STANFORD MEDICINE

Issue 2 / 2023

special report

HEALTH ON A PLANET IN CRISIS

Beyond climate dread
In pursuit of solutions at Stanford Medicine

It's not easy being green
Attaining greater sustainability in the OR

Wildfires, evacuations and power outages
Climate-proofing schools

America's dirty secret
An environmental justice advocate on our sewage problem

Mystery solved
The unexpected source of lead poisoning in Bangladesh

plus

Sniff
Making sense of smell

Special delivery
mRNA moves past COVID-19

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SELF-COMPASSION

A NIGHT SHIFT DOCTOR EXPLAINS HOW HE FINDS MENTAL FORTITUDE

In the middle of a recent overnight shift, Al'ai Alvarez, MD, got goosebumps after resuscitating a patient involved in a motor vehicle crash. He reminded his team during the debrief, "This feeling you're having right now, this is what it feels like to save a life."

He pointed this out because he knows that while we're good at remembering when we make mistakes, our memories of what goes right tend to fade quickly. Remembering these good moments is a key to practicing self-compassion — the ability to be kinder to yourself during tough times, said Alvarez, a Stanford School of Medicine clinical associate professor of emergency medicine and a national expert in teaching wellness practices to medical professionals.

Al'ai Alvarez, MD, an emergency medicine doctor and physician well-being expert, urges medical professionals to be kinder to themselves.

Alvarez is also a member of the emergency department's nocturnist team — the crew that works nights. He loves the sense of continuity found by working within the nocturnists' tight-knit, smaller community, he said, but the schedule can be straining. Learning to set strict boundaries with his time inspired his work in physician well-being.

The field emerged out of concern over rising levels of physician burnout, and solutions like Alvarez's approach are gaining traction.

Among his physician wellness leadership roles are posts as the director of well-being for the Department of Emergency Medicine, chair of Stanford WellMD and WellPhD's Physician Wellness Forum, and chair of wellness committees at two leading emergency medicine societies.

In a recent conversation, Alvarez shared lessons he's learned about caring for oneself while practicing medicine.

How do you cultivate self-compassion?

According to Kristin Neff, a pioneer researcher on the topic, there are three parts to self-compassion. The first is that we must be kind to ourselves. The second is knowing that suffering is common. And the third part is practicing mindfulness, micro-moments of self-awareness of what we're feeling and experiencing.

In the emergency department, we work with patients who are at their worst. When bad things happen we, as physicians, need to lean into self-compassion so we can understand our role versus what is beyond our control. Then we can be kinder to ourselves, including forgiving ourselves for not having all the answers.

Why is self-care key to your work as a physician?

What most people don't see is the list of failures I've had, the embarrassing moments, things physicians experience yet feel shame or guilt sharing. There's this idea in some professions of failing fast and often, so you can iterate and find the best solution. But failing is not an event to embrace in medicine, because failing fast for us can mean that patients die.

When I practice self-compassion, I own what I can change. And while the notion of embracing failing that may be associated with someone's death is a challenging moral dilemma, I can still be kinder to myself. I understand that even though I've been an attending doctor for more than 10 years, I still have room to grow. And I know this growth mindset is what we need to be better physicians for our patients and to be better colleagues.

How does caring for people help you find compassion for yourself?

It helps me recognize our common humanity: Just like me, my patients experience suffering. Knowing this gives me a sense of empathy. I also practice taking care of other health care workers, because they have been trained not to prioritize their own suffering so they can take care of others. To sustainably care for our patients, we need to understand that it's OK, and in fact necessary, to care for ourselves while also taking care of others. This includes allowing ourselves to pause and acknowledge the many goosebumps moments of simply doing good. **SM**

— EMILY MOSKAL

TIMOTHY ARCHIBALD

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letter from the dean

With every passing day,
we see frightening new examples of climate extremes impacting public health.
Uncontrollable wildfires now persistently threaten the western United States. Chronic exposure to their smoke increases rates of asthma and pneumonia while exacerbating the risk for lung cancer, stroke, cognitive decline and premature birth. The young and the elderly are hit hardest. Nursing homes struggle to protect their residents. Schools shut down or keep students inside.

This past winter, communities up and down the West Coast experienced a jarring ricochet as the drought gave way to a deluge of rain. Wave after wave of atmospheric rivers battered California — inundating entire towns, flooding vital farmland and paralyzing mountain communities under multiple feet of snow. This misfortune is a microcosm of a worldwide environmental crisis.

The sheer scope of climate change is daunting but, as physicians and scientists, we do not shy from big challenges. Look no further than early 2020, when a mystery virus raced around the world, and the biomedical community ran toward the crisis to provide vital patient care and research this new threat.

History is full of similar stories — from the development of life-saving cancer treatments to incredible advances in organ transplantation — that are marked by the relentless determination of scientists laboring for years before achieving success. When Dr. Norman Shumway and his Stanford team transplanted the first human heart in the United States in 1968, it was a landmark moment — and the first step on a long road. After the surgery, Dr. Shumway said, "Our work is just beginning."

Indeed, despite their success, they faced formidable hurdles. It would take another decade, with the advent of more effective immunosuppressive drugs, before organ transplantation success rates would climb significantly. Even today, Stanford Medicine researchers continue to investigate and improve transplantation science, unfazed by the magnitude and complexity of their work.

This issue of *Stanford Medicine* magazine illustrates how scientists go about tackling challenges that seem so intractable they're called "wicked" problems. In story after story, you'll see how Stanford Medicine physicians and researchers carve off a piece of the problem. They identify actionable targets. They gather data, analyze, test. They try again. And again.

The gamut of projects covered in this issue is remarkable, ranging from water safety and dust mitigation to greener, healthier housing materials and sustainable operating rooms. Here is how our Stanford Medicine community is improving human health right now while advancing our ability to address future threats. Here is what's possible when we engage the expertise and brilliance across our campus, health systems and local communities. Here are reasons for hope in the face of daunting challenges.

I am extremely proud of how Stanford Medicine students, physicians and researchers are rising to meet the array of challenges associated with climate change. I'm also mindful that we aren't alone in this task. We are one node of a potent global network of academic medical centers, industry labs and government institutes that are working toward the same goal.

This is science in action — and if you're like me, you will find it incredibly inspiring.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of Stanford School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

PHOTOGRAPH BY GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

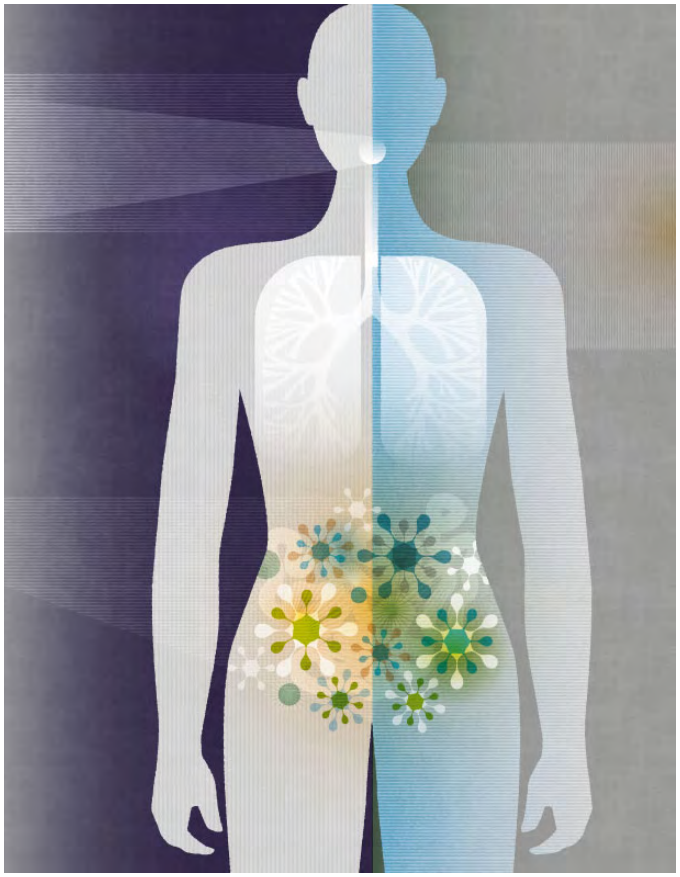
Designer dieting

THE BACTERIA LIVING IN YOUR GUT and the amounts of certain proteins made by your body can affect your ability to sustain weight loss, according to research published in the December 2022 issue of *Cell Reports Medicine*. And some people, it turns out, shed more pounds on low-fat diets while others do better on low-carb diets.

The research indicates a future for personalized diets.

"There are people who can be eating very few calories but still sustain their weight because of how their bodies metabolize fuels," said Dalia Perelman, a research dietician and co-lead author on the paper. "It is not for lack of will. It is just how their bodies work."

By measuring the ratio of inhaled oxygen to exhaled carbon dioxide in the study's 609 participants, the researchers could tell whether carbohydrates or fats were their body's primary fuel source.



That is one key biomarker the researchers identified — they also examined gut microbiome and proteomic analysis — and it will likely lead to a future in which diets are individualized via metabolic testing.

"If you are following a diet that worked for someone you know and it is not working for you, it might be that that specific diet is not as suited for you," said Xiao Li, PhD, co-lead author of the paper and a former postdoctoral fellow in the Department of Genetics.

ILLUSTRATIONS BY PAUL WEARING

Go get it

OFTEN, THE KEY TO cracking down on the mob is to "turn" one mobster into an informant. That's the approach researchers took in altering cancer cells so they train the immune system to fight back.

T cells, part of the immune system that learns to identify and attack new pathogens, can be trained to recognize specific cancer antigens — proteins that generate an immune response.

The researchers turned cancer cells into special cells that "inform" on the cancer, telling the T cells: "Here's what the cancer looks like — go get it."

"We couldn't believe it worked as well as it did," said Ravi Majeti, MD, PhD, a professor of hematology and senior author of a study published in *Cancer Discovery* in March 2023.

Chicken-inspired pain solution

CHICKEN FARMERS KNOW THAT FEED LACED WITH CAPSAICIN — the chemical that gives chiles their spiciness — is a turnoff for marauding squirrels and mice, while their chickens eat it up. This is because in squirrels, mice and other mammals, including humans, capsaicin activates a pain receptor, known as TRPV1, to cause a burning sensation. In most bird species, it has little effect.

"It turns out that birds are naturally resistant to capsaicin," said Eric Gross, MD, PhD, associate professor of anesthesiology, perioperative and pain medicine.

This difference led Gross and his collaborators to pursue a drug that makes mammalian pain receptors more like those in birds — and more resistant to some forms of pain.

In a study published in February 2023 in the *Journal of Clinical Investigation*, the team identified a rare genetic variant in humans that modifies the receptor and reduces pain sensitivity. Mice with this mutation were less bothered by capsaicin and would even eat spicy bird food.

Gross, senior author of the study, estimates that the mutation reduced pain by about 50%.

"You don't want to take away the full sensation of pain," he said. "You still want to have somebody, if they place their hand over a hot stove or step on a Lego, to have that pain sensation."

The researchers have designed a molecule that replicates the variant's effects and hope to modify it so it can relieve pain longer.

"We're really excited to see if this is a potential therapeutic for pain after surgery and to help us move toward an opioid-free approach," Gross said.

AN AI APPROACH TO EPILEPSY DRUGS

Current testing of less-costly seizure-reducing epilepsy drugs requires days to weeks of video and brain activity monitoring, said neurosurgery professor Ivan Soltesz, PhD. It's a major bottleneck in drug discovery for the disease, he said.

He and his collaborators are studying a new method that employs machine learning to do the job in just one hour, whether or not a seizure occurs during that time. In February 2023, they published a paper in *Neuron* describing the approach's success in mouse studies. Soltesz was the senior author.

A key to long COVID

Researchers have found a mechanism behind one of the most common symptoms of long COVID — shortness of breath caused by lung fibrosis — and a new avenue to pursue for remedies.

In lung fibrosis, normally thin walls in the lungs' air sacs become thick and scarred. In long COVID patients this scarring can be debilitating and hard to treat, said Gerlinde Wernig, MD, an assistant professor of pathology and senior author of a February 2023 study published in *Proceedings of the National Academy of Sciences*.

Previous Wernig research uncovered pulmonary fibrosis characteristics of scar tissue formation that played out similarly in the long COVID study: a spike in production of interleukin-6, a protein indicative of chronic inflammation and scar formation; an increase in production of CD47, a protein that helps fibroblasts responsible for scar tissue formation to proceed unchecked; and an increase in the pJUN protein, a promoter of scar formation.

The good news is that, in mice, the team found very little fibrosis after blocking CD47 and interleukin-6. "This hints at possible treatments for long COVID involving drugs that carry out targeted immune blockades," Wernig said.

Predicting preemie health

Scientists have developed a machine-learning algorithm that analyzes electronic health records of mothers and their babies to predict which premature newborns are likely to develop health problems in their first two months of life. Knowing which infants are vulnerable could enable targeted preventive measures. "This is a new way of thinking about preterm birth, focusing on newborns' individual health factors rather than only how early they are born," said Nima Aghaeepour, PhD, associate professor of anesthesiology, perioperative and pain medicine and of pediatrics. He was the senior author of a study describing the method, published in February 2023 in *Science Translational Medicine*. The study used data from the electronic health records covering 32,354 births between 2017 and 2020.

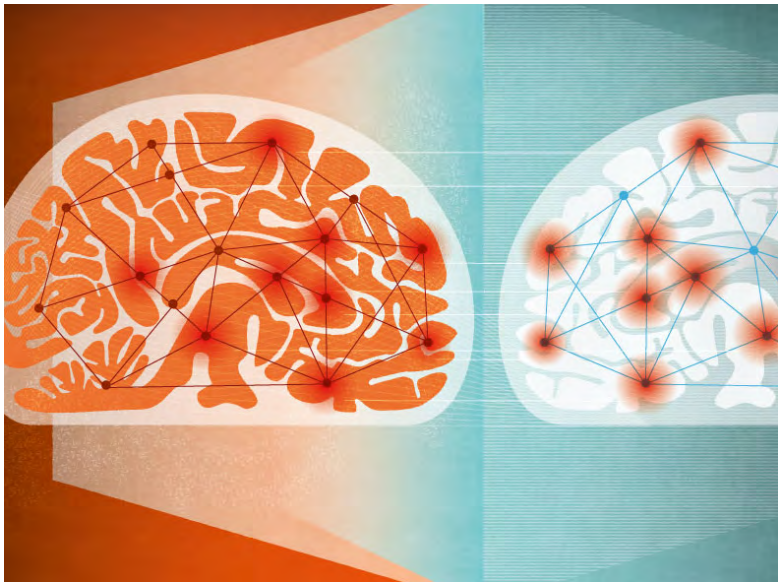
ANXIOUS HEARTS

IT'S INTUITIVE THAT feeling scared quickens the pulse, but is the reverse also true? Does a faster heart rate generate anxiety? Karl Deisseroth, MD, PhD, a professor of bioengineering and of psychiatry and behavioral sciences, first pondered the relationship between the body and emotions as a psychiatry resident, when he learned that certain cardiac diseases correlate with anxiety disorders — but nobody knew why.

Decades later, his team has found a way to study that relationship in mice. In an article published in March 2023 in *Nature*, they showed that a racing heart can make mice more anxious in risky situations.

They developed a non-invasive pacemaker, worn like a tiny vest, that precisely controls a mouse's heartbeat, then used it to boost the pulse to 900 beats per minute, typical of an anxious mouse. A faster heart rate alone made no difference. But if the mice were in a risky situation — like an open, unprotected space — the faster heart rate amplified their anxiety.

The researchers traced this change to the insular cortex, a brain region that "receives all kinds of information from all across the body, so it could be playing a general role across a broad range of emotional states," Deisseroth said.



Mirroring aggression

IN NATURE, TWO ANIMALS FIGHTING ARE SELDOM WITHOUT AN AUDIENCE. Stanford Medicine researchers wondered how animals watching from the sidelines perceive aggressive interactions.

"Aggression is usually not only to defeat the other animal but also to tell others in the vicinity, 'Hey, I'm the boss.' It's a public display," said Nirao Shah, PhD, a professor of psychiatry and behavioral sciences and senior author of a study published in February 2023 in *Cell*.

Shah's team recorded brain activity in two male mice fighting and in another observing the fight through a transparent divider. (Simply placing one male mouse into another's cage will trigger territorial aggression.) They found a nearly identical set of neurons in the "rage center" of the brain that fire in fighters and in observers during a brawl — making them the first mirror neurons discovered in mice.

