SUMMER 22

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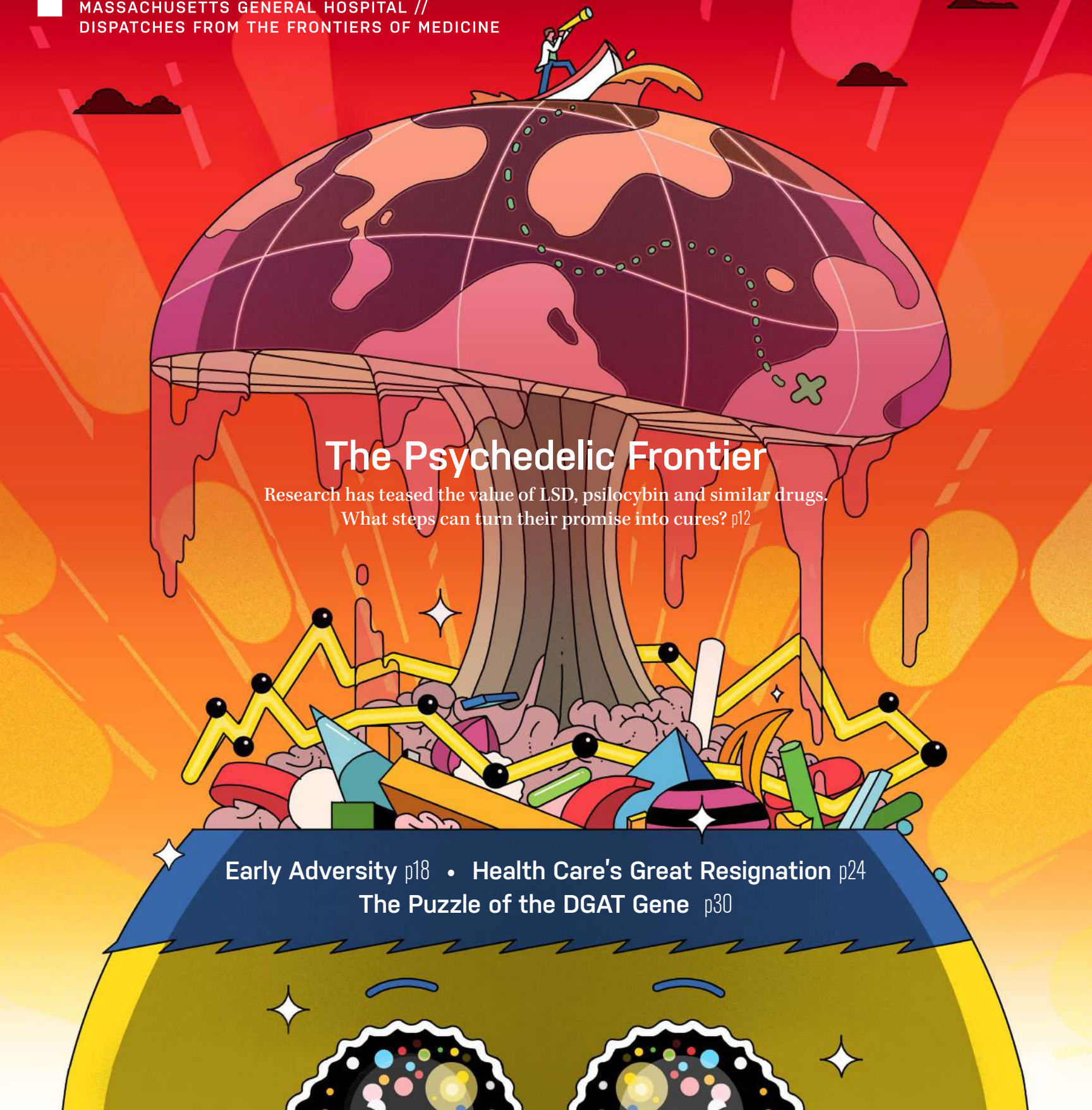
MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE



The Psychedelic Frontier

Research has teased the value of LSD, psilocybin and similar drugs. What steps can turn their promise into cures? p12

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on the cover

The renaissance of interest in psychedelic therapies has raised both hope and new questions. What are the mechanisms at play, and how can the drugs be made safe for all who might benefit from them?
// Illustration by Ori Toor

proto: a prefix of progress, connoting first, novel, experimental. Alone, it conjures an entire world of the new: discoveries, directions, ideas. In taking **proto** as its name, this magazine stakes its ground on medicine's leading edge—exploring breakthroughs, dissecting controversies, opening a forum for informed debate.

proto

EVERY DAY, MODERN ANTIDEPRESSANTS, anti-anxiety and antipsychotic medications and mood stabilizers help millions of people cope with mental illness. For those who treat patients suffering from psychiatric disorders, however, it can be tedious, frustrating and sometimes heartbreaking to search for the right medication or combination of drugs that will ease a particular person's symptoms. Figuring out the best treatment too often means cycling through a parade of drugs and their side effects. Some people aren't helped at all.

Psychedelic drugs, long outlawed, may have the potential to improve on that equation, perhaps dramatically. Mostly in small numbers and isolated studies, psilocybin, mescaline, LSD, MDMA and other compounds have shown an ability to relieve the suffering of people with depression, post-traumatic stress disorder and a range of other psychological conditions. Now, amid a resurgence of interest in these intriguing chemicals, scientists at leading research institutions are devoting themselves to solving the mysteries of what actually happens—in the brain, in the mind and in the body—when someone takes a psychedelic drug. Without such knowledge, it's highly unlikely that the stigma and fear related to these substances can be overcome and their therapeutic potential realized. "Where Psychedelic Research Goes Next," in this issue, looks at the state of this emerging science.

The MGH Center for the Neuroscience of Psychedelics, launched in 2021, approaches this research from multiple perspectives. One team is exploring how psychedelics affect brain networks that underlie how people think and feel; another uses advanced imaging to look at what happens in the brain during a psychedelic experience; and a third is probing the molecular and cellular mechanisms of brain plasticity.

For Jerry Rosenbaum, the MGH psychiatrist-in-chief emeritus, who now serves as director of the center—and for all researchers focused on unraveling the secrets and leveraging the power of psychedelics—this could be a pivotal moment. "Today in psychiatry we have many unsatisfactory pharmaceutical agents, and a lot of mental illness that's not being treated successfully," Rosenbaum says. "Our research here is based on the idea that we can do much better, dealing not just with symptoms, but actually grappling with causes and cures."

Clearly, an important pursuit to keep in mind.

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stat

FOCUS

Part of a Russian missile lies in a wheat field near the Ukrainian city of Soledar—a name that means "a gift of salt." About 30% of the world's wheat comes from Russia and Ukraine, with Russia also supplying 13% of global fertilizers. As a result, the war and its sanctions have had a profound effect on global nutrition. Half of the population of Somalia, which gets nearly all of its wheat from Russia and Ukraine, faces acute food insecurity, to cite only one example.

In early July, the United Nations delivered its annual food security and nutrition report. Hunger rose dramatically over the past two years, and now one in 10 people are affected. The war in Ukraine and the effects of climate change are likely to compound this crisis, resulting in migrations and starvation at "unprecedented levels," the report says. Medical problems associated with food deprivation—stunted growth and disorders associated with a lack of micronutrients—are all but inevitable.

BERNAT ARMANGUE/ASSOCIATED PRESS

INTERVIEW

From Genome to Pangenome

The reference genome is bracing for its next leap forward. Geneticist Ting Wang wants the process to embrace both science and social equity.

The Human Genome Project completed the first draft human reference genome in 2001. That started a new epoch in medicine, one that could better trace genetic differences and the roots of diseases. Yet the map established by the Human Genome Project still has its limitations, not least of which is that some 70% of the genome sequence came from a single man.

The Human Pangenome Reference Consortium, born in 2019, aims for an updated reference genome—one that is at once more complete and more representative of human diversity. Ting Wang, a geneticist at Washington University in St. Louis, leads the center coordinating the effort. When the project finishes up five years from now, he hopes the new pangenome materials will give a boost to diagnostics and therapies, as well as a more complete picture of who we are.

OPPOSITE PAGE: PHOTO BY MICHAEL THOMAS; THIS PAGE: THE NOUN PROJECT

Q: Your plan is to sequence 350 people from diverse backgrounds. How did you choose that number?
A: It was a calculation that required us to balance the limiting factor of funding with how to maximize the number of genetic variants represented. This is a rough estimate, but with 350 diverse genomes, we can cover the majority of genetic variants having at least a 1% allele frequency in the global population.

Q: Where will these samples come from?
A: During the first two years of the project, we took advantage of existing samples from the 1000 Genomes Project. This is an international effort that launched in 2008 and that has samples from individuals from diverse genomic and biogeographical backgrounds. Currently, we are recruiting participants through the Mount Sinai BioMe Biobank along with a cohort of African American individuals who were recruited by Washington University.

Q: Past projects ran into opposition from Indigenous groups. They felt autonomy over their own genetic data wasn't respected. What's different this time?
A: When the project launched, we formed a team of scholars devoted to the ethical, legal and social implications of our efforts to ensure that we do not repeat past mistakes. This team is made up of leaders at the intersections of genomics, biomedical ethics, law, social science and community engagement. The team is embedded in all aspects of the project, including very technical aspects, to ensure that the scientists working on this project understand and appreciate what is at stake. We are actively engaging with Indigenous geneticists, leaders and community members to collaboratively develop a truly inclusive pangenome.

