has even accepted some adult patients with COVID. In addition to his role as a nurse practitioner, Alvarez serves as a hospital supervisor, managing the high-stakes logistics of transport and care for COVID patients.

It's stressful work, but his time at UCSF prepared him for it. Administrators arranged for him to train at Valley Children's because he hoped to work there. Many migrant farm workers live in Fresno, and Alvarez knew a lot of them struggle to navigate the health care system. He'd seen firsthand how overwhelming it could be; when he was 21, he lost his own father to cancer, just a few weeks after his diagnosis.

"I try to recall how completely caught off guard we were," Alvarez says. "I always try to make sure families know what to expect and get their questions answered. It helps being able to speak Spanish fluently, being able to reassure families that are very underserved."

■ Elizabeth Daube

ILLUSTRATIONS: JOHN JAY CABUAY



GRADUATE DIVISION

John Chodera, PhD '06

Crowdsourcing a COVID-19 Drug

Last year, John Chodera and his colleagues accidentally created the fastest computer on Earth. The system, called Folding@home, is not a single, mammoth machine but a vast network of personal computers using their idle time to solve scientific problems. When the coronavirus pandemic hit, Chodera – who leads a computational biophysics lab at the Sloan Kettering Institute, the experimental research arm of Memorial Sloan Kettering Cancer Center – was about to jet off to Berlin for a visiting professorship.

Instead, he found himself holed up in his apartment repurposing Folding@home to fight COVID-19. He wrote up a blog post and, soon, almost a million new volunteers had linked their computers to the global network. By March, the system was crunching data nearly 10 times faster than the world's fastest supercomputer.

"It was completely nuts!" Chodera says over Zoom, against a background view of the cosmos from the bridge of *Star Trek's* USS Enterprise. Behind him, the starship's animated controls blink and whirl.

The extra processing power turned out to be a boon because Folding@home was about to take on its biggest challenge yet. It began with a tweet. Some scientists in the United Kingdom had identified a set of chemical fragments that attach to a vital coronavirus protein, and they posted the data online. Then scientists from PostEra, a machine-learning company, decided to try to turn the fragments into antiviral molecules that could treat COVID-19. But first, they'd need some drug-design ideas. So they asked the internet.

The response was overwhelming: Hundreds of people submitted more than 7,000 designs. That's when Chodera joined the fray. He realized that Folding@home, with its unparalleled processing power, could sort through the designs and then run the virtual experiments needed to turn the most promising leads into viable candidates for a COVID-19 oral antiviral drug.

And it did. The bootstrapped project, dubbed COVID Moonshot, is now preparing its candidate molecules for preclinical studies in anticipation of human trials.

"Usually, it takes years and millions of dollars to discover a new drug," Chodera says. "The fact that we've done this so quickly, with open-source tools and whatever we found in our sofa cushions, is pretty awesome."

■ Ariel Bleicher



SCHOOL OF DENTISTRY

Ramneek Rai, DDS '09

Championing Dental Safety

When the pandemic struck, Ramneek Rai was just two years into her role as director of health and safety for the School of Dentistry. In mid-March 2020, the UCSF Dental Center – which normally handles some 120,000 patient visits a year – had to suspend all but emergency services.

As news spread about the novel coronavirus's airborne transmission, "the anxiety was palpable among our staff, residents, students, and faculty," she says. "We were at high risk of exposure." Yet despite her colleagues' anxiety, Rai says, they were eager to return to campus to provide care.

It fell to Rai to help put safety measures in place so the Dental Center could reopen, not only to serve patients but also so dental students could complete their training requirements and graduate on time.

For the first few months, Rai had many sleepless nights. She felt that the safety of everyone who stepped through the School of Dentistry doors was her responsibility. "This is what my role is meant for," she says. "There was only one way forward: Step up to the challenge and do what needed to be done."