Finding mirror neurons in mice was "pretty shocking," Shah said. Most research on such neurons has focused on primates, in the cortex, the most evolutionarily advanced part of the brain, which controls processes such as thinking, reasoning and memory. But in mice, they were in the hypothalamus, which regulates basic bodily functions like temperature and appetite — hinting at a more primal origin for mirror neurons than previously thought.

Next, the team showed that these mirror neurons not only responded to behavior but also controlled it.

When researchers inhibited these neurons, the mice became less confrontational. When they activated these neurons, the mice became indiscriminately hostile.

The fact that aggression-mirroring neurons exist in such a primitive part of the brain indicates they may have been conserved across evolution, from mouse to human, Shah said.

"It suggests that we might have the same neurons, and maybe they encode some qualities of aggression in ourselves," he said.

BEYOND CLIMATE DREAD

Striving to improve health during the environmental meltdown

By Ruthann Richter

ILLUSTRATIONS BY ANUJ SHRESTHA

PORTRAITS BY TIMOTHY ARCHIBALD

When you think of the climate crisis and the major impact it will have upon all corners of the world, one nation stands out as the epicenter of the unfolding cataclysmic changes: Bangladesh.

When Stephen Luby, MD, began working there two decades ago, the South Asian country was facing tremendous climate stress brought on by intermittent floods, extreme heat, cyclones and drought that threatened human life. But as bad as it was then, the impact of climate on people's health there has become progressively worse, said Luby, an epidemiologist who worked for the U.S. Centers for Disease Control and Prevention in Bangladesh before joining the Stanford School of Medicine's faculty.

With shrinking land caused by the rising sea levels and changes in river flows that are reducing fresh water supplies, the low-lying nation is reaching a point where it will no longer be able to produce enough food for its people, he said. At the same time, the weather has become erratic. As one of the world's most densely populated countries with large portions near sea level and thus prone to flooding, Bangladesh is considered a canary in a coal mine for the climate crisis.

"For centuries we had dry years and wet years, but it was a stable system. More recently, though, greenhouse gas emissions, destructive land use and damaging fertilizers have pushed the country outside the area where it can come back into balance," he said. "We are biological creatures, and we have not tended to our life-support system — the health of the planet — in ways we need to."

Luby is among a growing number of Stanford Medicine community members dedicated to finding solutions to these urgent problems of planetary and human health.

"I do think we have an obligation because we are one of the world's leading universities and this is the great crisis of our time," said Luby, who's also a senior fellow at the Stanford Woods Institute for the Environment.

As signatories to the Biden administration's new climate pledge to cut greenhouse gas emissions by 50% by 2030 and eliminate them altogether by 2050, Stanford Medicine leaders are working toward greater planetary health and health care sustainability.

Though Stanford Hospital and Lucile Packard Children's Hospital Stanford have been certified as among the country's most sustainably constructed hospitals, the institutions leaders continue to scrutinize every aspect of operations — from heating and cooling, to supply chain management and even food services — to limit their carbon footprint.

"One of the primary reasons for Stanford Medicine to move very assertively into sustainability is that we can be a role model," said Helen Wilmot, chief facilities and sustainability officer at Stanford Health Care. "Not only do we have the resources, but we also have the intellectual energy — people who want to make a difference on this issue."

Christy Foster, the director of sustainability at Stanford Medicine Children's Health, said the need for action became starkly apparent after she and her colleagues took part in the first annual Global Climate Action Summit at Stanford in 2020.

"It was this 'aha' moment," Foster said. "We all had evidence that the climate crisis was a problem, but it was also having an impact on the very patients we were trying to heal."

She said climate change was no longer an abstract concept, as California was facing multiple weather emergencies — extreme summer heat and some of the worst wildfires in decades caused by intensifying drought — that led to an influx to Northern California hospitals of children with severe respiratory problems and pregnant women suffering heatstroke, high blood pressure and other problems.

"I feel we have a responsibility to deliver the same quality of medicine that we have for years, but we have to do it in a way that minimizes our impact, both locally and globally," she said.

Consequences for human health

Michele Barry, MD, director of the Stanford Center for Innovation in Global Health, has seen firsthand how changes in the environment have affected people's health, particularly in low-income countries. For instance, outbreaks of many of the hemorrhagic viruses — such as Ebola, which she has studied — are a result of land clearing for crops and domestic use that put humans in close contact with animals carrying deadly viruses.

"We have definitely seen spillover incidents such as the Ebola epidemic happen as our land use changes and we encroach on animal habitats," said Barry, a tropical disease doctor.

Additionally, climate change is leading to new patterns of disease and placing at risk global food supplies, water, personal safety and mental health, she said.

'... WE HAVE NOT TENDED TO OUR LIFE-SUPPORT SYSTEM — THE HEALTH OF THE PLANET — IN WAYS WE NEED TO.'

"I think we are on red alert. It should be all hands on deck with what is happening in our climate," she said. "When the new normal in California is atmospheric rivers and excessive wildfires, that should be a wake-up call domestically. Globally we're seeing huge shifts of disease due to climate and distribution of vectors like mosquitoes and ticks."

Her center identified it as a top priority in 2017 and funds dozens of initiatives to address the problem — from projects in South Asia to reduce coal consumption to studies of how dams and other agricultural systems are causing a rise in parasitic diseases.

Projects and programs aimed at solutions

STANFORD HEALTH CARE SUPPORTS research projects that address the problem locally. Nine faculty and staff have received funding under the health system's Seed Grant Program for Sustainability to find ways to reduce the carbon footprint of Stanford Hospital operating rooms, minimize waste in the emergency department and reduce hospitalwide water consumption. In addition, five nurses are using funds from the Stanford Health Care Sustainability in Nursing Fellowship to examine various methods to minimize waste, reuse products where possible and reduce employee commutes, among other projects.

The Stanford School of Medicine is co-sponsoring a program for redesigning living systems to tackle sustainability challenges. Seed grants for Synthetic Biology for Sustainability support multidisciplinary groups of researchers who can build or modify cells, molecules, organisms or other biological systems with the aim of solving environmental problems. The program is a joint effort with the School of Engineering and the Doerr School of Sustainability.

Luby is spearheading the creation of a Center for Human and Planetary Health within the Doerr School in a collaboration between the Woods Institute and the Center for Innovation in Global Health. He envisions it as an opportunity for environmentalists and physicians to collaborate on improving the health of humans and the Earth.

He is continually motivated by students who are profoundly concerned about the planet's future, he said.

"We have to think beyond climate dread. People are feeling disempowered and frustrated, and they turn to us and say, 'Where do we go? What do we do?'" he said. "We have a responsibility to give them a toolkit so they can advance solutions. We can train the workforce and motivate people so that we are all solution oriented."

The following examples illustrate how members of the Stanford Medicine community are striving for solutions.

Dangerous dust

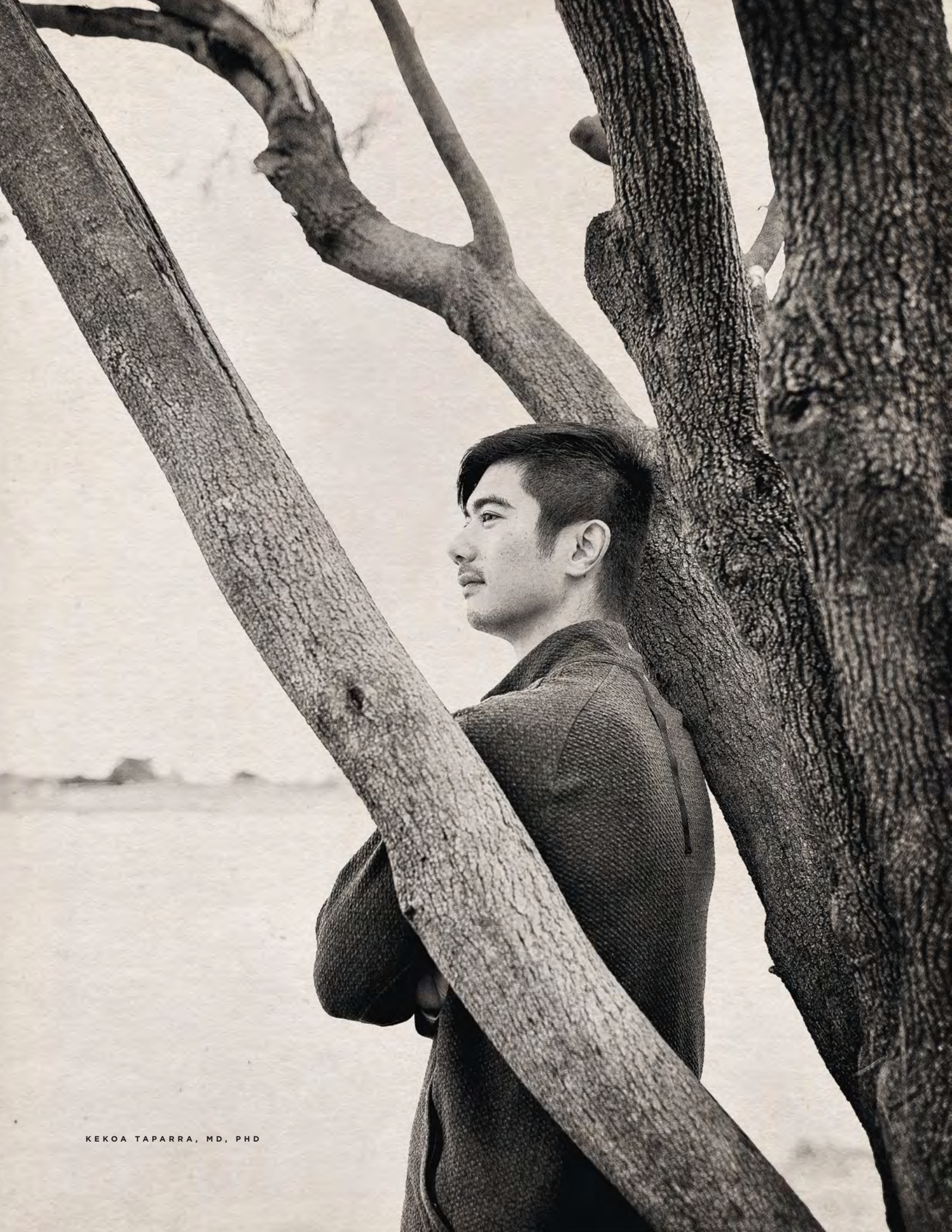
ERAN BENDAVID, MD, WAS STUDYING the effects of global warming on child health when he realized there was a far bigger environmental threat to kids: dirty air.

While poring over health data on a million children in sub-Saharan Africa, Bendavid and his colleagues discovered that poor air quality is as great a risk to the region's children as major killers like malaria or the flu, he said.

"We found that 15-20% of infant deaths were linked to poor air quality," said Bendavid, an associate professor of medicine and a senior fellow at the Woods Institute for the Environment. "We start seeing adverse effects as soon as air quality starts deteriorating. It raises the risk of pneumonias, stunted growth and other factors that increase a child's risk of death."

While air pollution in sub-Saharan African countries includes obvious sources like burning trash, indoor cooking and brush fires, one major source is underappreciated: dust that drifts from the Sahara Desert.

"Parts of the Sahara raise some of the world's biggest dust storms. They are so large that they cross the Atlantic Ocean and can be measured in the Amazon," he said. "When those dust storms pick up, it makes a big difference for air quality in most



KEKOA TAPARRA, MD, PHD

of Central and Western Africa, and it impacts these very young children who are especially vulnerable in the first year of life."

Experts predict that these storms will become more frequent and severe because of drought conditions brought on by climate change. The particulate matter from Saharan dust could account for as much as 24% of infant mortality, Bendavid and collaborators, including Stanford University environmental scientists Sam Heft-Neal, PhD, and Marshall Burke, PhD, reported in a 2020 study in *Nature Sustainability*.

The scientists suggested using underground water sources to dampen the surface of the desert, a technique found to be effective on a small scale in California, Bendavid said.

"We propose to pump a little bit of water from groundwater wells to improve the dust conditions in those areas," a low-cost solution, he said.

Conserving water in hospitals

A NATIVE HAWAIIAN, Kekoa Taparra, MD, PhD, grew up surrounded by water and appreciating the value of this precious resource. Now, he's researching ways to conserve it in one of the nation's top water-consuming industries: hospitals.

Among commercial buildings, hospitals are the country's leading users of water, with a 2017 U.S. Energy Information Administration study finding that they use more than double that of all large buildings in the country, Taparra said. Hospitals require water for cooling and heating, plumbing, cleaning and maintaining equipment, among other activities.

"We really have to be intentional about the water used throughout the hospital and per patient," said Taparra, a third-year radiation oncology resident, noting that water is becoming an increasingly scarce global commodity.

Unlike electricity, there is no metric or "gold standard" on acceptable levels of water consumption in hospitals, and there is little understanding of how much water is used or wasted in the medical care system. He hopes to help fill the gap through a new project at Stanford Health Care to quantify water use and see how that compares with other non-hospital facilities.

Supported by a 2022-2023 Stanford Health Care Sustainability seed grant, Taparra has developed a three-part approach to evaluating water use in hospitals. First, he has gathered data from 2018 to 2022 for seven hospital and clinic facilities and plans to contrast that with water usage in non-hospital buildings on campus and across the country.

He's also developing a model of how seasonal variations in temperature and hotter weather have affected hospital water usage: "With average temperatures rising and the occurrence of increased instances of heat waves, are we using more water in our hospitals?"

Finally, he plans to measure water usage in the Department of Radiation Oncology, where clinicians use technologies that deliver energy to target and kill cancers, producing heat as a by-product. These machines must be constantly cooled with chilled water, so Taparra plans to install a meter to gauge the flow to compare water use between different radiation therapy machines.

A leader in the field of radiation oncology, Stanford Medicine recently installed some next-generation machines for advanced cancer treatment, he said. "Stanford is known for these unique technologies, but we must ask, are they sustainable?" Taparra hopes to have some answers by early 2024.

Plastic: a mosquito's dream

DESIREE LABEAUD, MD, WHO HAS conducted epidemiology research in Kenya for two decades, was speaking to a group of Kenyan school children several years ago, when a previously unrecognized source of disease came into focus.

"I asked the students, 'Where do you see the mosquito vectors?" which are major breeders of many important infectious diseases. "They said, 'In the piles of trash behind our homes and schools.'"

Man-made containers like plastic bottles are a primary source of disease-carrying vectors in many low-income

'WE REALLY HAVE TO BE INTENTIONAL ABOUT THE WATER USED THROUGHOUT THE HOSPITAL AND PER PATIENT.'

‘THERE IS NO FORMAL RECYCLING HERE, ONLY AN INFORMAL RECYCLING TRADE, SO PLASTIC HAS LITTLE VALUE ON THE MARKET.’

countries like Kenya, as they provide the ideal habitat for the Aedes aegypti mosquito, which spreads dengue, chikungunya, Zika and yellow fever viruses.

In early 2021 in south coastal Kenya, LaBeaud, a pediatric infectious disease specialist, developed a community nonprofit, the Health and Environmental Research Institute-Kenya, to educate people in the community about the environmental and health hazards of leaving plastic lying around and mobilize them to recycle, reuse or remove it. HERI-Kenya is supporting the creation of circular economies of waste to find solutions to the ongoing pollution crisis and create local economic opportunities and jobs from this unlikely resource.

“There is no formal recycling here, only an informal recycling trade, so plastic has little value on the market,” said LaBeaud, a professor of pediatrics, a senior fellow at the Woods Institute for the Environment and an adviser at the Center for Innovation in Global Health. “About 75% of it is burned, creating toxic pollutants, or finds its way into oceans, choking marine life, or on land where it breeds mosquitoes. This is a problem not just in Kenya but in most of the world.”

The nonprofit aims to empower community members, scientists and policymakers to create a culture of sustainability while building expertise in environmental health research with the ultimate goal of improving community health, said LaBeaud, who is on sabbatical in Kenya to focus on the organization. In April, the group opened an environmental learning resource center to train people in waste management, circular economies and eco-friendly practices. And it is organizing regional community groups composed of varied stakeholders — from local business and government to nonprofits and recyclers — to implement new community-based initiatives and find local solutions.

Through the organization, whose acronym HERI means blessed or happy in Swahili, community members conduct beach and urban cleanups and plant trees. They also plan to work with recyclers to turn durable plastics into building products like pavers, roofing tiles and bricks, she said.