Q: What are the biggest technical challenges the project faces?
A: The current human reference genome is roughly 90% complete. The remaining 10% is missing. The missing parts are made of highly repetitive sequences, which are very important to the genome but very difficult to read with traditional short-read sequencing. So the T2T, or Telomere-to-Telomere, consortium, which is a partner in the project, is actually using long-read sequencing technology to try to decode the missing parts.

Another challenge, which is very dear to my heart, is to functionally understand the genome. We want to annotate the genome and understand how genomic variation leads to phenotypic variation. We want to understand what forces shaped our species evolution and what genomic signatures these forces made. We want to understand how genetic variants affect how cells behave. The current reference genome is a composite, so there is no single naturally living cell on this planet with the reference genome. Functionally annotating the pangenome presents many unique technical challenges, but the opportunity to address these challenges is exciting.

Q: So this project will wrap up in five years. What then?
A: Ultimately, we want this project to continue long after we have collected our 350 genomes and the funding from the NIH has run out. We are working to establish a global alliance of genomics partners. The United States can be a founding member and pave the way for developing the technology and tools, but we believe that the effort to create a resource to better serve humanity should be a global one. It should continue for as long as there are discoveries to be made.

BY THE NUMBERS

AlphaFold's Promise

10^{300}

Shapes the atoms in a typical protein might fold into, as estimated by molecular biologist Cyrus Levinthal. This observation gave rise to Levinthal's Paradox. Although proteins in nature fold into their native forms almost spontaneously, it would take longer than the age of the universe to map out the possible configurations for even one such protein.

$1.4 million

Cost of determining a protein's structure at the turn of the century via X-ray crystallography. This and other methods have since become more efficient, but by 2020 they had solved only about 17% of human protein structures.

92.4

Score out of 100 points achieved in a 2020 contest to predict protein shapes by AlphaFold, an AI program designed by Google's DeepMind division. The AlphaFold predictions had an error margin of only 0.1 nanometer, or the width of an atom.

170,000

Number of protein sequences and structures used to train AlphaFold. After a few weeks, AlphaFold was able to predict a protein structure within one or two days.

100 million

Number of protein-structure predictions that DeepMind plans to release in 2022. AlphaFold has predicted the structures of 98.5% of human proteins and the entire proteomes of key organisms such as mice and *E. coli*. Currently 992,316 structures and 48 proteomes are available on the AlphaFold website, and the company made the software free to use.

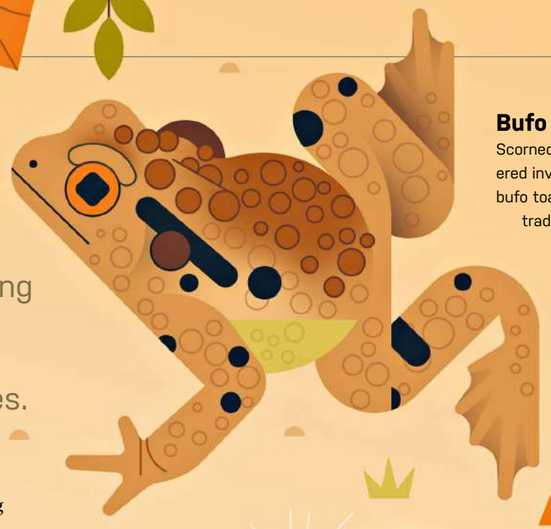
One Man's Poison

New genetic sequencing technologies have opened the door to animal venom therapies.

BY TIMOTHY GOWER

Plants have long been a source of raw materials for making medicines, including both traditional therapies and conventional drugs. Yet chemicals produced by animals—especially the venom that some 15% to 30% of all species use for defense and hunting—remain largely untapped. The Food and Drug Administration has approved just a handful of drugs derived from venom, including the antihypertensive Captopril (from the Brazilian viper) and the diabetes medication exenatide (from the Gila monster).

But with more than 200,000 venomous species walking the earth, many new therapeutics await discovery, says chemical biologist Mandë Holford, an associate professor of chemistry at CUNY Hunter College. Holford studies the medicinal potential of peptides in venom from marine snails. She explains that isolating the potentially curative components in animal toxins is becoming less challenging because of the emergence of techniques that include transcriptomics, which allows scientists to survey a venom's RNA sequence in hours instead of months. "That has been game changing. We now have the tools to mine these animals' arsenals to understand what's there and figure out how we can use it," says Holford. "This will help us make more effective drugs, faster."

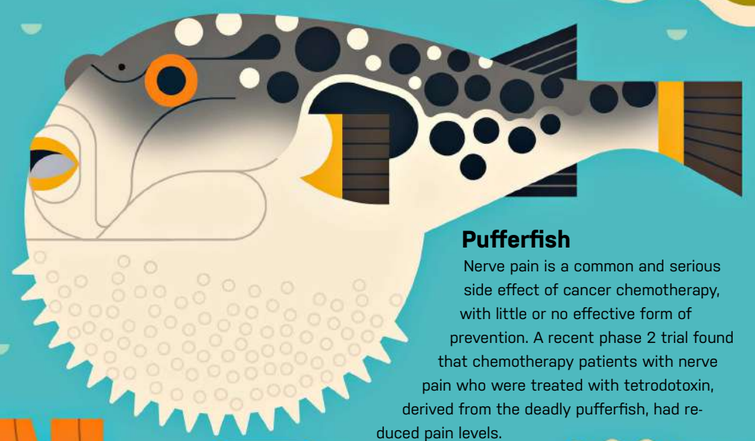


Bufo toads

Scorned in Florida, where they are considered invasive pests and a threat to pets, bufo toads secrete chemicals used in a traditional Chinese medicine known as cinobufacini. They are currently in clinical trials as adjunctive treatments for several malignancies, including esophageal cancer and lymphoma.

Shrews

Few mammals produce venom, but the short-tailed shrew's saliva contains a peptide called soricidin that paralyzes prey. A synthetic derivative of soricidin, called SOR-C13, is currently in a phase 1 trial for treatment of advanced ovarian, pancreatic and prostate tumors that no longer respond to treatment.



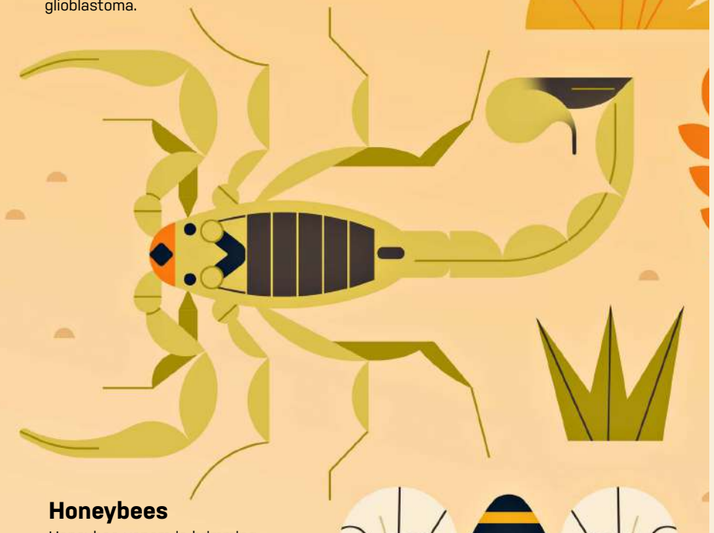
Pufferfish

Nerve pain is a common and serious side effect of cancer chemotherapy, with little or no effective form of prevention. A recent phase 2 trial found that chemotherapy patients with nerve pain who were treated with tetrodotoxin, derived from the deadly pufferfish, had reduced pain levels.

LEFT: ILLUSTRATION BY OWEN DAVIES; RIGHT: ILLUSTRATION BY CHRIS GASH

Scorpions

The venom of a scorpion known as the deathstalker contains a paralyzing agent called chlorotoxin, which has been shown to target cancerous glioma cells, ignoring healthy brain cells. Early clinical trials of a synthetic version of the toxin, paired with immunotherapy, are under way in patients with recurrent or worsening glioblastoma.



Honeybees

Honeybee venom is brimming with intriguing peptides and enzymes, and has shown promise as a treatment for Parkinson's disease, Alzheimer's disease, ALS, HIV and several cancers. In a recent study, honeybee venom and its major component, melittin, induced death of malignant cells in a mouse model of aggressive breast cancer.

Sea anemones

A small study showed improvement in psoriasis in nine out of 10 patients treated with dalazatide, derived from toxins that sea anemones emit to hunt prey. Such chemicals may prove useful for other conditions, including inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and neuroinflammations such as Alzheimer's disease.

MEDUCATION

Illegal to Learn

How will medical students complete their training in abortion procedures?

The overturning of *Roe v. Wade* has unleashed a downstream effect on the training of physicians, notably those who specialize in obstetrics and gynecology and related subfields. Abortion training has been a key part of their education. Now, in states where the procedure is illegal, the ability to teach the procedure is in limbo.

In a perspective published June 2022 in *The New England Journal of Medicine*, OB/GYN Lisa Harris outlined the important role of such training, noting that medical students who don't learn abortion procedures may not be able to perform them when they could be lifesaving to a patient. Harris is a physician and researcher at the University of Michigan Medical School in Ann Arbor and directs the school's Fellowship in Family Planning.

For Harris, the matter has some immediacy. Michigan still has an abortion ban on its law books, though it is not currently enforced. She began thinking in earnest about the future of abortion training in the fall of 2021, when the Supreme Court heard arguments related to the case that would overturn *Roe*. "We are trying to find a home for our learners and other institutions are doing the same thing," she says.

The logistics of cross-institutional training will be complicated and are still in the works across the country. Still, the task couldn't be more important. "If we are missing a generation in the training of a critical skill not only for abortions but for miscarriages, we'll see that in terms of complications," says Katherine Pocius, who directs family planning at Massachusetts General Hospital.