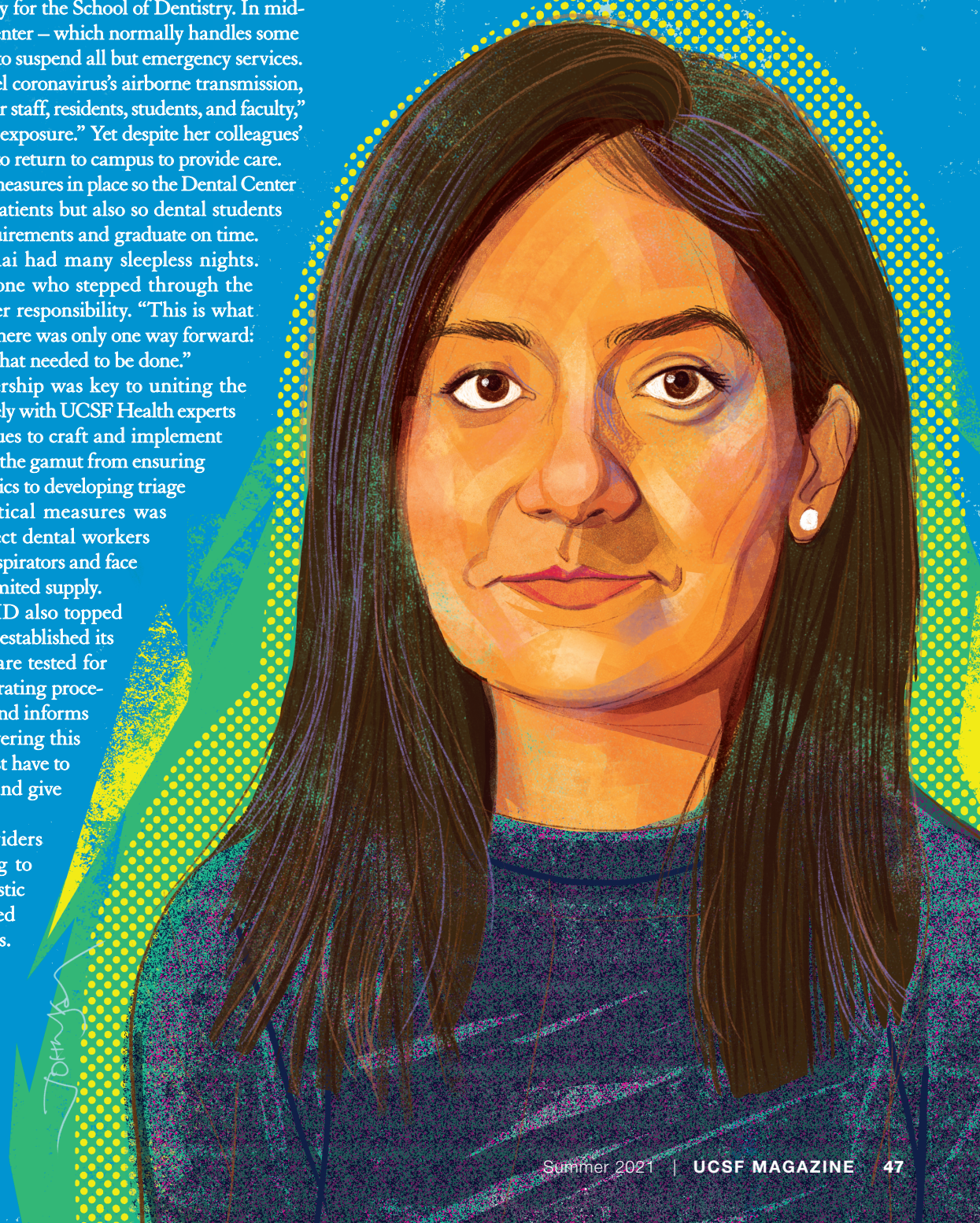
Dean Michael Reddy's leadership was key to uniting the stakeholders. Rai collaborated closely with UCSF Health experts and her dentistry faculty colleagues to craft and implement myriad safety protocols. They ran the gamut from ensuring adequate ventilation in all the clinics to developing triage strategies. One of the most critical measures was providing PPE designed to protect dental workers against aerosols, including N95 respirators and face shields – even through times of limited supply.

Screening patients for COVID also topped the list of safeguards. The school established its own testing site, where patients are tested for COVID prior to any aerosol-generating procedures. Rai reviews all the results and informs patients who test positive. "Delivering this news is never easy," she says. "I just have to support them as a human being and give them the best path forward."

Now that patients and providers alike feel comfortable returning to the clinic, "I'm cautiously optimistic the bulk of the hard work related to COVID is behind us," Rai says. "Everyone at the school was vested in coming back to provide care, safely. That's what I'm really proud of."

■ Miika Rivera

ILLUSTRATIONS: JOHN JAY CABUAY





In April 2020, I was assigned to document the 40 UCSF physician and nurse volunteers who traveled to the Navajo Nation when it suffered one of the country's highest infection rates of COVID-19. I followed the teams door to door as they provided care to Navajo residents sheltering at hotels. When Archna Eniasivam, a physician and assistant professor, visited Ronald Hood, he'd been struggling. He seemed grateful for her attentiveness and care and for the medicines and meals he received. Most of the residents, alone and separated from loved ones, had formed a bond with their caregivers over the weeks. Because of that trust, Ronald graciously allowed me to document his visit with Dr. Eniasivam. I felt privileged to have been allowed to capture the intimate moments between them.

— Barbara Ries

Bay Area photographer Barbara Ries's series of images from the Navajo Nation won a prestigious Grand Gold Award in the Council for Advancement and Support of Education's regional awards competition. The Navajo Nation project was coordinated through UCSF's HEAL (Health, Equity, Action, and Leadership) Initiative.

PHOTO: BARBARA RIES



Rebecca Amirault, CNM, left, an associate professor in the Department of OB-GYN & Reproductive Sciences, and her colleague Jessica Kim, MD, a fourth-year resident, get their COVID-19 vaccinations together.

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