With a grant from the Stanford Visiting Artist Fund in Honor of Roberta Bowman Denning, the nonprofit commissioned artist Jean Shin to create two sculptures out of plastic waste to highlight the plastic pollution crisis. In Kenya, the organization hired more than 50 residents to transform more than 7,000 single-use plastic water bottles into a massive wave. The sculpture was unveiled in the center of the Diani/Ukunda urban area on Earth Day 2023. The second sculpture will sit in the Biomedical Innovations Building on the Stanford Medicine campus.

The greening of cement

MILLIONS OF THE WORLD’S children grow up crawling around and playing on dirt floors, which can hide disease-causing bacteria and parasites, including soil-transmitted helminths. These worms lodge in the intestine and can cause persistent diarrhea, pain and malnutrition and can slow physical and cognitive growth.

Jade Benjamin-Chung, PhD, an assistant professor of epidemiology and population health, is experimenting with a


JADE BENJAMIN-CHUNG, PHD

sustainable approach to eliminating this risk and improving the long-term health of children and their mothers.

Before coming to Stanford Medicine, Benjamin-Chung worked with Luby as an epidemiologist in Bangladesh and saw the hardships of life in homes with dirt floors. Now she has a National Institutes of Health grant to replace dirt floors in some Bangladeshi homes with concrete, then measure the impact on the health of the children and their mothers. She said she believes the concrete floors could significantly lower infection rates.

But in planning the study, she decided to use a low-cost "green" form of cement — one of the key ingredients in concrete — in the interest of long-term sustainability. The production of such green cements emits less greenhouse gas than production of traditional cements.

The manufacturing of cement is one of the leading causes of greenhouse gas emissions and a major source of global pollution, she said. At least 8% of global carbon emissions caused by humans come from the cement industry, according to a 2021 article in the journal *Joule* by Imperial College London professor Paul Fennell and others.

"One of my engineering colleagues who is collaborating on this study encouraged me to look into these novel, green cements that could even be produced with existing materials," Benjamin Chung said.

She obtained a Woods Institute for the Environment grant to experiment with different concrete ingredients, including fly ash, an often-discarded byproduct of coal processing.

The researchers are planning to enroll 800 households in rural Bangladesh in a study that will test the green floors against traditional concrete and dirt in a subsample. The participants will all be pregnant women whom researchers will follow for two years as they give birth to and raise their children.

They will test the children and the homes for parasitic worms and other infectious agents, while assessing the mothers for depression, stress and quality of life. Benjamin-Chung speculated that the mothers' health will improve because they will find it easier to cook on and clean a concrete floor and will feel better generally about their home environment.

"The overarching question involves the health of the children and their mothers, but we are also taking planetary health into consideration from the very beginning," she said. "I hope this will be a template for future studies that will encourage researchers to consider potential impacts of health interventions on the climate."

Climate anxiety

IN 2021, BRITT WRAY, PHD, co-authored a study of more than 10,000 young people in 10 countries who said they were profoundly anxious about climate change. About three-quarters said the "future is frightening," and half experienced climate dread to a degree that affected their daily lives, according to the study in *Lancet Planetary Health*.

At the same time, they said they felt betrayed by an older generation they perceive as not understanding their plight or combating the crisis.

Wray, an expert in science communication and the mental health impacts of climate change, is trying to bridge that divide in a project that brings together people of different generations to share concerns and experiences and chart a path for change.

"We thought if we could bring young people into a meaningful relationship with elders who do care and are hungry for action, that could potentially be therapeutic and useful in a number of ways," said Wray, an instructor in the Department of Psychiatry and Behavioral Sciences, who is leading the Special Initiative of the Chair on Climate Change and Mental Health.

From November 2022 through February 2023, small multigenerational groups in three countries — Nigeria, England and the United States — met once a month over Zoom to express how the crisis is affecting their psychological well-being. A community facilitator guided the conversations to create a supportive environment where people could talk openly.

Wray sat in on all the conversations in New Orleans with people who are still grappling with psychological trauma from

THE MANUFACTURING OF CEMENT IS ONE OF THE LEADING CAUSES OF GREENHOUSE GAS EMISSIONS ... AND GLOBAL POLLUTION.

Hurricane Katrina, the 2005 storm that devastated the city, she said.

"People don't even have the vocabulary to recognize the emotional impact — the degrading sense of security — that the climate crisis has created," Wray said.

In Nigeria, she observed a strong sense of coming together over the crisis, while in London, there was friction among the participants, with some older people saying they believed global climate change was "not that big of a deal," she said.

The recorded conversations are now being analyzed by Wray's team using the Local Voices Network technology platform, created by the MIT Media Lab, that uses machine learning to identify key, meaningful themes.

Wray believes these kinds of small group conversations, replicated in hundreds of locations around the globe, can empower communities as they cope with the psychological impact of the crisis and forge connections to take action.

Ocean-friendly sunscreen

MORE PEOPLE ARE USING sunscreen to protect their skin, with the U.S. sunscreen market projected to grow from $1.8 billion in 2014 to $2.4 billion by 2025, market studies show. But these sunscreen users may be unwittingly putting ocean life at risk. The active ingredients in most approved products, such as zinc and oxybenzone, are toxic to marine life and are particularly damaging to coral reefs, said Paul Bollyky, MD, PhD, a Stanford Medicine immunologist and infectious disease specialist. (Despite its reef-friendly reputation, zinc oxide causes coral bleaching, which damages the algae on which the coral depend.)

Bollyky, an associate professor of medicine, and his collaborator Giulio De Leo, PhD, a Stanford Doerr School of Sustainability professor of oceans and of Earth system science, are investigating a new ocean-safe alternative that is based on bacteriophages — viruses that can infect bacteria but not humans. Bollyky is an expert on bacteriophages, the most abundant organisms on the planet. While studying how these organisms interact with light, he and his colleagues found that some are very good at absorbing ultraviolet light, which is also what sunscreens do to protect human skin from these harmful rays. Bollyky speculates that these bacteriophages evolved to absorb or reflect UV light as a way to shield their own DNA.

The researchers engineered versions of these bacteriophages so they would not infect bacteria, then incorporated these UV-protective organisms into sunscreens, which mostly contain moisturizers and other agents to help them adhere to the skin.

"Our idea is to swap out the active ingredients in sunscreens that are toxic to ocean life and instead use bacteriophage particles," said Bollyky. "Because they are organic, they will decay."

The research team has measured these bacteriophage sunscreens for their ability to absorb UV light and has begun experimenting with them on human skin tissues. Next, they plan

'OUR IDEA IS TO SWAP OUT THE ACTIVE INGREDIENTS IN SUNSCREENS THAT ARE TOXIC TO OCEAN LIFE AND INSTEAD USE BACTERIOPHAGE PARTICLES.'

‘HOW CAN YOU REUSE WATER BY GETTING RID OF CONTAMINANTS YOU DON’T WANT WHILE RECOVERING MATERIALS THAT YOU COULD REUSE?’

to test the protective effects of these new sunscreens in animal models, he said. If that proves encouraging, the scientists will collect safety and toxicity data as a prelude to a clinical trial.

The project is funded by a two-year grant from the Realizing Environmental Innovation Program at the Woods Institute for the Environment. His co-investigators are bacteriophage biologist and graduate student Julie Pourtois and materials scientist and postdoctoral fellow Maryam Hajfathalian, PhD — two team members with intersecting passions, Bollyky said.

Making wastewater drinkable

POLLY FORDYCE, PHD, IS A geneticist whose lab has created a microchip able to analyze gene sequences at hyper-speed, shortening lab experiments by years. But in talking with colleagues across campus, she realized these tools could be applied to an entirely different problem: water purification.

Motivated by the increasing scarcity of clean water supplies, Fordyce and engineering experts Will Tarpeh, PhD, and Eric Appel, PhD, are collaborating on a new technology to reuse sewage. Based on current demand, the global need for drinking water will exceed supply by 40% by 2030, the researchers said.

“We’re asking, ‘How can you reuse water by getting rid of contaminants you don’t want while recovering materials that you could reuse?’” said Fordyce, an associate professor of genetics and bioengineering.

To do that, researchers are developing new resins — molecularly designed plastic beads — that will attach to specific contaminants in wastewater and act like a sieve to filter them out. Appel, assistant professor of materials science and engineering, plans to screen thousands of polymers — large molecules made of multiples of simpler chemical units — and combine them in different ways to create new resins.

Resin technology is well established in the wastewater treatment field, but it’s not selective for specific pollutants, said Tarpeh, an assistant professor of chemical engineering and a wastewater treatment expert.

“With the approach we are taking, you could make designer resins for any contaminant,” said Tarpeh, noting that these designer resins could also extract useful compounds, such as ammonia or phosphorous, which can be recycled and reused.

Fordyce’s role is to miniaturize the experiments, which will speed up testing. Instead of testing one resin at a time in large columns of fluid in the lab — the old method — her system enables the testing of multiple resins at once in more easily manageable micro droplets.

“That would help us find the right polymer more cheaply and faster,” Fordyce said.

The researchers’ goal is to produce resins that can be manufactured inexpensively in large quantities. They hope to attract industry partners and patent and commercialize these new technologies. The two-year project is funded by the Woods Institute for the Environment. **SM**

— Contact Ruthann Richter at medmag@stanford.edu

Correcting failing sanitation in the most vulnerable communities

A CONVERSATION BETWEEN ENVIRONMENTAL HEALTH ACTIVIST CATHERINE COLEMAN FLOWERS AND DEAN LLOYD MINOR

IN A RECENT *MINOR CONSULT* PODCAST, Lloyd Minor, MD, dean of the Stanford School of Medicine, welcomed environmental activist and author Catherine Coleman Flowers for a conversation about widespread failures of public sanitation in the United States and the health and economic impacts on vulnerable communities.

Flowers, founder of the Center for Rural Enterprise and Environmental Justice, has brought national attention to wastewater inequality in the United States, particularly for marginalized, rural communities. Her persistent activism has earned her a MacArthur Fellowship "genius grant," a voice in guiding national policy as vice chair of the White House Environmental Justice Advisory Council and, most recently, a place among *Time* magazine's 100 Most Influential People of 2023.

Minor and Flowers explored root causes of systemic infrastructure lapses, the increasing threat of climate change, and how her research and advocacy have expanded across the country.

Parts of the conversation are represented in this Q&A, which is edited for brevity and clarity.

LLOYD MINOR: Many leaders I've spoken to for this podcast have drawn inspiration from their families, and I understand that you're no exception. Tell us about your parents, their activism in the Civil Rights Movement, and how their passion for social justice influenced you.

CATHERINE COLEMAN FLOWERS: I called my parents the jailhouse lawyers of our community because everyone in the community would go to them when they had a problem, and they would try to figure it out.

Now I look back and realize how smart my parents were, and how much trust they had built over the years from people in the community because of their activism. It has had a great influence on me.

They also felt that you have to give voice to the needs of the community. I feel that every step that I make, I'm walking in their shadow.

MINOR: You grew up in Lowndes County, Alabama, and though your life journey took you away for several decades, you returned in 2000. You were working as an economic development consultant when you become aware of the county's lack of adequate sanitation. What did you find out about the problem and the reasons behind it?

FLOWERS: In 2002, when I was working with Robert Woodson, the founder of the National Center for Neighborhood Enterprise [a nonprofit that empowers community-based leaders to promote solutions to problems in underserved communities], a county commissioner invited me to visit a couple who were arrested because their septic tank was failing and sewage was running onto a plot of land where several family members lived.

People started coming forward to share their own struggles, and a house-to-house survey showed that many septic tank systems were failing. The problem was much larger and more complex than we had been told by the state officials.

MINOR: What are some of the dangers of living in these circumstances?

FLOWERS: The National School of Tropical Medicine at Baylor College of Medicine worked with me and the Equal Justice Initiative on a 2017 study that found high rates of hookworm in Lowndes County and other rural areas of the country — especially where septic systems are failing.

A lot of people still complain about septic failures. I mean, who would want to wash dishes in a sink where sewage is coming back into it? Children are in a lot of these communities, and you don't want them playing around raw sewage. Also, during the height of the pandemic, Lowndes County had the highest per capita death rate from COVID-19 in Alabama.

I have to believe that some of it was because people living around raw sewage are vulnerable. Some of the worst epidemics in the world have come from the improper treatment of sewage.

MINOR: Your research showed inequalities in sanitation and clean water access across rural U.S. communities, which you've so aptly called America's dirty secret. How extensive is the problem and who is most affected?

FLOWERS: I've been surprised at the number of people who have told me this exists in places I didn't expect.

In California's Central Valley, we found places where people don't have adequate or working sanitation. We've found it in places where it rains a lot. There have been a lot of storms in California recently. I'm sure a lot of communities that are on septic tanks have been experiencing failures.

In areas where sea levels are rising and water tables are already high, septic systems are more vulnerable. In Miami-Dade County, Florida, for example, officials are expected to spend billions of dollars to convert people away from septic. Sewage from failing systems in these areas leach into water, causing problems such as algae blooms and fish kills.

And it's not just in places that are on septic. Hawaii and Puerto Rico have problems. Alaska is having failures because of melting permafrost. We are finding it in all 50 states.

MINOR: Why do septic systems fail, and how do you combat failures?

FLOWERS: They tend to fail when they are full of water or the ground is saturated. We were told by one engineer that a lot of the septic systems are made from the most degraded form of cement. So we think that there should be a move to redesign how septic systems are made.

Miami-Dade County officials are moving to a more centralized system, but that may not work everywhere, so we need to come up with a better way to treat wastewater. And I think we have the means to do it.

In the Huntsville area — where the Marshall Space Flight Center is — they are able to take urine and turn it into drinking water. Just imagine if we were to take some of that technology and come up with a new way to treat wastewater.

With climate change, it is more imperative than ever that we use innovation to come up with real, resilient solutions.

MINOR: What drove you to take on such a daunting problem with no clear path to resolution, and what's kept you motivated in moments of discouragement?

FLOWERS: If I didn't take the lead, my grandson was going to have to keep fighting that same fight. When I came back to Lowndes County and saw that a lot of things had not changed, I guess it was the spirit of my parents that propelled me to do something.

My faith also directs me. I can't pretend it's not existing and look the other way and not hold people accountable.

MINOR: I want to end with two questions that I ask all my guests. What do you think are the most important qualities for a leader today?

FLOWERS: Listen to the people. Oftentimes we feel we know all the answers and assume that if people don't have the degrees, they don't know. But if I hadn't listened to the people living in those Lowndes County communities, I wouldn't be where I am today.

MINOR: And what gives you hope for the future?

FLOWERS: When I ask my 7-year-old grandson, "What do you want to be when you grow up?" He says, "A scientist or an astronaut." That gives me hope for the future. **SM**

WEBEXTRA

Watch the full conversation at stan.md/flowers

ELVIS SWIFT

THE SPICE SELLERS' SECRET

A HUNT FOR THE SOURCES OF LEAD POISONING IN BANGLADESH

By Kris Newby

PORTRAIT BY TIMOTHY ARCHIBALD

The rural areas of Bangladesh are quilted with verdant rice paddies nestled between glittering, blue river tributaries.

Women wrapped in fuchsia, pomegranate-red and tangerine-orange saris walk among tan-and-brown cows. Market stalls are piled high with multicolored produce and spices. It is a country of vibrant colors.

This is where Jenna Forsyth landed in 2015, during the first summer of her PhD program with the Emmett Interdisciplinary Program in Environment and Resources at Stanford University. Armed with data that showed surprisingly high levels of lead in pregnant women in rural Bangladesh, her mission was to figure out where it was coming from and how to get rid of it.

At the start, there weren't any obvious answers. There were no lead-belching factories in the area. Leaded gasoline had been banned for years. And it couldn't be lead-based paint because few residents could afford to paint their homes. Her adviser thought the source could be lead-arsenate pesticides, but after spending days wading in muddy rice paddies, she ruled that out. She had hit a scientific dead end.

STEPHEN LUBY AND JENNA FORSYTH

Undaunted, she returned to Stanford University and joined an interdisciplinary team of researchers to look at the problem anew. Ultimately, using old-fashioned detective work and high-tech chemical analysis, the team identified the source and joined government officials in getting the lead out. Now, they hope to use the same approach to reduce lead exposure throughout the world.