POLICY

The Gift of Data

Data altruism sounds like a good idea. But can the strategy effectively be put into practice?

BY STEPHEN ORNES

ILLUSTRATION BY CHRIS GASH

Health care data are personal, plentiful and immensely valuable. In 2020, they made up an estimated 30% of the world's annual data production, and with a greater adoption of wearables and other data-gathering tools, that number is on the rise. The uses of medical data have proved to be revolutionary, including algorithms that can better predict disease and produce a more accurate picture of long-term outcomes. A 2013 study by McKinsey estimated that smarter data-driven health care could save $300 billion in spending per year.

But health care data is also deeply personal. While some might agree to let their medical records or specimen data be used to further science, those who do not—or who are never given the option—might be aghast to see it used without consent to drive a company's bottom line.

One proposed solution has come out of the European Union. While the United States has a sprawling patchwork of state and local laws around privacy, the EU has, for years, been passing sweeping and centralized legislation that emphasizes personal control. To unlock some of that data for research use, they have introduced the concept of "data altruism."

Data altruism could work a little like ticking an organ donor box on a driver's license. Patients agree to share their health data, selflessly and without compensation, but only for noncommercial purposes aimed at the greater good. The idea factors heavily into new legislation, the Data Governance Act, published by the European Commission in May 2022. Its architects hope that "data altruists" will increase the flow of data to researchers, including their health records.

Organizations that want to use the data have to be approved by the relevant oversight bodies. They must agree to use the data only for delineated scientific purposes, which must be conducted in the interest of the public good. Once altruists opt in, their health care data will flow into a central "pool," per the DGA, where registered organizations can access it.

"Basically, it is supposed to help make data sharing—including for altruistic purposes—transparent," says Mahsa Shabani, an attorney and data protection researcher at the University of Ghent in Belgium who studies how EU legislation may affect data sharing. The program also appears popular with the public: A survey published in 2017 of nearly 800 patients in Germany found that 87% were willing to share data for the right reasons.

Some critics have noted that the act could complicate the consent process and, ironically, add extra barriers to nonprofit research data use. In the short term, the European Data Protection Board and the European Data Protection Supervisor have warned about potential inconsistencies between the DGA and earlier privacy legislation, and during their review called for several changes, including a clearer definition of "purposes of general interest"—all of which may stall progress.

But more broadly, adding another layer of consent to the patient experience might deter potential altruists rather than free up their data, says Shabani. Existing EU law already has a strict consent process and the DGA doesn't simplify that process. "The regulatory framework is already complex," she says. "And this is yet another piece of the puzzle."

And any nudge to citizens or organizations to become data altruists must also be accompanied by strong assurances that those data will be properly protected, says Kristin Kostick-Quenet, a bioethicist and medical anthropologist at the Baylor College of Medicine in Houston. She notes, for instance, that some of the strongest privacy-preserving technologies available to date, including encryption and decentralized learning approaches, are not widely employed by major entities involved in data exchange—a concern she would like to see addressed in future efforts.

Shabani says that until the EU regulation goes into effect, it's hard to predict whether the idea will pay off. "We always talk about the importance of trust in the governance system, and for this system to be successful it needs to give the impression that the system has transparency. Citizens need to be able to feel that," she says. Whether or not the DGA will succeed in building that trust remains to be seen. "People have to know their data will not be used in a way that will harm them."

UPDATE

Slowing a Virus

Monkeypox infections are steadily on the rise. What steps should happen next?

BY ANITA SLOMSKI

On May 18, Massachusetts General Hospital physicians reported that a patient was being treated in their hospital's special pathogens unit—the first U.S. monkeypox case in the current wave. By the end of June, the Centers for Disease Control and Prevention had confirmed more than 350 cases nationally.

Although anyone can get monkeypox, the virus is currently spreading in sexual networks of men who have sex with men. This population has also felt the brunt of a rise in other transmissible diseases in recent years, especially those transmitted through sex and intimacy ("Danger in the Sheets," January 2019).

Past strategies for sexually transmitted infections, including efforts that include contact tracing and partner notification, ought to be useful in containing this crisis. But testing for monkeypox infection has proved limited and burdensome. Clinicians currently require permission to send samples to state public health department labs for initial testing and then to the CDC for confirmation.

"Ideally we should be over-testing for monkeypox infection to find all the existing cases, but public health departments won't be able to meet that demand," says Kevin Ard, director of the Sexual Health Clinic at MGH.

ILLUSTRATION BY FRANCESCO CICCOLELLA

Commercial laboratories and academic medical centers may be able to develop diagnostic tests for monkeypox, says Ard. "But at the same time, the bandwidth may be lower for monkeypox testing because labs are still overwhelmed with the magnitude of COVID-19 testing."

Another challenge is to locate the epicenters of infection. Keletso Makofane, a fellow at the FXB Center for Health and Human Rights at Harvard University, is leading a study that will map sexual networks among gay and bisexual men in New York City. Men can anonymously answer questions online about whether they have monkeypox symptoms and then forward the survey link to those they've had sex with. "The data will tell us where we should intervene, such as offering our limited supply of vaccine at sites that have the largest burden of infection," says Makofane.

If the track record with other STIs is any indication, however, managing monkeypox may be a long haul. "We are doing a terrible job preventing gonorrhea, syphilis and congenital syphilis, which increase year after year," says Matthew Hamill, STI expert and assistant professor of medicine at Johns Hopkins Bloomberg School of Public Health.

"Public health departments need to prioritize the health of people who acquire STIs and same-gender-loving people, who have traditionally been marginalized," says Hamill. "We have a window of opportunity to prevent the spread of monkeypox, and we need to grab it."

MILESTONE

A Death from Nostalgia

Wartime injuries go beyond the physical. A longing for home pervades conflicts past and present.

BY HANNAH THOMASY

PA COLLECTION / ALAMY

Frederic Whipple had only been married a short time when, in 1862, he was recruited into the Union Army's Tenth Vermont Infantry Regiment. Like many Civil War soldiers, he was fated never to return.

One day, Whipple presented himself to an army surgeon, who could find nothing wrong with him other than an extreme desire to return home. For today's physicians, homesickness is not a special cause for concern, but Whipple's case quickly became dire.

"His orderly-sergeant could do nothing with him in his company," wrote Chaplain Edwin Haynes. "He was finally put into the Hospital, where, refusing to be nursed, after a few days he died, moaning piteously all the time, 'I want to go home—I want to go home.'"

Whipple was one of more than 70 recorded deaths from "nostalgia" recorded by the Union Army during the Civil War. Around 5,000 more soldiers were diagnosed with nonfatal cases of the disease. At the time, nostalgia was considered a serious medical condition, a diagnosis with a long pedigree in the medical and academic literature of the eighteenth and nineteenth centuries.

The term "nostalgia" was first used medically in 1688 by Swiss physician Johannes Hofer. "He kickstarted the early modern trend in thinking about homesickness as a kind of pathological entity," says Agnes Arnold-Forster, a historian of medicine and the emotions at the Center for History in Public Health at the London School of Hygiene and Tropical Medicine.

Hofer described symptoms that involved both mind and body: anxiety, insomnia, loss of appetite, cardiac palpitations and fever. He hypothesized that the bodily symptoms of the disease occurred because the "animal spirits," energy that allowed sensation and movement, were "busied excessively in the brain, [and] cannot flow with sufficient supply and proper vigor through the invisible tubes of the nerves to all [body] parts."

> After a few days he died, moaning piteously... "I want to go home."

While the most effective treatment was a return home, other treatments appeared through the years. Some doctors, says Arnold-Forster, thought that nostalgia was related to a change in altitude, which was why the Swiss were especially vulnerable when they left their mountainous land. "One doctor thought it was a good idea to put them up in a tall tower to replicate their home environment," she says.

By the time of the Civil War, says Susan Matt, a history professor at Weber State University in Utah, soldiers and others who suffered from nostalgia were treated sympathetically. "Loving home in the nineteenth century was part of being a good man," she says. "Nostalgia was almost a virtuous illness to have, because it showed that you cared about the right things."

The last recorded military death from nostalgia was a soldier in the American Expeditionary Force in World War I, although nonfatal cases were reported during World War II as well. After that, the diagnosis faded.

Nostalgia fell from favor in part because social norms had changed. By the middle of the twentieth century, there was less sympathy for those who missed home. "There was a greater imperative to move, there was a greater imperative to start a nuclear family of one's own at a young age," says Matt. "Psychologists and sociologists argued that homesickness was something people should conquer in summer camp, certainly by the time they went to college. Americans were expected to cut ties and move on very easily."

Western medicine also underwent profound shifts in how it thought about disease. "In the early modern period, the boundary line between the mind and the body was much more fluid," says Arnold-Forster. "It was thought that all illnesses would have an impact on your mood, your optimism, your body, your thoughts, your feelings." Around the end of the nineteenth century, doctors established a more emphatic distinction between the mind and body, as well as the medical disciplines that handled each.

So how would these deaths be viewed today? Classic nostalgia does seem to share elements with depression and suicidality, says Arnold-Forster. Many cases involved disordered eating, as nostalgia sufferers would refuse food. But she cautions against simple interpretations of a disease from another age: "People's experience of illness—and this is as true today as it was in the past—is shaped by their cultural and historical context."

Today, the closest research field in medicine looks at the mental health of refugees. In May 2022, the U.N. Refugee Agency reported that the number of forcibly displaced persons had, for the first time, surpassed 100 million because of conflicts across the globe, including those in Ethiopia, Afghanistan and, most recently, Ukraine.