A heavy metal

FORSYTH'S MAIN PHD ADVISER WAS STEPHEN LUBY, MD, an epidemiologist who had been tackling the global lead problem since the early 1990s. His work began in Pakistan, where his research contributed to banning leaded gasoline in that country. But after he read a study (Bergkvist et al., 2010, in *Environmental Research*) about unexpectedly high levels of lead in pregnant women in rural Bangladesh, he knew his work wasn't done.

"There is no safe level for lead exposure," said Luby, a Stanford School of Medicine professor of medicine and the director of research for the Stanford Center for Innovation in Global Health. Early in his career, Luby spent eight years focused on improving public health in Bangladesh, so this was personal.

Lead is a toxic heavy metal that can seriously damage reproductive, neurological and cardiovascular systems. Exposure to it is a global problem, with an estimated 1 in 3 children with blood lead levels at or above 5 micrograms per deciliter, the level considered unacceptable by the World Health Organization. (In October 2021, the U.S. Centers for Disease Control and Prevention lowered this level to 3.5 micrograms per deciliter.) Between 24 million and 46 million children and teenagers in Bangladesh are estimated to have lead levels above this threshold, the fourth highest number in this age group behind India, Nigeria and Pakistan.

Lead poisoning has lifelong, irreversible effects on the cognitive abilities of children, and the social and economic impacts to a country can be devastating. Children with blood lead levels above 5 micrograms per deciliter may score 3 to 5 points lower on intelligence tests than unaffected peers, limiting their potential. In addition, preschool lead exposure is often associated with juvenile delinquency, violence and crime. In Bangladesh alone, the lower IQ levels caused by lead poisoning are estimated to cost $16 billion annually in lost lifetime productivity, 6% of gross domestic product.

After Forsyth returned from Bangladesh, she reviewed her disappointing findings with Luby. But she had a hunch. She'd recently read a lead study from that region (Gleason et al., 2014 in *Journal of Environmental and Public Health*) hypothesizing turmeric as a potential source of lead. Could it be the powdery, orange-yellow spice that permeates daily life in Bangladesh? Turmeric is used in curries, as a clothing dye, in cosmetics, in medicines and as an insect repellent. Luby was skeptical, but he let her run with it. "Show me the evidence," he said.

So, she analyzed 17 turmeric samples from her Bangladesh trip, and one had exceedingly high levels of lead and chromium. It was a start, and like any good medical detective, she began gathering more clues.

The golden spice

FORSYTH IS AN ENVIRONMENTAL SCIENTIST WITH WANDERLUST. She's spent nearly 15 years studying health problems in Bangladesh, Kenya, Tanzania, Costa Rica and Australia, looking for ways to reduce contaminants in air, water, soil and food.

When she was growing up in Logan, Utah, she loved mysteries. Early on, she decided to become a detective, and for her eighth-grade science fair project she went undercover to swab bathroom doorknobs at local restaurants, culturing bacterial samples to evaluate sanitation levels.

This love of evidence-driven puzzles set her on a course to carry on her detective work and, after studying biology as an undergraduate, then earning a master's in environmental engineering and global health at the University of Washington, she contacted Luby. He recruited her as a PhD candidate, and she joined his initiative to reduce lead exposure in pregnant women, along with icddr,b, a global nonprofit in Bangladesh formerly known as International Centre for Diarrheal Disease Research, Bangladesh.

TURMERIC IS USED IN CURRIES, AS A CLOTHING DYE, IN COSMETICS, IN MEDICINES AND AS AN INSECT REPELLENT.

TO MASK FLAWED TURMERIC, SOME PROCESSORS BEGAN DUSTING THE ROOTS WITH LEAD CHROMATE.

Back in Bangladesh, Forsyth and the team began a deep dive into the workings of the turmeric supply chain. They interviewed the stakeholders in the production, consumption and regulation of turmeric. They went to mills, wholesalers and spice markets, all the while collecting samples of turmeric, colorants, dust and soil in little baggies for analysis.

Turmeric, a member of the ginger family, is made from the rootstalks, aka rhizomes, of Curcuma longa. At the end of the growing season, farmers let the knee-high, leafy green tops dry out, then use hoes to dig up the rhizomes. Next workers, typically women, painstakingly remove dirt clods and break off the feeder roots. Then the naked rhizomes are washed, steamed and laid out to dry for a few weeks.

After drying, the rhizomes are polished to remove dirt and the skins, revealing the yellow inner root. This is done manually or, in larger operations, by placing the rhizomes in rotating drums made of an abrasive wire mesh. Next, the rhizomes are cut, crushed and ground into a powder.

Color matters to turmeric purchasers, and turmeric that is more vibrantly yellow typically sells for higher prices. The Stanford University team learned that this color-linked perception of quality may have started in the 1980s, when a flood interrupted the drying process, turning rhizomes brown and moldy. To mask flawed turmeric, some processors began dusting the roots with lead chromate — an orange-yellow industrial pigment used to color plastics and furniture. From the interviews, Forsyth learned that this coloration step continued for four decades after the flood and that most processors weren't aware that the pigments were toxic. But, with Forsyth's help, this would soon change.

Bring on the ray guns

AS A CHILD, SCOTT FENDORF, PHD, the Terry Huffington Professor and senior associate dean for integrative initiatives in the Stanford Doerr School of Sustainability, liked playing in the dirt. Fortunately for science, his parents encouraged this obsession, and today, he is a leading expert in soil chemistry.

Fendorf was one of Forsyth's PhD thesis advisers and was the first expert she consulted when she returned from Bangladesh with baggies full of spice, dust and dirt.

Sitting in his cozy office, overgrown with houseplants thriving on enriched soil, Forsyth presented Fendorf with her challenges: How could she figure out where the lead poisoning was coming from? Was it in food, pesticides, lead-soldered cans, silt from local water supplies, or impurities in the clay/ash pellets that many pregnant women chewed to alleviate mineral cravings? And what technology could be applied to verify that lead from a given source was poisoning the Bangladeshis?

Fendorf explained that a metal like lead can be composed of unique mixes of elemental isotopes that vary according to the source. These location-specific ratios can sometimes be used to pinpoint a lead source in the same way detectives use fingerprints to identify criminals. Analyze the lead isotope ratio in a blood sample to see if it matches one of the lead sources; if it does, bingo, you've found the culprit. But he warned that this approach doesn't always work, so they enlisted Katharine Maher, PhD, professor of Earth System Science, and Karrie Weaver, technical director at the SIGMA Shared Lab at the Stanford Doerr School of Sustainability, to evaluate how useful the analysis could be for this application.

The SIGMA, or Stanford Isotopic and Geochemical Measurement and Analysis, lab is home to several state-of-the-art devices — inductively coupled plasma mass spectrometers — that can analyze the precise elemental components of just about any material, from water, soil and tissues, to dinosaur bones. How do these mass spectrometers work? A sample is placed into a chamber where hot argon plasma breaks down a substance into its elemental components. Then the components are stripped of impurities, separated and analyzed by molecular weight and identified by custom software.

As a first step, Forsyth and Weaver characterized the unique isotope ratios for each Bangladeshi lead source — and they lucked out. The lead-isotope fingerprints varied enough to identify specific sources. After the techs analyzed the blood samples collected during their first trip to Bangladesh, there was a clear signal — the blood-borne lead was coming from the turmeric and the industrial pigments used to color it.

Next, the team had to figure out how to quickly identify tainted product in real time in the field; sending samples to a lab for analysis was too expensive and time-consuming to be practical.

For this, Alandra Lopez, Fendorf's PhD student at the time, showed Forsyth a bright yellow plastic device that looked like a toy ray gun. It was a handheld X-ray fluorescent analyzer. Their lab used it for identifying toxins in the soil, and Lopez was tasked with developing a test methodology and training protocol for its use in turmeric testing.

Then Forsyth bought one for the team for roughly $40,000, and they went back to Bangladesh, armed and ready.

The sting

GATHERING SCIENTIFIC EVIDENCE IN A foreign country to fix a public health problem is one thing. Getting the country to act on it is another. This is where Luby's deep understanding and love of the Bangladeshi culture came in handy.

"It's a profoundly hospitable culture, committed to education, with people who really want to make the country better," said Luby.

Bangladesh is one of the most densely populated countries in the world, surrounded by India to the west, north and east, and Myanmar to the southeast. Its soil is fertile, enriched by frequent flooding of the Ganges and Brahmaputra river systems. Close to 50% of Bangladesh's population is employed in agriculture, and turmeric is an important cash crop and export.

The government was highly motivated to do something about the lead problem, and Luby made sure that its Department of Agricultural Authority officials were partners in designing and implementing the lead study from the beginning.

In July 2017, three years into her PhD research, Forsyth and the team shared their stunning findings: Turmeric mixed with lead-chromate pigments contained lead levels up to 500 times the Bangladesh legal limit of 2.5 micrograms per gram, making it the most likely cause of the lead poisonings. Their presentation was attended by 21 governmental and non-governmental organizations, including Bangladesh's Food Safety Authority. Participants were alarmed, and word quickly spread to the highest levels of the government.

From September through December 2019, the Stanford University/icddr,b team and public health officials launched a get-the-lead-out plan, beginning with an effort to inform manufacturers and consumers about the adverse health effects of lead-based pigments. News releases were published, face-to-face meetings were held with key businesspeople, and 50,000 educational posters went up in the markets and public spaces. The government declared that turmeric adulteration was a prosecutable violation, and Bangladesh Prime Minister Sheikh Hasina discussed the problem on national TV. Then, the Stanford University researchers collected blood samples from workers at one of the larger processors to illustrate how the lead was not only poisoning consumers but also their employees.

Finally, the officials revealed the most important part of the plan to the Stanford University team — a sting operation.

Dusted and busted

FOOD SAFETY AUTHORITY representatives, flanked by soldiers in camouflage uniforms, magenta berets and guns slung over their shoulders, strode down the center of a busy street market in Dhaka, the capital city. The crowds parted. Men riding three-wheeled rickshaws pulled over. Street vendors stopped stirring their aromatic curries. The spice sellers wearing parti-colored lungi skirts fell silent. Some curious merchants, sitting atop stacks of potatoes, ginger, onions and garlic, jumped down to follow the entourage.

The spice SWAT team visited six turmeric sellers' stalls. At each, a Stanford University-trained technician pressed the nose of the X-ray fluorescent analyzer into dusty yellow bags of turmeric roots. After a minute or so, the tech could tell wheth-

er the root stalks were lead dusted. If they were, law enforcement officials moved in to confiscate and destroy the bags of tainted product.

Because the government is understaffed in food safety enforcement and has a slow judicial process, officials opted for a shock-and-awe approach to punishment. Mobile court officials followed the SWAT team and, as soon as a violation was confirmed, they issued on-the-spot fines in the equivalent of $9,288 in U.S. currency, about three years of an average Bangladeshi's salary.

To amplify the message, the whole sting operation was filmed by a Jamuna Television news crew and broadcast across the nation.

"It was law enforcement theater," Forsyth said. But she admitted it was a highly effective way of informing dirty turmeric producers and sellers, "You're being watched."

After the intervention, the team went back to the study sites to measure changes in lead levels in the turmeric supply chain, and they were amazed at the effectiveness of the campaign. At the markets, incidence of adulterated spice plunged from 47% in September 2019, to 5% in the first quarter of 2020, to no detectable lead in 2021. Evidence of lead-chromate pigment in the processing mills dropped from 30% in 2017 to 0% in 2021. And 16 months after the intervention, lead levels in the blood of sample test subjects dropped by a median of 30%.

Getting the lead out

BACK AT HIS office overlooking Stanford University's engineering quad, Luby multitasks in front of five computer displays. It gives visitors the impression that his ambitions for tackling our most challenging public health issues are much bigger than can be managed on one or two screens.

Luby grew up in Omaha, Nebraska, raised by an OB/GYN father and a nurse mother. As an undergrad, he immersed himself in philosophy, history and political science at Creighton University, a Jesuit school that emphasizes social justice. He went on to get a medical degree, then studied epidemiology and preventive medicine, eventually serving as the head of the U.S. Centers for Disease Control and Prevention agency in Bangladesh.

During college, Luby never thought he'd become a scientist, but his unique mix of compassion, determination and scientific rigor is making a significant dent in the global lead problem.

"Americans generally think we've solved the lead problem, but this is fundamentally not true," said Luby. "There are 800 million children in the world with lead blood levels greater than recommended standards, and many will go on to suffer permanent brain damage. One million adults die every year because of exposure to lead."

He emphasized that lead-dusted turmeric isn't just a Southeast Asian problem. Worldwide, turmeric is more popular than ever as an ingredient in teas, curries, anti-inflammatory supplements and coloring for processed foods like macaroni and cheese, yogurt, and ice cream. And while the major spice companies that sell it in the U.S. have good quality control procedures, a lot of turmeric is brought in by less conscientious importers, he said.

Luby is now looking at using the playbook that worked in Bangladesh — evidence gathering, education, media coverage and law enforcement — to see if it can be applied to other countries.

Meanwhile, Forsyth and the lead team are still hunting down other lead sources in Bangladesh.

"In Dhaka, we found this important cohort of young children, 2- to 4-year-olds, who have wildly high levels of lead poisoning," she said.

And like any good detective, she's keeping an open mind about possible culprits.

"Right now, we're exploring lead sources in battery recycling dumps, metal factories, and in pots and pans."

Looking back on the project to date, Forsyth reflected on the most important lesson she's learned: "Lead is pervasive in our environment, and the toxic effects are profound. This is why we need to keep working this puzzle." **SM**

— Contact Kris Newby at medmag@stanford.edu

'RIGHT NOW, WE'RE EXPLORING LEAD SOURCES IN BATTERY RECYCLING DUMPS, METAL FACTORIES, AND IN POTS AND PANS.'

greening the OR

ATTAINING GREATER SUSTAINABILITY IN THE OPERATING ROOM

By Erin Digitale

ILLUSTRATION BY ANUJ SHRESTHA

In 2018, Stanford Medicine anesthesiologist Praveen Kalra, MD, came across an article about climate change that surprised him.

He read that the anesthetic gas desflurane has an outsized environmental footprint: Pound for pound, its greenhouse gas effect is 2,600 times as potent as that of carbon dioxide.

"I had never heard about this," said Kalra, a clinical associate professor of anesthesiology, perioperative and pain medicine. He used desflurane regularly in Stanford Health Care's operating rooms. "The more I read, the more I felt a little embarrassed. I thought, if I'm not aware of this, my colleagues may not be, either."

Global warming threatens the health of billions of people around the world, and Kalra became a physician to improve people's health, not harm it. He thought it would be wise to stop using desflurane in his own operating rooms because other anesthetic gases work equally well with much smaller environmental effects.

"But the impact would have been low; I'm only one person," he said, noting that Stanford Medicine has around 300 anesthesiologists, including faculty, residents and fellows. "The real benefit would come if we could all do the same thing."

Kalra decided to try convincing all his colleagues to stop using desflurane. In doing so, he became part of a green movement now sweeping health care: Last year, Stanford Health Care and Stanford Medicine Children's Health became two of more than 100 organizations to sign the White House/U.S. Health and Human Services Health Sector Climate Pledge, which commits them to cutting health care-related emissions in half by 2030 and to achieving carbon neutrality by 2050.

About 8.5% of the country's greenhouse gas emissions come from the health care industry, and U.S. health care has the highest per-patient level of emissions of any country in the world. Leaders across Stanford Medicine are looking for ways to change these trends.

Operating rooms offer an especially stark example of the challenges of making health care sustainable — because while surgery is extremely resource intensive, it helps some of the sickest and most vulnerable patients. Greening the operating room requires a delicate balance: Surgeons, anesthesiologists and their colleagues must maintain patient safety and treatment success, while also scrutinizing their time-tested routines for ways to become sustainable.

To achieve this goal, "green teams" are forming and changing practical details, such as which anesthetic to use, and are gradually altering the culture of surgery by sharing evidence that convinces others to adopt environmentally friendly protocols.

"We're fortunate in that we have the resources by which we can make sustainability advancements," said Helen Wilmot, chief facilities and sustainability officer at Stanford Health Care. "People like us are required to put our resources to bear to make these changes."

Just as academic medical centers have a responsibility to study new medical treatments in clinical trials, such centers also have a duty to pilot methods for sustainable health care, Wilmot said. "Community hospitals and rural hospitals don't necessarily have the ability to be test cases. We have an obligation to do the work that others can benefit from."

Climate change hits the health of the most vulnerable groups hardest, another good reason for Stanford Medicine to lead sustainability efforts.