A recent meta-analysis showed that rates of post-traumatic stress disorder and depression were higher than 30% among these refugees and asylum-seekers. While war accounts for some of this trauma, separation from the culture, language and friendships of home can cause distress in themselves, with homesickness associated with greater symptoms of depression and anxiety. Experts call for addressing not only the physical but mental wounds—including homesickness—of those forced to be far from home.

SECOND OPINION

Trust and the "Infodemic"

The article "The Trust Crisis" (Spring 2022) describes in detail the dire problem of the public's declining trust in health care. While that decline has been wide-ranging, it is important to distinguish the distinct domains of trust discussed: (1) the trust that individuals have in their health care providers, who have long been among the most trustworthy professionals in society; and (2) trust people have in public health agencies and figures, which has suffered precipitously during the pandemic.

This growth in mistrust stems directly from the "infodemic" of misinformation and disinformation about COVID-19 that spread rapidly, and especially on social media. The problem is so profound that the U.S. surgeon general issued an urgent advisory, labeling it a public health threat and calling on health care professionals to speak out against misinformation. Tragically, much of this false information about vaccines is being spread by a small group of health care providers. Simultaneously, the public began to lose trust in both public health institutions and professionals, attacking them when providing guidance on public health measures.

To reverse this trust crisis, we must first hold health professionals who spread disinformation accountable. The Federation of State Medical Boards and several nursing and medical boards announced that they would take disciplinary action against disinformation-spreading clinicians, including suspending their licenses. Second, we should support and protect health professionals from harmful attacks when they counter misinformation. Social media companies need to flag and prohibit the spread of both false information and malicious attacks against those trying to spread truthful information. Third, we must train current and future health professionals to counter misinformation. At the University of Chicago Pritzker School of Medicine, we have implemented recent innovations in science communication, including teaching the creation of infographics to address misinformation, writing op-eds that reach a wide audience and creating dynamic TED-style talks for the public.

While the infodemic has damaged the public's trust in both the health care system and in health care professionals, clinicians can still leverage their trusted voice through the care of our individual patients and partner with patient communities to rebuild trust. Hopefully, as the article quoted Professor Adam Berinsky, "Even if patients don't know what to believe, and don't trust the health care system, most still trust their own physicians."

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WHAT'S YOUR TAKE? **Send your comments or suggestions for future topics to protoeditor@mgh.harvard.edu.**

Where Psychedelic Research Goes Next

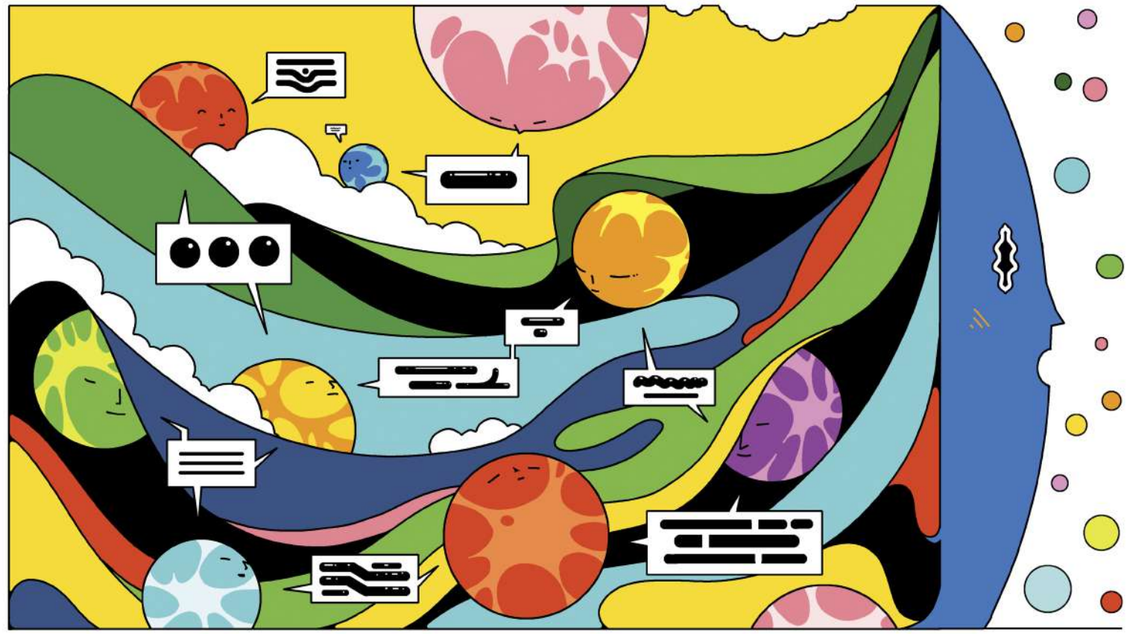
A new generation of research looks at psilocybin, LSD and other mind-altering drugs. Both the challenges and the therapeutic promise are enormous.

During his decades as Massachusetts General Hospital's Chief of Psychiatry, Jerry Rosenbaum observed that patients suffering from a range of mental illnesses would sometimes get stuck in a state of rumination, or unceasing cycles of unpleasant, self-deprecating thoughts. While they had what were thought to be discrete conditions—depression, anxiety, addiction, obsessive-compulsive disorder—Rosenbaum wondered if the differences among those pathologies might be less important than the one characteristic that connected them. Finding ways to break the endless loops of rumination might lead to real progress, saving patients and their physicians from the difficult and sometimes futile quest to sort out which of the existing indicated therapeutic approaches might be effective for them.

Rosenbaum became fascinated with a 2018 neuroimaging presentation by Robin Carhart-Harris, a psychologist and then head of the Centre for Psychedelic Research at Imperial College London. It appeared to show similarities between brain areas affected by rumination and those acted upon by psychedelic drugs. Psychedelics seemed to decrease activity in the part of the brain known as the default mode network, possibly undercutting the process of rumination. "These drugs seem to work across an array of indications," says Rosenbaum, who helped found and lead the new Center for the Neuroscience of Psychedelics at MGH. "There may be some broad, fundamental window that these drugs open that allows you to move from the state you're in—which may be dysphoric or disabling—to one that is more freeing."

That insight into how psychedelic compounds might actually operate on mental health represents a next step in a profound frontier. A resurgence of research into psychedelics—in new initiatives not only at MGH but also at Yale, Johns Hopkins, the University of California and the National Institutes of Health, among other places—is providing mounting evidence that the drugs might be effective alternatives for treating depression and other conditions. For optimal impact, and to minimize any danger to patients, researchers will need to figure out how they bring about their positive effects.

By Hannah Thomasy // Illustrations by Ori Toor



And the effects are sometimes extraordinary. In small trials, psilocybin, the most-studied psychedelic, has been shown to ameliorate tobacco addiction, alcohol addiction, obsessive-compulsive disorder, cancer-related anxiety and depression and treatment-resistant depression. Some patients who have taken the drug report feeling optimistic again after years of crippling depression that conventional treatments didn't improve. Psilocybin is also being studied as a therapy for myriad other difficult-to-treat conditions, including methamphetamine use disorder, post-traumatic stress disorder, anorexia, fibromyalgia and phantom limb pain.

Yet the newness of this research, coupled with the difficulty of working with controlled substances, can make gathering insights much more difficult. In one recent psilocybin trial, for instance, patients who received the highest of three doses had a reduction in depression symptoms that lasted at least three months—a welcome development, says psychiatrist Sharmin Ghaznavi, associate director of the MGH Center for the Neuroscience of Psychedelics. Yet the data came from a phase 2 trial, with only 233 patients, and rolling the project out to a phase 3 deployment, which often enrolls thousands of research subjects, will pose a challenge. "Compared with how much clinical research data we have on other classes of drugs, these are early days," says Ghaznavi.

More data will be needed to answer the many open questions about how psychedelics work their profound effects in the brain. "I do think this is potentially one of the most important advances in psychiatry that I've seen in my career," says Stephen Haggarty, who runs a chemical neurobiology lab in the MGH center. "But right now, from a fundamental neuroscience perspective, we understand so little."

Through their work at the center, Rosenbaum, Ghaznavi, Haggarty and other researchers hope to elucidate what happens at molecular, cellular and network levels. If that picture becomes clearer, these researchers—and others around the world—might use this understanding to develop better, safer or more accessible substances or treatments. More immediately, uncovering the mechanisms of psychedelic drugs may show who exactly these drugs can help and in what contexts.

Researchers will need to figure out how these drugs bring about their positive effects.

One day in 1943, a Swiss chemist studying ergot derivatives began to feel odd while working in his laboratory. Unsure what was happening, he abandoned his work for the day. "At home I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination," he wrote later. "In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors."

These psychoactive effects of the compound—lysergic acid diethylamide, or LSD—that Albert Hofmann had discovered were unintended. Yet Hofmann's invention would help usher in a mid-1900s explosion of Western psychedelic research. In 1954, Aldous Huxley published *The Doors of Perception*, in which he documented his personal experiments with mescaline. Hofmann himself continued his research, and in 1958 he identified psilocybin as the active ingredient in "magic mushrooms," a term coined a year earlier by *Life* magazine. In 1959, a closed conference at Princeton University addressed "the use of LSD in psychotherapy," and the next year saw the first major European conference on psychedelics. During this period, hundreds of studies were published on the effects of psychedelics, including their use to treat addiction and other disorders.

Yet this period of scientific ferment ended almost as abruptly as it began. In 1961, psychiatrist Jonathan Cole, head of the Psychopharmacology Service Center at the National Institute of Mental Health and a pioneer in studying psychedelics, expressed "very mixed feelings" about the research, noting potential harms for patients. Experiments with psilocybin at Harvard University, some involving students, added to the negative image of the research, and psychedelics, especially LSD, came to be associated with the anti-war movement. LSD became illegal in the United States in 1968.