"Children are particularly vulnerable to the impacts of climate change — and Black and brown people as well," said Dana Hiniker, sustainability program manager at Stanford Medicine Children's Health. "But there's also a cost-of-health care argument to be made; the efforts we're undertaking are huge cost-saving opportunities."

Like Kalra, many doctors and nurses end up joining the endeavor when they hear facts about the health effects of climate change that surprise them, according to Christy Foster, director of sustainability at Stanford Medicine Children's Health.

"The number of deaths attributable to U.S. health care pollution is already equal to the deaths from preventable medical errors," Foster said. "Every time I present that statistic [to our medical teams], I see jaws dropping, and people feel compelled to get engaged."

One widely cited 2020 study, published in *Health Affairs*, investigated the impact of pollution generated by the U.S. health care industry in terms of the disability-adjusted life years lost. The measure, abbreviated as DALY, counts years of healthy life lost to premature death or disability. The study estimated that the U.S. health care industry caused the loss of 133,000-188,000 DALYs in 2018, mostly due to health effects of small-particle air pollution generated when fossil fuels were burned to produce electricity.

Added Foster, "We're at a moment of realizing that all this research says climate change impacts the patients we take care of, and we have to start doing things differently."

A new approach to reducing waste

OPERATING ROOMS ARE HUBS OF HOSPITAL ACTIVITY: They earn up to 60% of a hospital's revenue; account for 40% to 60% of its supply budget; produce more than 30% of its total waste and two-thirds of its regulated medical waste — such as drugs, sharps and biohazardous materials — that requires special disposal; and consume three to six times as much energy per square foot as any other part of a hospital.

All this activity creates opportunities for green initiatives — such as those spearheaded by surgeons frustrated by how much they throw out, including product packages, unused items such as surgical towels, and single-use versions of devices like blood pressure cuffs that come in reusable options.

"Every time I do a surgical case, we typically throw away, on the low end, four or five large garbage bags of stuff, and in some cases nine or 10," said Kevin Shea, MD, an orthopaedic surgeon at Lucile Packard Children's Hospital Stanford, whose commitment to improve sustainability applies to his whole life.

He and his family, for instance, recently installed solar panels on their roof and swapped their gas-powered furnace and water heater for electric heat pump models. He bikes to work most days, and the family uses mainly hybrid electric cars. However, he realized that because surgery uses so much stuff, he could make an even bigger environmental impact at work.

To start, Shea's team is identifying surgical products with the least-wasteful packaging. For common orthopaedic procedures — such as anterior cruciate ligament reconstruction, a knee surgery — that the team performs hundreds of times per year, buying the same product in cardboard instead of non-recyclable plastic could keep a lot of trash out of landfills.

"We need to start giving feedback to manufacturers saying, 'We are surgeons — your product users, your customers — and the environmental impact of the packaging choices you make matters to us,'" Shea said, adding that the team of students and surgeons he has built to pursue this project will also share their findings with surgeons at other institutions and encourage them to modify what they use, too.

"We're always going to have waste to deal with; we do complicated things in the OR," he said. "But if we can reduce that waste by 40% or 50%, we'll look back and say, 'It was worth making those changes.'"

Starting with fewer supplies

HAND SURGEON PAIGE FOX, MD, PHD, associate professor of surgery, recently led a similar push to reduce waste by buying less in the first place. Fox and her colleagues perform about 500 minor hand surgeries a year, primarily carpal tunnel release and trigger finger release procedures. These surgeries involve cutting a small band of tissue — a ligament or the casing on a tendon — to create space for an irritated tendon or nerve, improving mobility and sensation for patients.

Although the surgeries require a 1- to 2-inch incision, the supply packs Stanford Health Care surgeons used in the past were the same as those provided for much more invasive operations. "We were draping the patient from head to toe in multiple layers of sterile drapes, for instance," Fox said.

In late 2019, Fox began wondering if she could develop a smaller supply pack for use during minor hand surgeries, which are performed at the Stanford Medicine Outpatient Center in Redwood City.

"It was something I was really excited about, but it had very little traction," she said, explaining that she was unsure whether her fellow surgeons would want to test new supply packs when they had long assumed their habits added to patient safety. "Then the pandemic hit, everything was disposable, and I felt this backslide."

She eventually realized the pandemic was creating a silver lining that helped her project: After experiencing 2020's disruptions in global shipping and manufacturing, her colleagues knew more about supply chains and were invested in improving these once-hidden aspects of hospital operations.

In the spring of 2021, Fox began working with her team, including other surgeons, nurses, scrub techs and operating room leaders, to gauge their openness to the project. She then collaborated with medical-supply vendors to come up with a phased rollout of a supply pack that eliminated the extra plastic, drapes, gowns and equipment needed for bigger surgeries.

Over the following 18 months, Fox and her colleagues tracked surgical outcomes as they switched to using fewer supplies and saw no difference in complications such as infection.

"It's important for us to demonstrate to patients that it's just as safe," she said.

The smaller supply pack, now used by all of Stanford Health Care's hand surgeons for minor surgeries, contains less than half as much material as the original pack, which weighed almost five pounds, including unneeded sterile drapes, gowns and surgical tools. The switch to the new packs averts nearly three pounds of trash per surgical case and saves $70 in supply costs per case, for a total of more than 1,400 pounds of trash avoided and $35,000 saved each year.

Other projects to reduce waste are underway. For instance, surgical resident Jaclyn Wu, MD, is evaluating supply packs used in common general surgery procedures, such as rectal exams under anesthesia and laparoscopic appendectomies, with

the goal of eliminating unnecessary supplies.

"As physicians, the first part of our oath is, 'Do no harm,' but if in the practice of medicine, we're generating significant emissions, we're directly contributing to the problem," said Wu, adding that she wants to lead sustainability efforts as part of her overall commitment to global health.

"I think to patients it signifies that your doctors and health care system see the bigger picture," she said.

Updating reuse protocols

SEVERAL OPERATING-ROOM leaders are starting programs to reuse as many materials as possible, a high priority because surgery traditionally uses a large volume of single-use items. Stanford Medicine's adult and pediatric hospitals are piloting programs to recycle blue wrap, the polypropylene fabric that wraps sterile operating room trays. By collecting it during surgery setup and sorting it into its own clean collection bin, the majority of the 36,000 pounds of blue wrap needed each year can be recycled, not sent to landfills.

Both health systems' operating rooms are being equipped with waste bins that make correctly sorting waste more intuitive. For example, the rooms now have smaller bins for disposing the most hazardous types of drugs, which must be shipped out of state for disposal — an operation with safety benefits but a big carbon footprint and high cost. The small size encourages people to put only the hazardous drugs in these bins, not other items such as plastic waste.

Stanford Medicine Children's Health is also investigating reusable options for several supplies used in its pre-op area, including pulse oximeters, blood pressure cuffs and tourniquet sensors, which can be wiped clean between patients, potentially saving $8,500 per year per operating room or procedural suite. For Lucile Packard Children's Hospital Stanford, with 19 operating rooms and two procedural suites, this could mean a total savings of about $178,500 each year.

For medical devices that require complete sterilization — catheters, for instance — the hospitals are shifting toward purchasing products that can be sterilized off-site, by companies that have obtained FDA certification to reprocess medical devices between uses. They're also evaluating the impact of choices such as laundering surgical towels, including tallying the environmental effect of dirty, soapy laundry water.

It has taken time, but it's becoming second nature to account for the environmental impact of everything purchased for operating rooms, said Danielle Shoaf, interim director of surgical services at Stanford Medicine Children's Health, who plays a big role in purchasing decisions.

"I would urge anybody in a similar role to understand that everything they purchase has an impact beyond patient care," Shoaf said. "Items can be functionally exactly equal, but one choice has a more positive impact on the environment. When looking for new supplies, we always ask, 'Do you have a

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SUSTAINABLE SUCCESSES

After opening in 2017, Lucile Packard Children's Hospital Stanford became one of five new hospitals in the world to earn LEED Platinum status, the highest designation for sustainability given by the U.S. Green Building Council. In March 2022, the council also recognized the new Stanford Hospital, which opened in November 2019, awarding it LEED Gold status.

The hospitals were hailed, in part, for designs that feature optimal energy efficiency and water use and acres of drought-tolerant gardens. But neither Stanford Health Care nor Stanford Medicine Children's Health were new to mitigating health care's environmental impact — a commitment that continues today.

Both organizations have signed the White House/U.S. Health and Human Services Health Sector Climate Pledge. And Stanford Health Care recently joined the Health Care Climate Council, an industry coalition that seeks to reduce health care's contributions to climate change.

Here are some of their sustainability initiatives:

FOOD: Both organizations compost tens of thousands of pounds of kitchen food waste annually and donate surplus meals to community organizations. In fiscal year 2022, 1,480 pounds were donated by Stanford Medicine Children's Health and 9,664 pounds by Stanford Health Care.

LIGHTING: LED fixtures are in place in most areas within the new Stanford Hospital. Lucile Packard Children's Hospital Stanford is replacing all lighting with LED lights, which will save at least 730,000 kilowatt-hours of electricity — a 48% reduction — in the first year after the project is completed. As of June 2023, 70% of the children's hospital's lights had been replaced.

WATER: Both hospitals cut water use through water conserving appliances and irrigating with rainwater and water extracted from dehumidifiers and dialysis equipment. The children's hospital ranks above the 90th percentile of hospitals in water conservation, according to Practice Greenhealth, a sustainable health care organization with members in the U.S. and Canada.

During the week of Nov. 12, 2018, more than 1 million California students missed school.

Wildfires raged across the state. The Camp Fire had destroyed the town of Paradise, California, a few days earlier, and went on to become the most expensive natural disaster in the world that year. Though schools in some communities burned, most closures occurred after wildfire smoke rendered air quality so bad that officials decided it was unsafe for kids to come to class.

The extreme number of school closures — affecting 18% of the state's K-12 public school students in a single week — caught the eye of Lisa Patel, MD, a clinical associate professor of pediatrics at the Stanford School of Medicine. Patel worked as a U.S. Environmental Protection Agency scientist before attending medical school and remains interested in studying links between climate change and children's health. Schools weren't equipped with air filters able to keep their indoor air clean on smoky days, but with climate change driving worsening wildfire seasons, she thought they should be.

Though California has long been a leader in clean air regulations — becoming, in 1966, the first state to enact tailpipe-emission standards to reduce smog, for example — its intensifying heat and wildfire seasons are beginning to erase these gains. The American Lung Association's 2023 air quality report card gave F grades for ozone pollution to 30 of 49 California counties that collect ozone data, and 41 of 46 counties with particulate data received F's for their particle pollution levels. Poor air raises the risk of premature birth and poses a

how to climate-proof schools

REVAMPING SCHOOLS TO WITHSTAND WHAT'S COMING

By Erin Digitale

ILLUSTRATION BY KEITH NEGLEY

variety of health risks for children, including heat stroke during heat waves and asthma.

"Climate change will be the single greatest determinant of health for a child born today," Patel said. In the past few years, her work has increasingly focused on how to improve the air in California's K-12 public schools, where children spend 180 days per year.

To address the problem, Patel assembled a coalition of experts in late 2021 to produce a Stanford Medicine-led report (online at stan.md/climate-schools) that explains the gaps in schools' climate resilience and proposes a 10-year, $150 billion statewide master plan to address them. Since its publication this year, the white paper has attracted attention from California legislators, who have proposed six bills targeting aspects of school sustainability. Among them is Senate Bill 394, which calls for the California Energy Commission to convene other state agencies and education stakeholders to develop a statewide master plan for ensuring schools are climate resilient.

Work on the report began after leaders at the 11th Hour Project, a program of The Schmidt Family Foundation focusing on climate mitigation and resilience, noticed a *Stanford Medicine News Center* story about Patel's effort to raise awareness of new state and federal funding for upgrading schools' air filtration systems. The funds had been allocated to help schools reopen after COVID-19 closures. But Patel realized the money could also help relieve the effects of longer, worse wildfire seasons.

"Kids in places like Marin County [north of San Francisco], which was hit by smoke from devastating fires, missed upward of three weeks during the 2018-2019 school year due to wildfire smoke, evacuation orders or power outages," she said in the article.

As a result of the story, the 11th Hour Project sponsored a comprehensive report on how California schools could become more climate resilient. Patel began recruiting collaborators from Stanford Medicine, the University of California, Berkeley, and local school districts, trade and teachers unions and nonprofits to describe the problem and set goals for how the state could address it, leading to this year's report.

Educators will be increasingly challenged by California's aging schools, thousands of which were built more than 50 years ago, before climate change was on anyone's radar. "Our schools are not built to handle what's coming," Patel said.

A BIG TASK

The state's approximately 10,000 public K-12 schools need major upgrades to their physical facilities to make them climate resilient, protecting students as the climate shifts, the report says. Such upgrades should include installing highly efficient air filtration and cooling systems; equipping schools with solar panels, batteries and electric appliances so they can operate on clean power sources rather than gas (and function if the power grid is out); and constructing schoolyards with shade and drought-resistant landscaping to give children safe outdoor spaces that also provide them with respite.

The report also calls for resources for educators to support students living with the stress of climate disasters. In addition, schools need curricula that help kids understand what is being done to stem climate change and how they might pursue careers that help preserve or restore the quality of the environment. Perhaps most important, the changes need to be carried out in ways that prioritize giving funds first to the regions of the state that are hardest hit by climate change, typically economically disadvantaged areas with schools that are already chronically underfunded.

The task ahead is substantial, but the news isn't all bad. "The state already has all these goals for carbon neutrality and other aspects of sustainability, and this is a really potent way to move toward those goals," said Erika Veidis, the planetary health program manager for the Stanford Center for Innovation in Global Health, who led the report's development with Patel.

Last year, California committed to reaching carbon neutrality by 2045. Since school infrastructure is so large — 125,000 acres of grounds with 730 million square feet of buildings — schools will be key to the state reaching this goal, Veidis said.

"It's not a drop in the bucket: Schools are responsible for 9% of emissions from nonresidential buildings in California and cover a huge amount of land."

WAKE-UP CALL

The global COVID-19 pandemic provided an extreme example of why children and communities need well-functioning schools. Days after the World Health Organization declared the pandemic, on March 11, 2020, California's public schools shifted to remote learning. Most of the state's students spent the next year online, causing learning setbacks and exacerbating inequi-

'Climate change will be the single greatest determinant of health for a child born today. ... Our schools are not built to handle what's coming.'

'Youth see people who are supposed to protect them not upholding their end of the deal. That feeds into making climate anxiety worse.'

ties. Kids in poorer households struggled on many fronts. For instance, they were less likely to have internet access and connected devices for online learning and less likely to have a parent working from home who could help with schoolwork.

Not only did the pandemic highlight how school closures damage kids' well being, but it also drew attention to schools' unreadiness for climate change, Patel said.

In 2021, leaders in her own children's school district, San Francisco Unified, asked her for advice on how to reduce students' risk of catching COVID-19 when they returned to in-person instruction.

"I'd say 'Oh, we'll just open the windows,' and then I'd learn that the windows had been painted shut," Patel said. Or she would suggest upgrading filters in schools' heating, ventilation and air conditioning systems, "and they would look at me crazy because so many schools in California, including in San Francisco Unified, have no HVAC systems. They were built for a different climate era."

At present, an estimated 38% of California students attend public schools that fail to meet basic facility standards.

THE NEED

Many children are already suffering the health and academic effects of climate change, particularly from extreme heat and wildfire-related air pollution. Children with asthma are especially vulnerable. Patel, a hospitalist at Stanford Health Care Tri-Valley in Pleasanton, California, has seen that children of color and children living in poverty are over-represented among those who come to the hospital with asthma episodes on hot or smoky days.

"This is borne out in the literature: We know those two populations are at higher risk," she said. "They tend to live closer to areas of pollution to begin with, and often have poorer access to medication or care that would prevent their asthma from flaring."

Wildfires are a growing concern in California, where the three worst-ever fire seasons — 2018, 2020 and 2021 — all occurred in the past five years. Recent research suggests wildfire smoke is bad for kids, and not just those with asthma.

A Stanford Medicine study published in 2019 found that smoke from a 415-acre wildfire that burned in September 2015 near Fresno, California, had higher levels of toxins than smoke from a similar-sized controlled burn carried out to reduce underbrush. Children near the wildfire were more exposed to pollutants such as nitrogen dioxide, polycyclic aromatic hydrocarbons, elemental carbon, carbon monoxide and particulate matter. Their blood had lower levels of a group of cells involved in the immune response, type-1 T helper cells, and reduced activity of a gene, Foxp3, that plays an important role in modulating allergic and other immune responses. The study, led by senior research scientist Mary Prunicki, MD, PhD, was published in the *European Journal of Allergy and Clinical Immunology*.

A 2021 study, which assessed records of pediatric emergency-room visits for respiratory complaints in San Diego County, estimated that exposure to ultrafine particulate matter, made of particles smaller than 2.5 microns, was about 10 times as harmful to children's respiratory health when the tiny particles came from wildfires compared with other pollution sources. The findings, from the Scripps Institute and the University of California, San Diego, appeared in *Pediatrics*.

"It isn't surprising because what's burning in a wildfire includes houses and cars," Patel said. Ultrafine particles get deep into the lungs and can enter the bloodstream, potentially setting off inflammatory cascades, she added.

Extreme heat, such as the September 2022 "heat dome" that brought temperatures above 110° F to much of California, also puts kids at risk, including for heatstroke. And the lack of air conditioning in many schools, especially in poorer communities, interferes with learning. A study published in 2020 in *American Economic Journal: Economic Policy* (led by R. Jisung Park, PhD, at the University of Pennsylvania) found that heat exposure in school disproportionately harms Black and Hispanic students, accounting for roughly 5% of the racial achievement gap in standardized test scores.

Other hazards of heat waves are power outages or rolling blackouts. These can occur if the electrical grid becomes overtaxed or power is shut off to reduce wildfire risk, making it harder for schools with air conditioning to use it.

Climate change is also taking a toll on young people's mental health. One of the largest studies exploring this phenomenon, a survey of 10,000 teens and young adults from 10 countries, was published in 2021 in *The Lancet Planetary Health*. It found that climate-related anxiety interfered with daily function for 45% of all respondents, with greater impairment in youth living in areas more affected by climate change.

Being exposed to more extreme weather events, seeking in-

'As a teacher, one of the first things you learn is "the hook." Young people are already engaged in this issue,' so it's easier to draw them into lessons.

formation about climate change in a doom-scrolling fashion and seeing little action from leaders all contribute to climate anxiety, said Britt Wray, PhD, a psychiatry and behavioral sciences instructor and study co-author.

"There are links to feelings of being betrayed by leaders," Wray said. "Youth see people who are supposed to protect them not upholding their end of the deal. That feeds into making climate anxiety worse."

UPDATING SCHOOLS, EQUITABLY

Closing schools is a common, but unsustainable, response to heat waves, wildfires and other extreme climate events.

"Kids are losing out on learning time," said Jonathan Klein, a cofounder of UndauntedK12, a nonprofit that helps schools reduce their carbon footprint, and a co-author of the report. His organization is tracking school closures around the country related to extreme weather and working toward solutions to make schools more climate-resilient.

Not only do closures interrupt children's education, there's no guarantee that kids will have safe conditions such as clean air elsewhere, Patel said, adding that children in low-income households are less likely to have those conditions at home.

Upgrading schools equitably will require modifications to how school building projects are funded, according to Jeffrey Vincent, PhD, a co-author of the report and director of the Center for Cities and Schools at UC Berkeley.

"School facility finance remains the most regressive aspect of public-education finance in California," Vincent said. Facility upgrades are generally funded by bond measures, levied in local elections as a percentage of property taxes. "This means the wealthier districts can access more local money and state matching grants for facility upgrades."

Wealthy districts are also more likely to have staff who can sort through a mishmash of existing funding opportunities.

"A lot of the funding we're calling for already exists, but it's too small given the scale of needs, and it's not coordinated," Veidis said. For instance, schools can tap government funds through such programs as CalSHAPE, which pays for plumbing, air conditioning and efficiency upgrades at California schools, and the Elementary and Secondary School Emergency Relief Fund, part of the federal response to the COVID-19 pandemic.

Greater awareness among school district staff of county and state sustainability initiatives is also essential, said Andra Yeghoian, a report co-author. Yeghoian, formerly the environmental literacy and sustainability coordinator for the San Mateo County Office of Education, recalled speaking with a school district official who had just invested in new gas-powered boilers for schools in his district.

"I said, 'Did you know that the county is working on shutting off its natural gas pipelines by 2035?'" Yeghoian recounted. "He said, 'What are you talking about?' He didn't have a statewide master plan to guide decisions on replacing equipment."

Next steps must make it easy for school officials to make climate-friendly decisions, Patel said. "It's about creating the right incentives. So, for example, when the next statewide educational bond measure comes up in 2024, there are ways to write the measure that say, 'This is what the money can go toward,' and make sure it isn't invested in more fossil fuel infrastructure."

CURRICULUM AND COMMUNITY

Readying school buildings, as important as it is, will not fully prepare California's K-12 educational system for climate change, the experts agree. Schools also need to prepare kids for the climate reality they'll live with for the rest of their lives.

That means updating curricula and support programs for students with more material about climate science and equipping teachers and other school staff to act on it — whether by explaining what an atmospheric river is in elementary-school science lessons; offering high school students programs in climate-related career pathways, such as environmental engineering or agricultural science; or hiring more counselors to meet mental health needs during and after climate catastrophes.

Even though the California Department of Education produced the 2015 "Blueprint for Environmental Literacy," as of 2020 just 29% of the state's teachers said they were incorporating environmental concepts into their instruction.

"It's a topic that should be included in every subject area," said Yeghoian, who began her career as a teacher and became engaged with environmental issues after seeing the film, *An Inconvenient Truth*. She found that her secondary students were eager to learn about climate change, too. "When kids learn about it, they're highly concerned and want to take action," said Yeghoian, now chief innovation officer at the environmental literacy nonprofit Ten Strands.

LISA PATEL'S TEAM PRODUCED A REPORT EXPLAINING THE GAPS IN CALIFORNIA SCHOOLS' CLIMATE RESILIENCE AND PROPOSING A PLAN TO ADDRESS THEM.

Klein, himself a former fifth grade teacher, said, "As a teacher, one of the first things you learn is 'the hook.' Young people are already engaged in this issue," so it's easier to draw them into lessons. "And they have a right to learn; it's a generational justice issue. They have a right to understand how different ecological forces are unfolding and what are humanity's best thoughts and the tensions among them about the solutions."

Equipping schools to be safe havens and to prepare students for climate change will have knock-on mental health benefits, Wray said. Schools' leaders can counter the psychological distress and sense of institutional betrayal kids experience when they see inaction from people in power.

"It's a direct antidote to those things," Wray said. "Taking action helps young people feel supported and understood, all the things that are good for resilience and belonging."

"They can feel proud that their school is part of the solution," Patel added.

WHAT'S NEXT

Today, the team that produced the report is seeking ways to expand its reach, especially among California legislators. To that end, they hosted an online policy forum on April 21, 2023, featuring two state senators, Lena Gonzalez of the 33rd district and Nancy Skinner of the 9th district; Santa Clara County superintendent of schools Mary Ann Dewan, PhD; and other leaders, with the goal of inspiring legislators to advocate for laws and policies that will put the report into action.

"The work I do is very personal to me as a mom," Gonzalez said at the forum, noting that her oldest child is a public school student in her senate district, which covers part of Los Angeles County. Her district includes schools "so dilapidated it's awful," she said, noting that she's worried about extreme temperatures on asphalt schoolyards and poor air quality from diesel particulate matter.

Schools need a master plan for how to decarbonize, Gonzalez said, with a focus on equity and on making sure that the money California spends on school infrastructure — $7 billion annually — goes toward environmentally sustainable options. She hopes SB 394, which she introduced to the legislature, will be signed into law and fulfill this role. She also hopes the legislation will help tap funds available through the federal Infrastructure Investment and Jobs Act and the Inflation Reduction Act, which were both passed in the last two years.

"There is $6 billion that could be leveraged at the federal level if we get this plan into place ASAP," she said.

"During the pandemic, chronic underinvestment in our schools really showed," Patel said. As a pediatrician, an environmental scientist, and a mom, she saw that more investment is vital. "The value that I came away with, especially after dealing with a kindergartner at home doing Zoom school for a year, is that our children's access to education and the community that comes with it should be sacrosanct."

Although there is a lot of work to do, Patel is excited by the engagement she's already seen in people working in California schools. "On a macro scale, there are big problems that the state needs to address, but on a micro scale, there are so many amazing people enacting solutions every day. I've learned so much talking to people who really want to be part of the solution. That's been really heartening to see." **SM**

— Contact Erin Digitale at digitale@stanford.edu

special delivery

mRNA moves past COVID-19

BY BRUCE GOLDMAN

CATASTROPHE OCCASIONALLY APOLOGIZES for itself by coughing up a consolation prize. World War II gave us penicillin.

So, let's count our blessings.

The COVID-19 pandemic, from which we're still struggling to emerge, has expanded our working vocabulary, gifting the public lexicon with new, if admittedly mostly gloomy, words and concepts. (Examples: spike protein, intubation, N95, rapid antigen test.) We may not flood our speech with these terms, but we're at least passingly familiar with them now.

Emerging last but not least, like hope climbing gamely out of Pandora's box, is an exotic little acronym: mRNA. Once known only to biology majors, mRNA — more formally named messenger RNA — has entered society's word list, courtesy of a brand-new kind of vaccine.

Rarely has vaccine development exceeded the speed of paint peeling. But mRNA vaccines were hustled into commercial viability by Operation Warp Speed, a federal program set up in 2020 to accelerate the development of any vaccine that might stave off COVID-19's most severe symptoms.

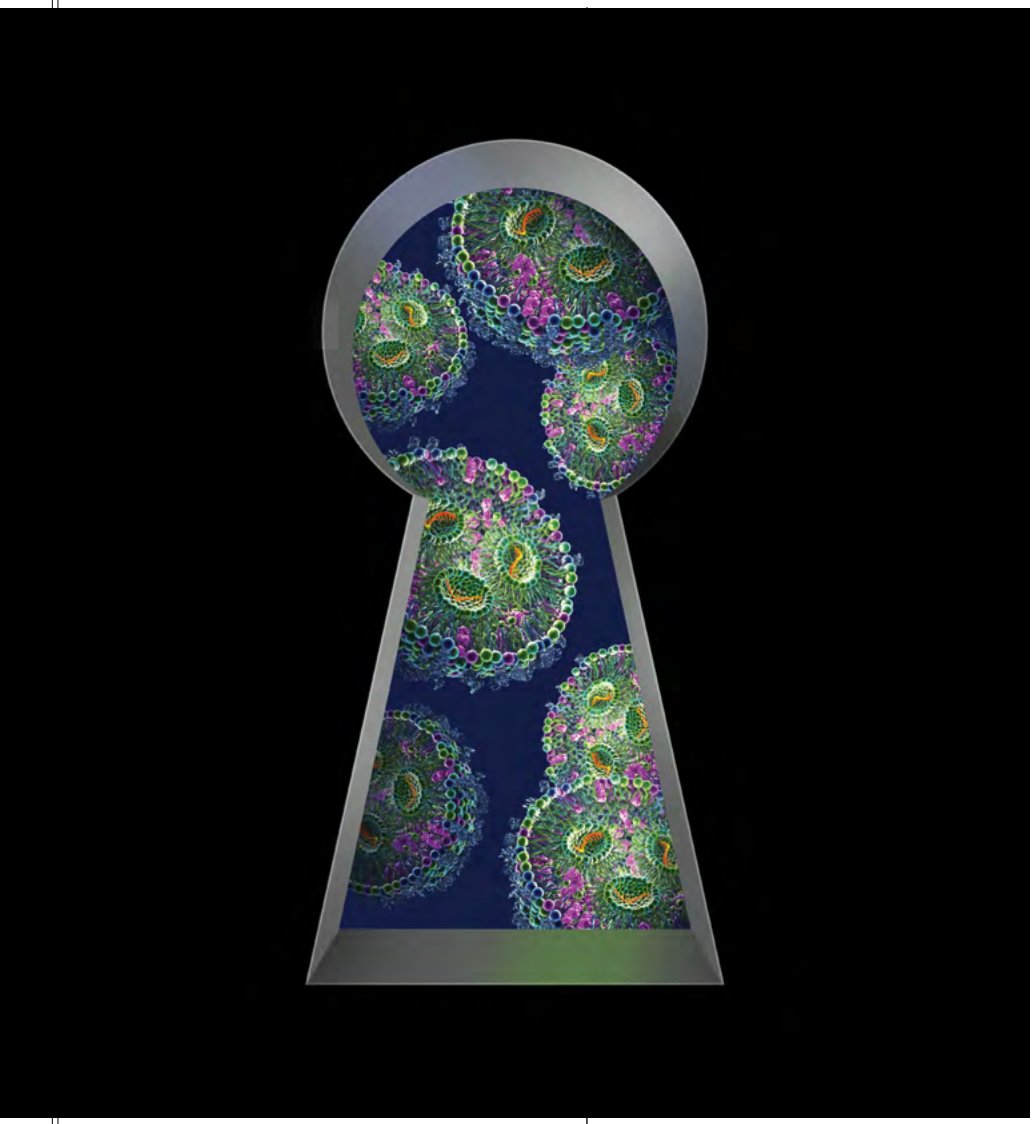
Since receiving an emergency use authorization from the Food and Drug Administration in December 2020, many hundreds of millions of mRNA-based COVID-19 vaccine doses have been shot into people's arms in the United States alone. They've equaled or exceeded COVID-19 vaccines made through traditional means, with respect to both safety and efficacy. And they can be developed or modified with ease and rapidity. Today, scientists are developing mRNA vaccines for all kinds of other infectious diseases, as well as cancer.

There are solid reasons why mRNA may be a superior material for many vaccines, especially when pathogens keep swiftly evolving new strains. But realizing mRNA's full potential means addressing some non-negligible challenges, which Stanford University researchers are tackling. Among them: how to get more bang for the dose, how to send that dose to only where it's supposed to go and how to ensure it sticks around once it gets there.

The sudden appearance of a new kind of vaccine has generated concerns ranging from the spurious to the undeniable. For example, the shots can have side effects — a problem that may have a lot to do with how mRNA currently gets delivered and that, as we shall see, researchers are addressing.

The biggest source of mRNA-vaccine skepticism, according to vaccinologist Bali Pulendran, PhD, the Violetta L. Horton Professor and professor of microbiology and immunology, is rooted not in biology but in our own psychology —

MATT CHASE



specifically, an amorphous, free-floating fear of the unknown.

"The human mind rejects any new idea like the body rejects a transplanted organ," he said.

Making proteins

UNLESS YOU'RE A CELL, making proteins is a tricky business. Just as different culinary creations require vastly different recipes — cooking vessels, timing, mixing methods and oven temperatures — every protein has its own peculiar manufacturing specs. That's a hurdle for fast production of traditional vaccines, which have specific proteins as key components.

Making proteins is easy for cells, though. It's what they do. The cell nucleus, home to our genome, doesn't let any of the 22,000-odd genes it encloses leave the premises. But those DNA-constituted genes can be copied in the form of smaller strands of RNA, a DNA-doppelganger substance that can exit the nucleus.

Every mRNA molecule's mission is to carry the genetic recipe for whatever protein it encodes (hence the "m" for "messenger") to the cytoplasm — all the cell's territory outside the nucleus. That's where abundant numbers of a type of molecular machine — protein-printing presses called ribosomes — hang out. Ribosomes know how to read any mRNA recipe and cook up a batch of the indicated protein in a jiffy. These are well-oiled machines honed by eons of evolution.

The success of mRNA technology lies in outsourcing the heavy lifting of protein manufacturing to the ultimate protein factories: our own cells, which can host millions of ribosomes apiece.

Because biotechnologists can rapidly synthesize buckets of mRNA molecules specifying any desired protein, it's a reasonable strategy for creating a vaccine, pronto. (Proteins from pathogens, or chunks of those proteins, are what make up most vaccines. Exposure to them trains the immune system to launch an attack on that pathogen.)

Fine. So, making mRNA is a snap. But getting it to the right cells and, once inside, to the ribosomes — the key to gaining great protection with minimal side effects — requires ingenuity. Simply shoot naked mRNA into someone's veins and it will quickly get chewed up by enzymes in the blood or tissues. It's very delicate. And mRNA can't whiz effortlessly through cells' protective outer membranes.

You need a delivery vehicle.

mRNA's wild ride on the fat-blob express

THE COVID-19 mRNA vaccines have been ushered into our cells via workhorse delivery trucks called lipid nanoparticles (lipid being a scientific term for "fatty stuff"). Lipid nanoparticles, or LNPs, are glorified fat globules.