Interest in the therapeutic potential of the drugs came back slowly. The nonprofit Multidisciplinary Association for Psychedelic Studies was founded in 1986, and in 2000, researchers at Johns Hopkins were granted approval to study psychedelics—almost all of which today remain illegal, as Schedule 1 controlled substances. In 2006, those scientists published a landmark study showing that healthy volunteers experienced sustained "positive changes in attitudes and behavior" from single doses of psilocybin. Other research centers opened across Europe and North America, and public awareness and perception of psychedelics shifted favorably, aided in part by books such as Ayelet Waldman's *A Really Good Day* (2017), about the author's experiences with microdosing—taking very low doses that don't trigger full hallucinations but may have beneficial effects—and Michael Pollan's *How to Change Your Mind* (2018), in which the respected science journalist not only traces the history of psychedelics use and research but also details his own experiences with the drugs.

Classic psychedelics include drugs such as mescaline, psilocybin, LSD and DMT that appear to exert their effects primarily by binding to the 5-HT2A receptor in the brain, which normally responds to the neurotransmitter serotonin. (Ketamine and MDMA, which also have psychedelic properties, have different mechanisms of action.) The drugs' subjective effects vary widely depending on who is taking them and the environment in which they're taken. Some users experience changes in visual perception as well as how they perceive time and their own bodies. Other effects include feelings of awe and peace as well as spiritual or mystical experiences. Some users describe losing their sense of self and feeling unity with the greater world. Other users have a negative episode, or "bad trip," which can also leave a lasting mark.

In one current frontier of psychedelic research, teams are working out what happens when 5-HT2A receptors are activated by psychedelics. Psychedelics seem to alter brain activity and connections among areas that are important for perception (including the visual cortex and the thalamus) and the prefrontal cortex, involved in cognition and self-referential thought, as well as altering communication between large-scale brain networks.

A related question is how those neurobiological reactions sometimes translate into long-term changes in well-being. Drugs such as psilocybin get washed out of the body rather quickly, notes Alex Kwan, an associate professor of neuroscience at Yale University. "One of the most important mysteries about these compounds is that while the 'trip' lasts only three or four hours in humans, there seem to be effects that can persist weeks or even months," Kwan says. That's in contrast to selective serotonin reuptake inhibitors (SSRIs) and other drugs for mental illness that have to be taken every day.

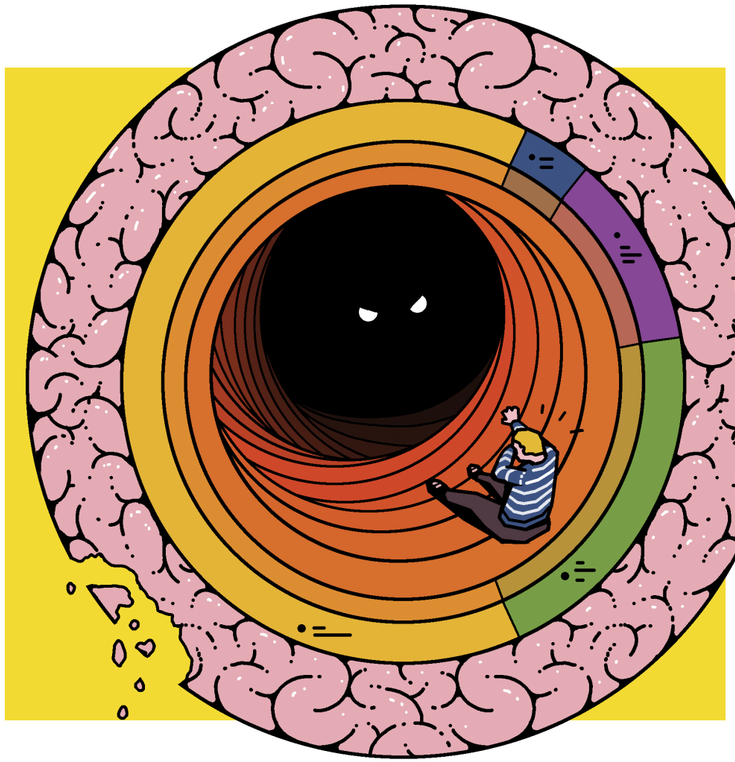
One potential explanation, says Kwan, is that psychedelics enhance neuroplasticity—the ability of neurons to make or strengthen new connections. There is a large body of evidence in both animal models and in people suggesting that chronic stress and depression are associated with reductions in plasticity and loss of synapses. But a single dose of psychedelics can kickstart plasticity at the cellular level. Kwan's work has shown that within 24 hours of receiving psilocybin, mice had significant increases in the density of dendritic spines, tiny cellular projections that neurons use to gather incoming signals from other neurons. This increased spine density was still apparent one month later,

indicating that a single short exposure may produce long-lasting changes in the brain.

LSD and DMT also promote neuroplasticity, and researchers are beginning to elucidate which genes and proteins are involved in 5-HT2A-mediated neuroplasticity. Expression of one of those proteins, brain-derived neurotrophic factor (BDNF), increases after a single dose of a psychedelic and results in greater dendritic complexity, a change that outlasts the acute effects of the drugs. In animal trials, repeated administration of a psychedelic was shown to stimulate creation of new neurons and increased BDNF levels for as long as a month after treatment.

Human imaging studies also enable scientists to observe changes in brain activity in real time, another avenue into understanding psychedelics' dramatic effects. One hypothesis has been that, beyond promoting plasticity, short-term changes in brain activity and connectivity during a psychedelic trip could serve a sort of "reset" function, allowing people to break out of rumination and other pathological patterns of thought or behavior. The research on the default mode network that Jerry Rosenbaum found so intriguing suggests that normal activity and integration in that network seems to be reduced during a psychedelic experience and increased afterward. Perhaps this allows the brain to shake off bad habits and then function in a more normal way after treatment.

Changes in other brain networks could also be important. Psychedelics alter connectivity within feedback loops that run from the cortex to the striatum to the thalamus, and back to the cortex (the CSTC feedback loops). The effects in this network could explain some long-term benefits of psychedelics, says Manoj Doss, a researcher at the Johns Hopkins Center for Psychedelic & Consciousness Research. Doss notes that the striatum may be home to ingrained patterns of thought and behavior, and that it is involved in patterns of motor function and reward that



go awry in addiction. "Altering this circuit with psychedelics might allow the rewriting of crystallized, automatic, maladaptive behaviors such as those in addiction or even depression," Doss says.

Tripping on psilocybin or other drugs also produces thoughts and emotions in the conscious mind, and some—but not all—researchers believe this is crucial in explaining the long-term benefits psychedelics often seem to have. "It strikes me as pretty implausible that effects lasting months or even years could be explained solely by changes to neuroplasticity," says David Yaden, an assistant professor at the Johns Hopkins Center for Psychedelic & Consciousness Research. Long-lasting changes must require cognitive alterations of some kind, he says, including "shifts in the way you view yourself, other people or the world as a whole."

"There's a lot of power in the psychedelic experience," agrees Natasha Mason, a psychopharmacologist at Maastricht University in the Netherlands. "It gives patients agency and a lot more control over their healing, compared with just having a therapist tell them how they need to change. Psychedelics allow them to have their own insights."

Indeed, multiple studies have shown correlations between subjective experiences during a trip and long-term benefits. As Yaden notes in a 2020 review paper, people who score higher on the Mystical Experience Questionnaire—which seeks to measure feelings of unity, sacredness, truth and transcendence—have greater reductions in tobacco cravings and symptoms of anxiety and depression. Participants in other studies reported that taking psychedelics gave them important insights into themselves and their

problematic behaviors. Clinical psychologist and researcher Peter Hendricks at the University of Alabama at Birmingham proposed in 2018 that feelings of awe during a psychedelic experience may be a key part of the long-term changes in well-being and openness that many people report.

In an ongoing study, Christopher Nicholas, a clinical psychologist at the University of Wisconsin, is testing the insights-drive-change hypothesis in a novel way. His team is giving healthy volunteers psychedelics along with a dose of midazolam, a drug that relieves anxiety and also causes amnesia. His trial subjects have a psychedelic experience, but are not likely to remember it. That could help answer the question of the relative importance of neurobiological effects compared to subjective factors related to insight and emotional processes. If the volunteers show the improvements in mental health that psychedelics often produce but don't have any memory of the experience, Nicholas says, then that could suggest that much of the change is driven by the drug's psychopharmacological properties.

A separate frontier is looking at how to conduct this new generation of psychedelic research safely and effectively. One perplexing problem is how to conduct placebo-controlled trials. It's easy for patients (and the clinicians monitoring them) to tell the difference between a drug that causes major alterations in cognition, emotion and perception and a placebo that doesn't.

Another issue is patient safety, especially the need to avoid harm to trial participants who may have bad trips. In a survey of nearly 2,000 recreational psychedelic users, some 40% reported their worst trip to be one of the most challenging experiences of their lives, 11% put themselves or others in danger and 7% sought treatment for ongoing psychological problems afterward. To manage the serious risks associated with taking psychedelics, researchers must conduct studies in tightly controlled settings with substantial therapeutic support. At a minimum, says Sharmin Ghaznavi at MGH, patients need specially trained therapists to prepare them for the experience and to guide them through it and help them cope with any distress. They also need help afterward processing what happened to them. Sessions can take as long as eight hours, and researchers don't yet know how often the process may need to be repeated. All of this makes psychedelic therapy resource-intensive, and if ongoing research confirms its effectiveness in treating a range of disorders, it could be challenging to make it widely accessible.

Patients need specially trained therapists to prepare them for the experience.

Many researchers are now exploring ways to increase accessibility. A non-hallucinogenic psychedelic, if proved to be effective, might reduce the need for supervision, and psychedelic-assisted group therapy could enable therapists to treat larger numbers of patients. Psychedelics that produce a shorter "trip," such as 5-MeO-DMT, might also help.

Those and other issues will have to be addressed as the scientific understanding unfolds. "I think we're still in the first inning here," says Haggarty. "How do we make these agents safer? How do we think about a second generation of these drugs? How do we bring the concept of precision medicine into this—treating the right patient at the right time with the right drug?"

In addition to gathering more data, researchers also emphasize the need for accepting nuance and complexity. David Yaden at Hopkins says that in recent years the pendulum of public opinion has swung from overly negative, alarmist views on psychedelics to unrealistically positive expectations.

"It appears that there's genuine promise for psychedelics to be effective treatments for some mental disorders," he says. "Our society, all of us, have a role to play in this—to think critically about the evidence for psychedelics in a balanced way. And to avoid the temptation to fall into one extreme or the other."

DOSSIER

"The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects," by David B. Yaden et al., *ACS Pharmacology & Translational Science*, December 2020. The authors discuss the evidence for subjective effects relating to thoughts and emotions as an important mediator for the long-term, beneficial effects of psychedelics.

"Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics," by Cato M.H. de Vos et al., *Frontiers in Psychiatry*, September 2021. This paper provides an overview of neurobiological changes engendered by psychedelics at the cellular and molecular level and highlights areas for future research.

The Tender Years

Adversity in early childhood too often equals poor health later. Now researchers are looking for ways to change the equation.

Tierra Lemon was just 13 when she had her first experience with gun violence. She was playing with friends at a park on Chicago's South Side when nearby gunfire sent people racing for cover—but not before many of her friends were struck. In high school, Lemon says, "there was so much loss and grief from friends and family suffering gunshot wounds." In her closest circles, at least 10 people would be shot, some fatally.

Lemon survived her childhood and earned a graduate degree in social work. She returned to the South Side to serve as an advocate for youth who have been injured. As a violence recovery specialist at University of Chicago Medicine, Lemon helps traumatized young people heal, a process that begins with providing emotional and psychological support for teens who arrive in the hospital's emergency department.

Lemon often shares her own stories of surviving violence in the neighborhood, and she remembers trying to comfort one anguished 16-year-old, injured in a shooting, when he found out his best friend had died in the attack. "People often naturally turn to the coping strategies they know, but those strategies may not always be the healthiest," Lemon says. "Being able to support patients by adding new coping skills to their toolboxes has had many positive impacts."

Researchers have a term for the kinds of terrible things that Lemon encounters in her work with children. They're called adverse childhood experiences, and they include a long list of horrors: violence; parental neglect; emotional, physical and sexual abuse; the death or incarceration of a parent; growing up in a household with substance use problems; and having a family member attempt or die by suicide.

More than two-thirds of children have experienced at least one traumatic event by age 16, according to the U.S. Substance Abuse and

By Anita Slomski // Illustrations by Melinda Beck

Mental Health Services Administration. One in seven kids has experienced child abuse or neglect in the past year, and every day, more than 1,300 children are treated in emergency departments for violence-related injuries.

The COVID-19 pandemic has added a new kind of trauma. By July 2022, more than 218,000 children in the United States had lost a primary caregiver to COVID-19, according to estimates by researchers from Imperial College London. "These deaths were unpredictable and sudden, and children often weren't allowed to see a dying loved one or attend a memorial service to help process the death," says Sarah Edwards, director of Child and Adolescent Psychiatry at the University of Maryland School of Medicine. "Those circumstances can make grieving traumatic in itself."

> *Opening the black box of early adversity is crucial, researchers say.*

Kids growing up with adversity are about twice as likely to develop a mental disorder as children with uneventful childhoods. And the damage persists. Researchers have found associations with 60 mental and physical illnesses, as well as premature death, in adults who experienced extreme stress during childhood. One recent study estimates that these childhood experiences ultimately result in more than 400,000 deaths each year in the United States. That mortality—largely tied to heart disease, cancer and chronic respiratory disease—accounts for 15% of all deaths. More than a third of suicide attempts and sexually transmitted infections can also be associated with childhood adversity.

"Many adult diseases should be viewed as developmental disorders that begin early in life and are associated with poverty, discrimination, maltreatment or violence," says Jack Shonkoff, a researcher at Massachusetts General Hospital and director of the Center on the Developing Child at Harvard University. Preventing heart disease shouldn't be only about better nutrition and more exercise in adult years, says Shonkoff. "We should also focus much earlier on prenatal exposures and early childhood experiences that increase risk for cardiovascular problems that won't appear until decades later," he says.

Now, research measuring biological and genetic processes in kids living through harsh experiences may drive more attention to these consequences. "There have been tremendous advances, especially during the past five years, in our understanding of how genetic variation, the environment and timing operate together to influence the outcomes of children's exposure to trauma and adversity," says W. Thomas Boyce, chief of the Division of Developmental Medicine at the University of California, San Francisco.

Opening the black box of adversity is crucial, researchers say. "The currency for physicians and basic science researchers is understanding biological mechanisms," says Greg Miller, co-director of the Foundations of Health Research Center at Northwestern University in Illinois. Getting a handle on the biology of adversity will also help researchers and clinicians identify which kids are most at risk so that they can intervene and mitigate the clinical effects. Adds Shonkoff: "We need to leverage advances in biology to develop more refined, science-informed strategies to protect the developing immune responses, metabolic regulation and brain circuits from the disruptive effects of excessive stress activation."

When someone is threatened or afraid, the body produces large quantities of epinephrine, cortisol and other stress hormones, and the autonomic nervous system ramps up, creating a "fight or flight" response. Those reactions affect blood sugar and insulin levels, blood pressure and heart rate, and cause the immune system either to underperform, impairing the body's ability to resist pathogens, or to go into overdrive, creating excessive inflammation. When stress responses are activated too frequently, they can become toxic.

Young children are particularly vulnerable to the effects of overwhelming stress. Imaging studies show that being raised in harsh or dangerous environments can change the architecture of growing brains, resulting in faulty neural connections and reduced brain electrical activity.

Developing brains are exquisitely sensitive to their environments, says Margaret Sheridan, assistant professor in the Clinical Psychology Program at the University of North Carolina at Chapel Hill and director of a child imaging research lab there. A child living under constant threat develops an enhanced ability to predict danger because of differences in how their amygdala and ventral medial frontal cortex—brain regions that process risk and fear—activate, she says. This can make it difficult to keep emotions in check as an adult. Neglect or deprivation, meanwhile, can cause the brain to adapt in other ways, which Sheridan says can lead to deficits in the structure and function of the frontal lobe, causing trouble with impulse control, working memory, problem-solving and goal-setting.

Other effects of adversity could manifest through epigenetic changes in DNA that affect gene expression. In children exposed to harsh environments, researchers have found alterations in epigenetic markers, which may provide a cellular explanation for differences in cellular responses to stress and immune function. These can increase chronic

inflammation, a major contributor to obesity, diabetes and cardiovascular disease. "Epigenetic changes shape children's biology in ways that could have lifelong consequences," says Erin Dunn, associate investigator at MGH and associate professor of psychiatry at Harvard Medical School.

Such changes can also accelerate biological aging, causing children who have grown up in harsh environments to reach puberty ahead of schedule. Their neural networks sometimes develop faster, perhaps to help them deal with adversity. But growing up more quickly could make children more vulnerable to chronic adult diseases. Childhood adversity has been associated with heightened risk of strokes, cancer, asthma, chronic obstructive pulmonary disease, kidney disease, arthritis, gastrointestinal disorders and immune disorders.

In a new study of more than 700 children, Dunn and her colleagues compared epigenetic changes in kids who did not experience adversity with those in children exposed to certain kinds of adverse experiences: physical abuse by caregivers, sexual or emotional abuse, maternal mental illness, poverty and others. She wanted to uncover whether the magnitude of epigenetic alterations depended on how many kinds of adversity a child suffered, the child's age when the adversity happened and whether recent exposures were the most potent.

Dunn found that for every type of adversity, children under three had the most profound epigenetic changes. Now she is studying how long those changes last. "Some might be short-term to help a child adapt to a stressful environment, but others may persist and cause long-term health problems," she says.

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Complicating efforts to study childhood adversity is that its impact is uneven. "Many kids who sustain these events go on to have absolutely successful, healthy lives," says UCSF's W. Thomas Boyce, who has spent decades working out why some children are more susceptible to adverse events than others. In one experiment, he gave three- to eight-year-olds a 20-minute standardized test of nonthreatening but challenging tasks and measured the children's stress responses, testing cortisol in saliva and using electrodes on the kids' chests to record electrical events in the heart. He found tremendous variation in how non-traumatized children reacted to stress, with about 20% of kids showing a very high response and an equal percentage with a remarkably subdued reaction.

Boyce then applied this data to the general population of children and found that the most reactive kids, when they grew up in conditions of adversity and trauma, "had terrifically high rates of all of the health outcomes that we were concerned with—respiratory disease, injuries, mental disorders, behavioral disorders," he says.

Highly reactive kids who grew up in nurturing environments, in contrast, had lower levels of respiratory disease, behavior problems and injuries, and in the general population of children, they were the healthiest of all. The highly reactive children, he

says, "were the most responsive and sensitive to both good and bad environments." Boyce believes that improving the environment of the most reactive kids facing adversity could have a profound impact on their health, perhaps through adulthood.