"An LNP is a crude attempt to do what a virus does for a living," said Stanford University professor of chemistry Bob Waymouth, PhD. "Viruses are really good at getting inside cells so they can replicate themselves."

A lipid nanoparticle is a four-ingredient sphere roughly 100-200 nanometers in diameter (coincidentally, the size of the virus that causes COVID-19). Two ingre-

dients stabilize the lipid nanoparticle's chemical composition. A third prevents lipid nanoparticles from clumping up, as fat blobs are inclined to do. The fourth, linchpin, ingredient is a bunch of linear, fatty molecules carrying a generally positive electrical charge along their lengths.

An mRNA strand is negatively charged along its length. And, as we all know, opposites attract, particularly in electronics. So, the two stick together, anchoring the mRNA to the lipid nanoparticle. A single lipid nanoparticle can encase multiple mRNA molecules.

Lipid nanoparticles are formulated to deliver their mRNA cargo safely into cells and release it. This frees the mRNA molecules to skedaddle into the cytoplasm and clamber onto its resident ribosomes. But in practice, only around 10% of mRNA smuggled into a cell by lipid nanoparticles ever winds up producing proteins.

"LNPs have a problem with letting go," Waymouth said.

Another problem: Most lipid nanoparticles never get to the desired cells in the first place. Once injected, lipid nanoparticles tend to gravitate toward certain organs and cell types. Left to their own devices after intravenous injection, the vast majority head for the liver — super, if you're trying to medicate liver cells. (Companies all over the world are working on mRNA-based medicines designed for this purpose, Waymouth said.)

Otherwise, not so great.

COVID-19 shots are, of course, injected into muscle tissue, not veins. Even so, some of the lipid nanoparticle-borne mRNA lands in the liver, animal trials suggest. More gets into muscle cells. Small amounts wind up in still other places, which Waymouth said could cause some of the side effects of the vaccines.

Fortunately, a fair amount of it reaches front-line sentinel "show and tell" cells of the immune system that hang out in muscle tissue or nearby lymph nodes. These immune cells are ideal vaccine targets. They gobble up lipid nanoparticles, follow the ingested mRNA's instructions and make proteins, which they chop up into little pieces and display on their surfaces for other immune cells to recognize as foreign material — a key step in kicking a coordinated immune response into gear.

Lipid nanoparticles aren't overly toxic in themselves, but they do cause some inflammation and are suspected of being responsible for some of the more common COVID-19 vaccine side effects, such as sore arms, fever and redness.

Some side effects are more worrisome — for instance, myocarditis, a rare inflammation-driven heart problem experienced primarily by young men and adolescent boys. Whether lipid nanoparticles' inflammatory potential, plus their tendency to wander off, might contribute to some of these less frequently observed, but troubling, COVID-19 vaccine-associated symptoms is an open question. (Having COVID-19 itself imparts a greater myocarditis risk.)

It's a reasonable bet that if biomedical scientists could direct mRNA to targeted cells or organs and nowhere else, this might lower the risk of side effects. What's inarguable is that less of the vaccine would need to be injected. With less going to waste, there'd be more to go around. That's worth considering when you're trying to vaccinate the world's whole population, or close to it, all at once.

There may be a way to do just that. Newer, more efficient, more targeted ways of packaging mRNA could provide a powerful boost for its expanded use in treating conditions beyond COVID-19.

Shopping for CARTs

WAYMOUTH AND chemistry professor Paul Wender, PhD, have been working together for more than a decade on simplified, more efficient mRNA delivery vehicles. These vehicles are called charge-altering releasable transporters, or CARTs.

CARTs (described in a January 2017 paper in the *Proceedings of National Academy of Sciences*) are little spheres about the same size as lipid nanoparticles. But CARTs are not mere fancy fat globules. They consist mostly of a single stringy substance that's part fat and part protein-like. As with lipid nanoparticles, molecules of this substance are positively charged, so they can hang onto mRNA, which has a negative charge.

Fine-tuning the makeup of CARTs — say, by swapping out one type of building block for another — can radically change where they go in the body. Constituted one way and injected intravenously, they'll almost all head for the spleen, an organ practically bursting with immune cells awaiting orders to attack any pathogen that crosses their path. That's a plus for any scientist hunting for a new way to deliver potent vaccines.

Constituted just a little differently, CARTs will mainly lunge for the lungs.

"Where they go depends on what they're made of," said Wender, who's working with Waymouth on additional variations that could expand the list of

IT'S A REASONABLE BET THAT IF BIOMEDICAL SCIENTISTS COULD DIRECT MRNA TO TARGETED CELLS OR ORGANS AND NOWHERE ELSE, THIS MIGHT LOWER THE RISK OF SIDE EFFECTS. WHAT'S INARGUABLE IS THAT LESS OF THE VACCINE WOULD NEED TO BE INJECTED.

'THIS MIGHT ALLOW US TO DIAL IN THE PARTICULAR IMMUNE RESPONSE WE WANT TO INDUCE. KEEPING IT IMMUNOLOGICALLY INERT WOULD PREVENT MULTIPLE INJECTIONS OVER TIME FROM TRIGGERING AN UNWANTED INFLAMMATORY RESPONSE.'

designated destinations in the body. That list could come in handy for, say, developing a gene therapy meant to induce production of a particular protein in a single organ or cell type.

mRNA 2.0: special-delivery service

WHEN CARTS ARE administered intramuscularly (in mice, anyway) they mostly stick around the injection site until local immune cells spot and ingest them. Or, even better, the CARTs head for a nearby lymph node where teams of immune cells suck them up and initiate a response.

Once inside any cell, immune or otherwise, a CART doesn't wait around long before its wheels come off. It literally falls apart. Soon after gaining entry to a cell, its hybrid fat/protein-like carrier molecules lose their positive charge, release their grip on the cargo they were holding — mRNA strands — and break into tiny pieces.

"We designed them that way," Waymouth said.

The overarching result, said Wender, is that "the mRNA molecule gets released on time, virtually all the time." In other words, the CARTs let go of their mRNA cargo in the right place and in good condition, and that's the recipe for the successful delivery of any medicine or vaccine.

Broken down, CARTs' pieces are nontoxic, as are intact CARTs. In fact, CARTs are non-immunogenic, meaning you actually have to add immune-stimulating enhancements to rev up the immune response.

Waymouth suggests the inert nature of CARTs makes them potentially tunable. "This might allow us to dial in the particular immune response we want to induce," he said. "Keeping it immunologically inert," he added, "would prevent multiple injections over time from triggering an unwanted inflammatory response."

In 2021, Wender, Waymouth, professor of oncology Ronald Levy, MD, and coworkers conducted a study to test this idea, the fruits of which were published in *ACS Central Science*. Onto mRNA-filled CARTs, they loaded an additional stretch of genetic code. This stretch, common among viruses, alerts intracellular receptors to the presence of microbes within a cell. Its inclusion substantially boosted the immune response to the mRNA-encoded protein in mice — a promising sign for future vaccine development.

Levy, who is widely known for his innovations in cancer immunotherapy, began collaborating with Waymouth and Wender a half a decade ago. In a mouse study published in 2019 in *Cancer Research*, they injected a CART-drawn combo of mRNA snippets directly into a tumor. The three snippets were recipes for three well-known immunity-stimulating substances. The researchers witnessed a strong immune response not only to the tumor they'd injected with the immune-stimulating mRNA — a not entirely unexpected result — but also to a separate, similar tumor located elsewhere in the body, suggesting that this method might someday have application in ridding a cancer patient of metastases.

Bigger bang theory

A STANDARD, homemade mRNA molecule doesn't last long inside a cell. It's not built to last. Otherwise, a cell would keep cranking out proteins after they were no longer needed. Enzymes inside cells prevent that by biting off an mRNA molecule's ends piece by piece, like whittling down a stick of beef jerky.

But an RNA molecule whose ends have been joined to form a ring is impervious to those chomp-and-chew enzymes.

Seeking a bigger bang for the dose, Waymouth and Wender have been collaborating with professor of dermatology and of genetics Howard Chang, MD, PhD, a world expert in exploring and exploiting circular RNAs, or circRNAs. These are, as the name implies, single RNA molecules joined head to tail, enhanced with built-in entry sites that ribosomes — cells' protein-printing presses — can grab onto. Once they've snagged the mRNA, they can spew out proteins abundantly and for longer. (Picture a single mRNA molecule spinning around and around like a vinyl disk on a turntable.)

A paper by Chang, Wender and researchers, published online in *Nature Biotechnology* in April 2022, showed they could cobble together circRNA that stays stronger for longer. It resists degradation on its way to cells, yields copious copies of the protein it encodes, and lasts longer inside cells before breaking down.

"In our own work, linear mRNA typically survives inside of a cell for about 24 hours," Wender said. "By 48 hours, it's gone." But, the *Nature Biotechnology* paper showed, in mice, circRNA delivered on CARTs lasted inside the cells it penetrated for more than seven days. So a single molecule of it could churn out a lot more of the desired protein than if it were more ephemeral.

CARTs have yet to be tested in

CONTINUES ON PAGE 45

sniff

Making sense of smell

BY NINA BAI

AMONG THE HUMAN SENSES, smell — or more formally, olfaction — is often considered the most dispensable. In a recent survey, 1 in 6 college students said they would rather lose their sense of smell than their little left toe, and 1 in 4 would forgo their sense of smell to keep their phone.

But for people who've found themselves suddenly unable to smell — a more common predicament since the COVID-19 pandemic — the loss can be surprisingly, profoundly devastating.

Zara Patel, MD, a sinus and skull base surgeon and smell specialist at Stanford Medicine, has dedicated her practice to our most underappreciated sense. She sees the effect of its absence in her patients. "People tell me, 'My life has gone gray. It's really difficult to find joy in my life anymore,'" she said. "Some might think, why is it that big of a deal?"

Scent permeates our lives so completely — it is literally the air we breathe — that we rarely make conscious note of it. But pay attention and you'll notice that scents enrich our daily lives, connect us with each other, warn us of danger, and evoke memories and emotions more immediately than any other sense.

More than 1 in 5 Americans has experienced smell loss since the start of the pandemic. The surge has led to a closer look at the underdog sense and its intimate ties to brain health. Smell dysfunction is linked with depression and anxiety. A sudden loss of smell might be the earliest sign of neurodegenerative diseases such as dementia and Parkinson's, detectable long before any cognitive deficits appear.

Patel believes that smell has more to tell us and that olfactory testing might one day become as routine as mammograms and colonoscopies. But first, someone — why not her? — needs to invent a device that can easily and objectively measure smell ability.

The standard treatments for the loss of smell often take months to work — if they do at all. Her patients' despair has spurred Patel to develop a faster, more successful solution: injections of a substance derived from the patient's own blood. She is urging other smell specialists to learn what she says is a simple protocol.

Chemistry

OF THE FIVE SENSES, smell is the most evolutionarily ancient and one we share with the most primitive creatures. Even single-celled bacteria — blind to light and deaf to sound — can sense and react to chemical molecules. That is essentially what smell is — chemosensation. Every pleasing aroma and noxious odor is caused by molecules that have wafted into our noses and been recognized by the specialized neurons deep inside.

PAUL WEARING

Taste is also a type of chemosensation, but if we consider only our tongues, our palate's palette is limited to sweet, sour, salty, bitter and umami (a savory taste). The myriad complex flavors of food often attributed to taste are largely a result of their smell. Taste alone is like a basic set of crayons next to the nearly limitless shades of oil paint that is smell.

That's why one of the most noticeable effects of losing one's sense of smell is strange-tasting food.

Distortions

JOHANNA TA REALIZED something was wrong last summer, several weeks after recovering from COVID-19. She had opened a can of Coke Zero, something she did every day, and thought it tasted funny — like juniper. "Did they change the formula again?" she thought. It was probably just a bad batch, she decided, and went to the grocery store to buy another 12-pack. But those tasted off, too. Later that day, she got into a rental car and realized that the car, too, smelled like the weird Coke Zero.

"It was almost like a switch had been flipped off in my brain," she said.

Soon she was smelling scents that weren't there — a variety of smell dysfunction known as phantosmia. Her home smelled like cigarette smoke without anyone lighting up. Actual smells were distorted beyond recognition — a variety known as parosmia. Coffee smelled rancid. Garlic, onions and anything fried or charbroiled reeked of decay.

Nearly half of people with smell loss also experience phantosmia or parosmia.

When Ta, who works in biotech in the San Francisco Bay Area, went on a business trip to Las Vegas, the crowds there smelled like "walking carcasses," though, funnily enough, she couldn't smell the cigarette smoke that filled the casinos.

"My family absolutely thought I had lost my marbles," she said.

Biology

PATEL CAN GIVE some patients back a normal sense of smell by excising tumors or polyps blocking their nasal or sinus passages. But these surgeries don't resolve cases involving damage to the olfactory neurons.

Of all our sensory neurons, the olfactory neurons are the only ones that make direct contact with the environment. The receiving ends of these neurons — 12 million of them — are exposed in a small patch of the mucus-covered lining of the upper nasal passages known as the olfactory epithelium.

Each olfactory neuron recognizes a narrow selection of similar-looking odor molecules. Yet it's hard to look at a molecule and predict what it smells like or even if it has a smell at all. Chemical structure can hint at smell, but exceptions abound. Molecules that look nothing alike can smell the same, whereas two nearly identical molecules can signal mint and butter to the brain.

Most scents consist of a mix of odor molecules, which activate a combination of olfactory neurons, like a code that the brain then deciphers into bacon, or jasmine, or gasoline.

After recognizing their odor molecules, olfactory neurons carry electrical signals upward — through a thin bony partition

called the cribriform plate, which forms the roof of the nasal cavity, about level with the eyes — then straight into the brain.

Sensory neurons responsible for touch, vision and hearing make their first stop in the brain in the thalamus, which relays their messages to other parts of the brain. Olfactory neurons are the only ones that skip the relay station. Instead, they take an express route to the olfactory cortex, which processes smells, as well as to the amygdala, which regulates emotions, and the hippocampus, which encodes memories.

These anatomical connections could explain why smells can trigger memories more intensely than sights and sounds, said Patel, a professor of otolaryngology - head and neck surgery.

Damage

THERE ARE MANY WAYS someone can lose their sense of smell. Sinus inflammation and tumors can block odor molecules from reaching the olfactory epithelium. A type of head trauma, known as a coup-contrecoup injury, in which a hard hit to the back of the head pushes the brain forward in the skull, can shear the neurons at the cribriform plate.

Viral infections were known to cause smell loss long before COVID-19. Most people with post-viral smell loss recover thanks to the ability of olfactory neurons to regenerate, which they do every three to four months. But damaged neurons don't always regenerate correctly.

By the time patients with long-term smell loss find their way to Patel's clinic, they've tried the conventional therapies: steroid rinses to calm inflammation and months of tedious smell training, in which they practice smelling specific scents while concentrating on their memories of these scents. Yet they still cannot smell.

"You want to be able to help every single person who walks in the door. It was very frustrating for me to not have the answer for that group of patients," Patel said. "As I looked into the literature, I realized we really didn't have anything to offer these people."

But after reading a study showing that platelet-rich plasma injections could treat carpal tunnel syndrome, which is also caused by nerve injury, she developed a protocol to use them for smell loss. Platelet-rich plasma, or PRP, is derived from the patient's own blood, with blood cells removed, leaving a concentrated serum of platelets and growth factors. The serum is injected directly into the olfactory epithelium to help damaged olfactory neurons regrow.

At Ta's first visit to Patel, six months after the weird Coke Zero, she realized she was one of many. She'd become used to perplexed reactions to her strange symptoms, but as she described them, "Dr. Patel had this knowing look of 'Oh yeah, yep, yep,'" she said. "Just having visited her made me feel hopeful."

Ta decided to try the PRP injections, even though as an experimental treatment they wouldn't be covered by health insurance.

After the second of the three injections, given two weeks apart, she was overjoyed to find that garlic and onions began to smell normal. Now, a few months after her third injection, she feels she has regained most of her sense of smell, with notable exceptions. She has yet to have a cup of coffee that doesn't smell like dead rat.

Last year, Patel published the results of a small clinical trial, which found that 57% of patients receiving the PRP injections reported clinically significant improvement in their ability to smell. These days, Patel's clinic is booked six months out.