In looking for ways to help all at-risk children—highly reactive kids among them—Greg Miller at Northwestern teamed up with Gene Brody, professor of human development and family science at the University of Georgia. Brody had developed a program for improving the psychological and academic trajectory of low-income African American youth growing up in rural Georgia. His initial trial randomly assigned 667 mothers and their 11-year-old children to either a seven-week intervention or to a control group. The intervention focused on factors he thought would best mitigate early trauma: building supportive families, enhancing communication between kids and parents, teaching coping strategies for managing stress, and encouraging parents to stay vigilant and engaged when their children were struggling. The intervention led the youth who participated to have fewer conduct issues, delayed the onset of sexual behavior and decreased drug use.

Eight years after the trial ended, Miller. Brody and their colleagues revisited the study participants—who were then 19—to measure markers of inflammation in their blood. The ones who had participated in the intervention had significantly less inflammation than those in the control group. And in a neuroimaging study of some participants when they were 25, the team found that those who had the brief childhood intervention showed improved brain connectivity, particularly in brain networks that help regulate emotions, cope with stress and make decisions under stress. Now a larger study underway, with a new group of children, will evaluate cardiovascular and metabolic disease markers and inflammation before and after a similar intervention.

Other researchers are attempting to mitigate the effects of poverty starting at birth. A recent trial randomly assigned 1,000 low-income new mothers in New Orleans, New York City, Omaha and Minneapolis/St. Paul to receive $333 a month or $20 per month for one year. When the scientists measured the brain activity of the children at age one, toddlers in the intervention group that had received $333 a month had more high-frequency brain activity—which is associated with development of thinking and learning—than those in the control group. The researchers don't yet know whether those brain changes will persist and ultimately lead to better cognitive and behavioral development, but the trial has been extended, with payments to the mothers to continue until the children are four years and four months old.

Other researchers are trying to mitigate the effects of poverty starting at birth.

Although it appears that interventions during the vulnerable first years of life may have the greatest potential, the teen years could also offer an opportunity to right the wrongs of childhood adversity. "There is an explosion of studies and a renewed excitement about plasticity in the adolescent brain," says Sheridan. Adds Boyce: "The literature suggests there is a reopening of susceptibility to positive interventions during adolescence."

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At the University of Maryland Children's Hospital in Baltimore, clinicians expect the children who are admitted to have suffered a broad range of traumatic experiences. "About 80% of our kids have had layers upon layers of trauma and adversity in their lives," says child and adolescent psychiatrist Sarah Edwards. Last year, the university opened Maryland's first "trauma informed" child and adolescent inpatient unit, designed to provide kids with a safe and healing place to recover.

"Victims of trauma feel a tremendous loss of control," says Edwards. "It's important for kids to have a voice and be actively involved in making choices about their own treatment." Every patient room has a white board for kids to express emotions through drawing or writing. They can choose the music or sounds they want to hear, and Edwards notes that their voice matters when determining treatment goals and plans.

On the South Side of Chicago, where violence is common and 12 is a common age for children to be recruited into gangs, UChicago Medicine is using some of a recent $9.1 million gift to expand its "ecosystem" of trauma-informed care for children and their families. "So many of the kids we see are basically child soldiers just trying to survive," says Bradley Stolbach, associate professor of pediatrics at UChicago Medicine. When they're brought to the emergency room after being injured by gun violence or physical or sexual abuse, they receive one-on-one crisis support, and patients and their families may be visited by a trauma intervention specialist, social worker, psychologist, psychiatrist or chaplain.

Also in Chicago, a hospital-based violence intervention program called Healing Hurt People–Chicago helps youth injured by community violence cope with the trauma, avoid retaliation and stay off the streets. Staff members bond with the kids, mentor them, accompany them to appointments, and help them find safe housing and stay in school. "We focus on their goals, not ours," says Stolbach, and it seems to be working: "Ninety percent of people who are in our program for six months avoid reinjury and we see reductions in post-traumatic stress disorder."

At the University of Maryland Children's Hospital, Sarah Edwards prescribes trauma-focused cognitive behavioral therapy for kids six and older who meet the criteria for PTSD—which affects some children who have traumatic experiences. The youngest may receive psychotherapy with their parents, an approach that in clinical trials has reduced depression and PTSD and led to greater resilience and better performance on cognitive tests. "We don't want people to remain hopeless—treatments do buffer traumatic stress and help kids develop resiliency," says Edwards.

She and other child-adversity researchers say their work is hindered by a lack of recognition and funding. "The United States spends massive amounts of money studying and treating cancer and heart disease," says Northwestern University's Greg Miller. "But by failing to invest in children's health, we are missing opportunities to help kids with challenging backgrounds thrive psychologically and build sustainable healthy behaviors."

The need to respond to what researchers now know about childhood adversity couldn't be more pressing. "Culturally, scientists are very conservative," says Erin Dunn of MGH and Harvard. "We hedge, saying that more research is needed or we don't know how our findings apply to the real world. But the evidence that childhood adversity causes long-term damage is undeniable. We must be ready to take action now."

DOSSIER

The Orchid and the Dandelion: Why Some Children Struggle and How All Can Thrive, by W. Thomas Boyce, Vintage, 2019. Boyce recounts results from decades of research to explain how adversity affects children.

"Association of Childhood Adversity with Morbidity and Mortality in US Adults," by Lucinda Rachel Grummitt et al., *JAMA Pediatrics*, October 4, 2021. An analysis of data on more than 20 million people was the first to estimate the staggering annual mortality rate from long-term poor health attributed to childhood adversity.

"Leveraging the Biology of Adversity and Resilience to Transform Pediatric Practice," by Jack P. Shonkoff et al., *Pediatrics*, February 2021. The authors call on pediatricians to prevent future illness in their young patients by protecting them from the effects of childhood adversity.

I QUIT

Burnout, the pandemic and other pressures have sent record numbers of health care workers rushing for the exits. What would make them stay?

In the earliest months of the COVID-19 pandemic, a sense of mission carried Molly Phelps through the days. As an emergency room physician on the front lines, she was able to remind herself that this was the work she'd signed up for. "I knew there was a real chance I might die," Phelps says. When reports surfaced of physician fatalities in China and Italy, she and her husband prepared a new will to make sure their two children would be taken care of. Then she put on her gear and went to work.

Yet during the many months that followed, as one COVID wave after another rose and crested, Phelps began to wonder how long she could keep at it. The safety challenges didn't go away, working conditions continued to be grueling and there was a constant struggle to get supplies and support. As culture wars over COVID vaccination and treatments grew, clinicians found themselves facing the ire of patients taken in by rampant disinformation. Anxiety and exhaustion wore her down, she was barely eating or sleeping and she had a hard time containing her anger at patients who chose not to be vaccinated. "I didn't want to give the last bit of me to unvaccinated people," she says. Finally, after nearly two decades in the ER, Phelps worked her last shift in September 2021. "I will never return to emergency medicine," she says.

Stories like hers are dishearteningly common. The "great resignation" has ravaged health care as physicians and nurses give up their posts at hospitals, nursing homes and medical practices. Nonclinical positions are also going empty, with housekeeping workers, security guards, administrative managers and C-suite executives heading for the door faster than their replacements can be found. Since May 2021, nearly 70 million American workers have left their jobs, according to the U.S. Bureau of Labor Statistics. The rate of departures shows no sign of abating.

As the nation's largest employer, the health care sector has been particularly hard hit. A recent survey found that almost one in five health workers has resigned since the pandemic's start, and nurses are departing at a rate of nearly one in three. Those who don't retire are taking other jobs, often outside of nursing, that offer better pay, greater flexibility and less stress. Among those who have stayed on, more than a third say they may leave by the end of 2022.

"The U.S. health care workforce is in peril," says Christine Sinsky, a physician who serves as vice president of professional satisfaction at the American Medical Association. "If even half of nurses and physicians who say they want to leave go through with their plans, we won't have enough staff."

With patient volumes expected to rebound to above pre-pandemic levels, and as seemingly endless waves of COVID continue to fill emergency rooms and hospital beds, facilities across the country are searching for ways to persuade workers to stay even as they scramble to hire replacements for those who don't. Pressure is rising for industry leaders to provide solutions. "Ask any hospital chief executive and you'll hear that bolstering the workforce is priority one, two and three," says Akin Demehin, senior director of policy at the American Hospital Association. How to do that is still not clear.

Burnout was a problem for physicians and nurses long before the pandemic, and resignations and retirements had already been increasing. The health care workforce itself is aging just as almost 70 million baby boomers in their 60s and 70s have been fueling an exploding demand for care. In 2019, the country had 20,000 fewer physicians than it needed, according to the Association of American Medical Colleges, and in a 2021 update, the group estimated that the shortage could rise to 124,000 physicians by 2034. There aren't enough nurses, either. Gerard Brogan, director of nursing practice at

By Linda Keslar // Illustrations by Dan Saelinger

National Nurses United, the nation's largest nurses' union, cites a lack of jobs that offer competitive pay, union protection and safe and healthy workplaces.

Long hours, hostile patients and safety concerns aren't the only factors driving the exodus. Many in health care are also worn down by the emotional toll of losing patients in devastatingly high numbers. In a June-September 2020 survey, health care workers reported that providing care during the pandemic had increased stress (93% of those surveyed), anxiety (86%), frustration (77%) and exhaustion and burnout (76%), and three out of four said they felt overwhelmed by what they'd lived through. Since that survey, rates of depression, insomnia and post-traumatic stress disorder have soared.