Loss

OF THE EFFECTS of COVID-19 Shannon Colon, PsyD, still feels a year and a half after she caught the virus, including fatigue and brain fog, the loss of smell has had the greatest impact on her enjoyment of life, she said. It's meant missing the new baby smell of her grandniece. Missing the taste of guacamole, one of her favorite foods. Missing the fragrance of honeysuckle that reminded her of growing up in Hawaii and Louisiana. Missing the scents of pine, and leather, and fresh dirt, even the manure from roadside farms along the drive to her mother's house in California's Central Valley.

The loss has brought her to some dark places, said Colon, a school psychologist in Reno, Nevada. The pandemic had already taken away the comfort of touch; the loss of yet another sensory pleasure was hard to bear.

"It's very much like being in prison," she said. "Other people might appreciate how lonely or devastating that may be, but they've never experienced it. It's just very isolating."

According to one study, 40% to 76% of patients with smell loss also have depression. The more significant the smell impairment, the more severe the depression.

"Across all of our societies, cultures, in any geographic region in the world, the way we come together as human beings, whether it's friends, family or strangers, is almost always over food and drink," Patel

'YOU WANT TO BE ABLE TO HELP EVERY SINGLE PERSON WHO WALKS IN THE DOOR. IT WAS VERY FRUSTRATING FOR ME TO NOT HAVE THE ANSWER FOR THAT GROUP OF PATIENTS.'

TIMOTHY ARCHIBALD

ZARA PATEL HAS DEVELOPED A TREATMENT FOR SMELL LOSS USING PLATELETS DERIVED FROM A PATIENT'S OWN BLOOD.

said. "If you can imagine not being able to enjoy that, or in some situations feeling repulsed by it, you can imagine why people withdraw and socially isolate."

After searching for and trying all manner of treatments — from supplements to an injection of anesthetics to nerves in her neck — Colon found Patel's clinical trial.

Within days after each PRP injection, Colon noticed improvement. Six months after her last one, some smells and flavors have come back. She can taste about 80% of a pickle, by her own estimation, and, when driving through Gilroy, California, she can smell why it's known as the "garlic capital of the world." Other scents are still faint or warped echoes. She can barely taste a peanut butter cup, and on some days, guacamole still tastes like soap.

It's not only the pleasant scents that people miss. Many people develop anxieties around safety or personal hygiene. They might not perceive smoke from a fire or the rancid odor of spoiled food. Scents are such effective warning signals that, since a deadly school explosion in 1937, utility companies have added mercaptan, a chemical that stinks of rotten eggs, to normally odorless natural gas as a safety measure.

Ta still can't smell her son's dirty diapers — which isn't always a good thing. "Sometimes he can go a couple of hours with a soiled diaper, and I wouldn't know," she said.

Misconceptions

DESPITE SMELL'S ANCIENT ORIGINS, our understanding of its biology is still catching up to that of the other senses. It wasn't until 1991 that Columbia University microbiologists Richard Axel, MD, and Linda Buck, PhD, described in detail how the olfactory system works, which earned them the Nobel Prize in 2004. Studying mice, they found that some 1,000 genes, 3% of the mouse genome, are dedicated to capturing odors. Humans have about a third as many olfactory genes, which still make them the largest family of genes in the human genome.

It's a myth that humans don't smell very well. More likely, we're just out of practice. "We simply don't exercise our sense of smell as much as we exercise our other senses," Patel said. "It doesn't necessarily mean we don't have the capability."

Another common misconception is that

smell loss is a normal consequence of aging. Though there's some decline, it shouldn't be a huge drop-off, Patel said. A sudden unexplained loss of smell could be a telltale sign of disease brewing in the brain.

"I suspect that the more we investigate these cases longitudinally over time, the more we're going to realize that many people who we used to put in an idiopathic category — meaning we don't know why they've lost their smell — will eventually end up in the neurodegenerative category," she said.

Post-mortem studies of brains have found the plaques and tangles tied to dementia appear first in the olfactory system. Numerous studies now suggest that olfactory impairment may be the earliest detectable marker of neurodegenerative diseases.

For smell loss to be a truly useful biomarker, however, we first need a better way to test for smell.

Objectivity

NEW PATIENTS AT Patel's smell clinic are screened with the UPSIT, the University of Pennsylvania Smell Identification Test, a commonly used, 40-item, multiple-choice test with scents ranging from rose to gasoline embedded in the pages of a scratch-and-sniff booklet. Some are further assessed with the more detailed Sniffin' Sticks test, in which they're scored on their ability to detect, identify and discriminate between a series of scent-soaked felt-tipped pens.

In all, there are dozens of such smell tests, but none is considered a universal standard, and results from one test are hard to translate to another. Moreover, they all suffer from an element of subjectivity, such as a person's past experience with particular scents. How many millennials, for instance, could identify the smell of turpentine?

Sound can be measured in decibels and frequency, light can be gauged by wavelength and brightness, but there's no analogous way to quantify smells or smell ability.

Patel thinks there should be. With the help of a Stanford Biodesign Faculty Fellowship, she is developing a device that could measure and record the activity of olfactory neurons. The handheld instrument with a malleable probe would be inserted (with local anesthesia) into the nose to reach the olfactory epithelium. The measured electrical activity indicates the severity of smell loss.

"The most important thing is that it's purely objective. There's nothing between the electrical signal of these nerves and the answer that we're looking for," Patel said.

Patterns of activity might even distinguish between smell loss from neurodegenerative diseases, viral infection or physical trauma. The device also could be used therapeutically to deliver electrical stimulation to the olfactory epithelium to encourage nerve regeneration. It would be a game changer for the study of olfaction.

Patel envisions such a smell-testing device becoming a standard screening tool for early signs of dementia. "What I realized is that not everyone, when you start talking about smell, cares that much," she said. "But when you start talking about Alzheimer's disease, people pay more attention."

If people can accept colonoscopy as a normal screening tool, "they could, hopefully, understand having to put something up their nose," she said. "They're numbed up; we place it inside. No big deal." SM

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FEATURE

Greening the OR

CONTINUED FROM PAGE 29

recycling program? Do you offer reprocessed items?' It's something we've built into our culture."

She added: "It's a win-win for everyone: It's better financially for the hospital and contributes positively to the environment without impacting the care we provide our patients. There's no reason not to do it."

Succeeding in changing culture

THE BIGGEST OBSTACLE to creating greener operating rooms may be surgical teams' reliance on time-tested routines, checklists and rules to keep patients safe.

"Change always begins with education," said Kalra, whose campaign to remove desflurane from operating rooms began with a seminar for Stanford Medicine anesthesiologists on its environmental footprint. "My colleagues are an educated, highly intelligent audience, so I had to make it convincing and a bit personal."

He shared his own philosophy that "the environment is also a patient we cannot neglect," he said, along with compelling data, including a study from the U.K.'s National Health Service showing that 40% of the carbon footprint of surgery came from anesthetic gases.

He also pointed out that desflurane is twice as expensive as other anesthetic gases and has the highest global warming potential among inhaled anesthetics. Vaporization of one bottle (240 milliliter) of desflurane for anesthesia has the same global warming effect as 886 kilograms of carbon dioxide, he explained.

His colleagues came on board: By mid-2019, desflurane had been eliminated from all Stanford Health Care operating rooms, reducing the organization's carbon footprint from fluorinated anesthetic gases by 83% and saving $200,000 per year. Fluorinated gases are the main gases used to induce general anesthesia, helping patients "fall asleep," sometimes in combination with another gas, nitrous oxide.

He also developed a two-week elective rotation for anesthesia residents, equipping them to become leaders in spreading sustainable practices to other hospitals.

Stanford Medicine leaders want the whole health care industry to rethink how to achieve surgical success and safety with a reduced environmental footprint.

"Medicine is a highly regulated environment," said Wilmot, adding that many regulations were designed with safety, but not sustainability, in mind. "We need to create coalitions with other large organizations and bring regulators to the table to ask about the value of some regulations. We want to bring evidence to regulators that there could be different, more sustainable ways to achieve safety and maintain clinical outcomes."

In future green operating rooms, said orthopaedic surgeon Shea, one thing will remain constant: Patient well-being will be the top priority.

"Taking care of patients is the North Star for health care, and we never stop

navigating by it," he said. "But we can be careful, thoughtful and proactive about how we navigate, and guide our ship toward that North Star in a better way that includes thinking about the environmental impact of what we do." SM

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WEBEXTRA

Watch a video on how Stanford Medicine students and physicians are making changes for the environment: stan.md/greening

PLUS

Special delivery

CONTINUED FROM PAGE 39

rigorous clinical trials. That looks to be a few years off — although, as we've seen with COVID-19, perceived need can vastly accelerate treatment.

"CircRNAs can also be packaged and delivered in lipid nanoparticles," noted Chang, the Virginia and D.K. Ludwig Professor of Cancer Research. Some companies developing circRNA medicines are using lipid nanoparticles as delivery vehicles, he said.

Whether delivered by lipid nanoparticles, by CARTs or by some yet-to-emerge breakthrough technology, mRNA is going to play an increasingly prevalent role in vaccine development.

Everything everywhere all at once

COVID-19 WAS THE launchpad for mRNA vaccine technology. As the world emerges from the worst of the pandemic, can the same platform dispatch mRNA vaccines aimed at pretty much any microbe of choice? Pulendran, the vaccinologist, answers with a resounding yes.

"Any vaccine you can think of, the mRNA-frontrunner companies are working on it," said Pulendran, who has consulted with BioNTech, Moderna and Pfizer, three companies closely associated with the technology. "Their world view is that mRNA technology will replace all preceding ones. The future is extremely bright for mRNA vaccines."

Pulendran noted a couple of criticisms that have been leveled at the mRNA-based COVID-19 vaccines. "They've been very good at preventing severe disease, hospitalization and death," he said. "So far, they haven't been so good at preventing infection for long periods of time — particularly in the face of ever-newer viral variants — and they haven't been great at preventing transmission."

But transmission is a problem common to all respiratory infections, he said. It's tough to completely prevent infection of the nose and throat with any vaccine, since these outward-facing cavities' cells are constantly exposed to the air — and, consequently, the microbes — we inhale.

"To me, the most critical goal of a vaccine is to prevent severe or even moderate disease," Pulendran said. "A mild COVID 'cold' may even *benefit* us by keeping our immune system on its toes." On the other hand, he said, mRNA vaccines employing delivery systems that target the mucus-secreting linings of our airways and gut may prove more effective at durably preventing infection.

Was the technology that rescued those most susceptible to depredations of SARS-CoV-2 — the virus that causes COVID-19 — a one-hit wonder, or was it a cornucopia conferring protection from microbial menaces of every stripe? Time will tell.

And it won't take long. Clinical testing is underway for mRNA-based vaccines for influenza, HIV, cytomegalovirus, dengue, rabies and several other viruses, as well as for malaria, tuberculosis and other non-viral microbes. Moderna is submitting its mRNA-based vaccine directed at respiratory syncytial virus to the FDA for approval. Moderna and Merck are collaborating on a personalized skin-cancer vaccine employing mRNA, now in clinical trials.

These are all familiar, if uninvited, maladies. What humanity should most fear — and what the plug-and-play mRNA vaccine technology promises to provide the most valiant and rapid defense against — are those next unfamiliar monsters climbing over the hill toward us, which science-fiction movies always seem to depict as giants but are actually microscopic. SM

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ECO-CURRICULUM

A STUDENT CHANNELS CLIMATE FEARS INTO THE MEDICAL SCHOOL'S COURSES

On the morning of Sept. 9, 2020, medical student Ashley Jowell awoke, like others across the San Francisco Bay Area, to an eerie orange sky. The surreal phenomenon was brought on by a thick layer of smoke from massive California wildfires and a marine layer that combined to choke out the normal blue hue.

Now, as every wildfire season approaches, Jowell, a fourth-year Stanford School of Medicine student, experiences anxiety as more climate-related damage is laid bare.

That dread is lessened somewhat by Jowell's knowledge that she is taking action: In 2019, she began helping to lead a drive to weave information about climate change's health impacts into medical education. She and her team were the first to bring the proposed changes to those responsible for overseeing the curriculum at the medical school. Jowell has been involved since the beginning.

"As future physicians, we need to be prepared to care for patients affected by climate change and also know how to help our patients adapt and respond with resilience to a changing environment," Jowell said.

According to the World Health Organization, climate change is the biggest health threat facing humanity. From the exacerbation of asthma symptoms by wildfire smoke and pollution to the increased preeclampsia risk for pregnant women exposed to extreme heat, examples of the environment's impact on health abound.

Medical student Ashley Jowell led a group of other students to weave material about the environment and health into the school's curriculum.

In 2019, Jowell co-founded the Stanford Climate and Health group, made up of students and faculty who organize symposia and conduct community engagement events on climate change. She and three other medical students joined the group's education subcommittee, aiming to enhance the school's curriculum.

Daniel Bernstein, MD, the associate dean for curriculum and scholarship, joined the effort when Jowell approached him about proposed changes.

"Environmental change touches every single disease. Reflecting the pervasive nature of climate is paramount," said Bernstein, the Alfred Woodley Salter and Mabel G. Salter Endowed Professor in Pediatrics. "We didn't want a separate two-hour lecture on climate change. What we do is integrate it into each organ system course."

As a first step, students evaluated and presented papers to Bernstein that could be added to the course slides. The biggest challenge, Jowell said, was folding new literature into already packed medical school curriculum materials — rather than creating new lectures — to ease adoption for lecturers.

"The students were methodical and gave the faculty the information and resources they would need to succeed," said Barbara Erny, MD, a faculty adviser to the group and adjunct clinical associate professor of medicine.

Bernstein piloted the curriculum enhancement in the cardiology and pulmonary courses, adding content such as how heatstroke affects the cardiovascular system and how air pollution affects patients with asthma and chronic lung and heart diseases.

As the students' team has grown, they have worked with faculty to expand the climate curriculum to 12 subject areas — including psychiatry, dermatology and neurology — and continue to evaluate and add content.

Though the students had no peer-reviewed climate-curriculum resource available when they launched their effort, that has changed. Now faculty can draw on standardized materials provided by Climate Resources for Health Education, a collaboration of several U.S. medical institutions.

The Stanford Climate and Health group is integrating these materials into every preclinical course along with clerkships and residencies.

The group's success so far is a salve to Jowell's eco-anxiety: "Channeling this concern into climate and health education has given me a tangible way to help address the climate crisis." BY EMILY MOSKAL

Photograph by Timothy Archibald

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Breathing anxiety away

A FEW MINUTES OF SIGHING CAN RELAX YOU QUICKLY AND KEEP YOU FEELING BETTER ALL DAY LONG

What's your go-to way to relieve anxiety? Take a walk? Have a cup of tea? Scream? What about simply taking a breath? Turns out if you do the latter for about five minutes using a technique called cyclic sighing, you'll likely calm down quickly.

When worry starts, your heart rate speeds, you breathe faster, your muscles tighten, your armpits get sweaty, and you feel restless and fidgety.

"As soon as you notice what's going on in your body, your brain thinks, 'Oh no, this must be really bad,' and you get more anxious," said David Spiegel, MD, associate chair of psychiatry and behavioral sciences, who co-led a study of cyclic sighing's effects published Jan. 17 in *Cell Reports Medicine*. "It's like a snowball rolling downhill."

Cyclic sighing stops the momentum. To do it, first inhale through your nose. Next, take a second, deeper breath to fully expand your lungs. Then slowly exhale all the air through your mouth. Spiegel recommends repeating this for about five minutes.

The study's team, led by Spiegel; neurobiologist Andrew Huberman, PhD; and former Stanford Medicine senior research scientist Melis Yilmaz Balban, PhD, compared cyclic sighing with two other controlled breathing routines, one emphasizing inhalation and another calling for equal inhalation and exhalation, and to mindfulness meditation. Each of the 111 volunteers was asked to perform the assigned exercise for five minutes a day for a month.

Researchers assessed the results through two questionnaires answered before and after the exercises: a standardized measurement of current anxiety levels and a tool that assesses good and bad feelings on a scale from 1 to 5.

All groups reported lower anxiety and a better mood, and the controlled breathing groups reported significantly greater increases in energy, joy and peacefulness, rising an average of 1.91 points above baseline on the "good feelings" scale. Cyclic sighers reported the greatest daily improvements, an effect that increased over time.

Spiegel and Huberman plan to use MRI to study brain activity during the controlled breathing exercises and see if they help people with anxiety or mood disorders.

"We may be able to identify certain kinds of anxiety that respond substantially to this simple treatment," Spiegel said. **SM**

— HADLEY LEGGETT

MARCO