In addition to the stress, many are having second thoughts about the dangers of COVID infection on the job. One analysis found that more than 3,600 U.S. workers in the industry perished during the pandemic's first year, and one in three of those who died were nurses. Last winter's omicron virus variant was particularly deadly for health workers, according to the Centers for Disease Control and Prevention.

While the burnout crisis predated the pandemic, the past year has been the final straw for many workers. U.S. hospitals have lost more than 75,000 employees since the pandemic's start, and in March 2022, nearly a quarter of those institutions reported a critical staffing shortage. A few months earlier, during the omicron surge, 30% of reporting hospitals were struggling to find the bare minimum of clinicians and support personnel to keep the doors open. Spiraling labor costs, which make up more than half of health system budgets, have left fully a third of hospitals operating in the red, with rural hospitals most at risk of financial peril. "Workforce shortages forced many rural facilities to double what they were paying employees before the pandemic," says Alan Morgan, chief executive officer of the National Rural Health Association. Federal pandemic funding helped cover those higher costs, but with that money now running out, more than 20% of rural hospitals are at risk of closing.

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The size of the problem makes finding solutions daunting. In the month of April 2020 alone, for instance, the rate of attrition for physicians leaving their practice was nearly four times what it was April 2019, which amounted to a loss of several thousand doctors. If current trends continue, health care could have a shortfall of 3.2 million lower-wage workers by 2026, including medical assistants and home health aides, according to a report from HR consultant Mercer.

Long hours, hostile patients and safety concerns aren't the only factors driving the exodus.

Gail Gazelle, assistant professor of medicine at Harvard Medical School and a Master Certified physician coach, believes the problem may even be accelerating. "There's a domino effect," Gazelle says. "Understaffing is causing more people to leave because their situations are becoming untenable in terms of patient safety and their responsibilities as clinicians." In one survey, four out of five health care workers said they had felt the effects of the national labor shortage. They cited not only their increasing workloads but also the rushed or substandard patient care that resulted from a lack of personnel.

"With so many nurses retiring or moving on during the past two years, we're being asked to take care of more patients, and we often find ourselves working with less experienced team members," says Beth Wathen, a critical care nurse and the 2021-22 president of the American Association of Critical-Care Nurses. A recent AACN survey found that nine out of 10 nurses said their careers would be shorter than intended because of the new staffing pressures. "The overwhelming fear is that this is the new normal," Wathen says.

Finding new workers to bolster the workforce is the clear solution, but amid the exodus, most hospitals and other health care organizations can hire only staff that are expensive and temporary. The average pay for "travel" nurses, who fill in wherever they're needed, is now more than twice what it was before the pandemic, according to the AHA, and another survey found that roving "locum tenens" physicians can earn up to 30% more than permanent staff doctors.

In 2020, demand for travel nurses grew by more than a third, and it is expected to expand an additional 40% in the near future, according to one analysis. High salaries are motivating some on staff to quit and become travel nurses, who now account for at least 2% of the nursing workforce. "ICU nurses who choose to stay may find themselves working with a travel nurse making three to four times what they earn," says Wathen.

Some physicians, too, are shifting to contract work. Rohit Uppal, a physician and chief clinical officer of TeamHealth Hospitalist Services in Knoxville, Tennessee, says the firm now has more than 3,000 hospitalists working in more than 200 health care systems around the country. The company had a banner recruiting year in 2021, Uppal says. "Physicians are stressed out and don't feel valued," he says.

Roni Devlin, an infectious disease physician, gave notice at her job at a community-based teaching hospital just weeks before the start of the pandemic. "Being a doctor had always been stressful, but it had become more burdensome throughout the years," Devlin says. For the past two and a half years, she has worked as a locum tenens physician on several out-of-state assignments that allow her to return to her Midwestern home at least twice a month. Working at temporary jobs has given her relief from full-time administrative burdens and helped her recover from the exhaustive symptoms of burnout. Still, giving up job security and the benefits of her staff position, as well as having to take time away from her family, required consideration."I might still retire early," she says.

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Any solutions to today's staffing crisis will also have to finally address the crisis of mental health. The physicians that Gail Gazelle coaches are "exhausted, emotionally drained, cynical and feel like cogs in a wheel," she says. Even now, with stress levels running high, only 13% of American doctors have sought treatment to address mental health concerns. Many worry about the stigma of seeking help, which means it will be up to institutions not only to normalize avenues for relief, but to create less stressful work environments.

Indeed, research from the National Academy of Medicine suggests that most factors fueling burnout and resignations are beyond the control of clinicians. While health care has long depended on the resilience and dedication of its workers, that reliance on personal responsibility is past the breaking point. "We have to focus on fixing the workplace rather than the worker," says the AMA's Christine Sinsky.

To that end, Sinsky and physician Heather Farley, chief wellness officer at ChristianaCare in Delaware, among other experts, helped create the 2022 Healthcare Workforce Rescue Package. It includes evidence-based strategies that health care systems can adopt right away as a foundation for longer-term solutions. Those include peer-support programs, crisis documentation protocols and better staffing and workflow tools, all of which can help ease clinicians' burdens while enabling them to recognize when they or their colleagues are nearing their limits.

Chief among the recommendations is to put an executive leader in charge of implementing wellness programs. Indeed, "chief wellness officer" has become an in-demand

job posting. Farley's own appointment as CWO of ChristianaCare preceded the pandemic, and many initiatives she and her staff implemented—wellness resources, peer support and a mental health hotline, among other changes—proved effective when stress levels escalated.

Luminis Health Doctors Community Medical Center in Maryland has also taken steps to expand its wellness culture, says Deneen Richmond, president of the hospital. In one seemingly minor effort, Richmond and her team now walk the halls several times a week with an "exhale cart" stocked with snacks and other comfort items. There's also an "exhale room" with coloring books and massage chairs. "This is less about giving someone a bag of crackers than about connecting with people," Richmond says. "Just from casual chats in the hallway I've learned so much about the obstacles making it hard for our people to do their jobs."

Amping up pay and benefits also helps. This year, Luminis implemented a $29 million program for its 6,700 employees that includes tuition assistance and loan repayment programs, a $17 minimum wage for hourly workers and bonuses for nurses and others in high-demand, high-vacancy positions. "We did a full compensation review," Richmond says. Increasing what existing employees earned made more sense than paying exorbitant rates for temporary workers, she says.

Yet as departures continue, many hospitals and health care systems are necessarily focused on hiring. Northwell Health, New York state's largest health care provider and private employer with 80,000 workers, currently has about 5,000 vacancies. It has sent recruiting teams to places of worship, malls and job fairs, and uses social media videos to attract qualified candidates. "We're doing anything and everything to market ourselves," says Maxine Carrington, Northwell senior vice president and chief human resources officer, who estimates that the health care system interviews about 4,000 job candidates a month.

"It's an extremely competitive hiring environment," says Carrington, who notes that the organization has had to increase starting salaries and benefits to meet market conditions. But Northwell has also added perks to help retain current employees, increased investment in professional development and instituted new programs for employees overwhelmed by the stress of patient care in one of the nation's epicenters of COVID infection. In 2021, Northwell opened its Center for Traumatic Stress, Resilience and Recovery, which provides coaching, grief counseling, a 24/7 hotline and other features to clinicians, support workers and their families.

One program, Northwell Celebrates, is designed to show Northwell's appreciation for its workforce. "We wanted to push gratitude," Carrington says. Frontline workers got a $2,500 bonus in 2020 and an extra week off. There are gift boxes, free appointments at a mobile on-site spa, prepared meals delivered to workers' homes and family movie and concert nights.

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The government also has a part to play in reducing medicine's unsustainably high attrition rates. In a March 2022 letter to Congress, the AHA called health care's workforce shortage a "national emergency" requiring immediate action. The hospital group called for increased funding for workers' mental health needs as well as a number of moves that would ease the personnel gap—including lifting the cap on Medicare-funded physician residencies, increasing funding for nursing schools and fast-tracking visas for international health workers.

In January 2022 the Biden-Harris administration allocated $103 million in American Rescue Plan funds to establish evidence-based programs promoting the mental health and well-being of health workers. In addition, the Dr. Lorna Breen Health Care Provider Protection Act, which became law in March 2022 and is named for an emergency department physician who took her own life early in the pandemic, provides up to $135 million over three years to train providers about suicide prevention and behavioral health.

Other federal legislation is designed to combat burnout and increase the supply of new clinicians and other health workers, and states are relaxing licensing requirements and expanding training programs and

The government has a part to play in reducing medicine's unsustainably high attrition rates.

compensation, according to the National Academy for State Health Policy. Last January, Pennsylvania appropriated $225 million to fund retention and recruitment payments for health workers, and in April, New York announced a $20 billion plan to pay higher wages and bonuses for frontline health workers as well as home care workers.

As they wait for such efforts to bear fruit, some nurses and others in health care are doing what they can to improve their lives at work. Nerissa Black left a corporate career to become a nurse, and she loves what she does. Yet during the winter COVID surge in early 2021, the California telemetry nurse found herself overwhelmed after her state lifted a cap on the ratio of patients to nurses. She had just 10 minutes an hour to check on the severely sick patients under her care, and that was barely enough time to switch in and out of protective gear between patients. "The trauma of those three months was horrific," she says.

Black began seeing a therapist and taking medication for anxiety. "There was no peer support at the hospital; you had to seek help on your own," she says. Yet by the end of last summer, amid continuing staff shortfalls and looking ahead to other anticipated COVID surges, she considered exiting nursing altogether. "I thought, 'I can't go through this again.'"

Months later, she found a nursing position in a gastroenterology lab at her hospital, where she attends to patients undergoing procedures. "It's not as all-consuming as being at the bedside of acutely ill patients," Black says.

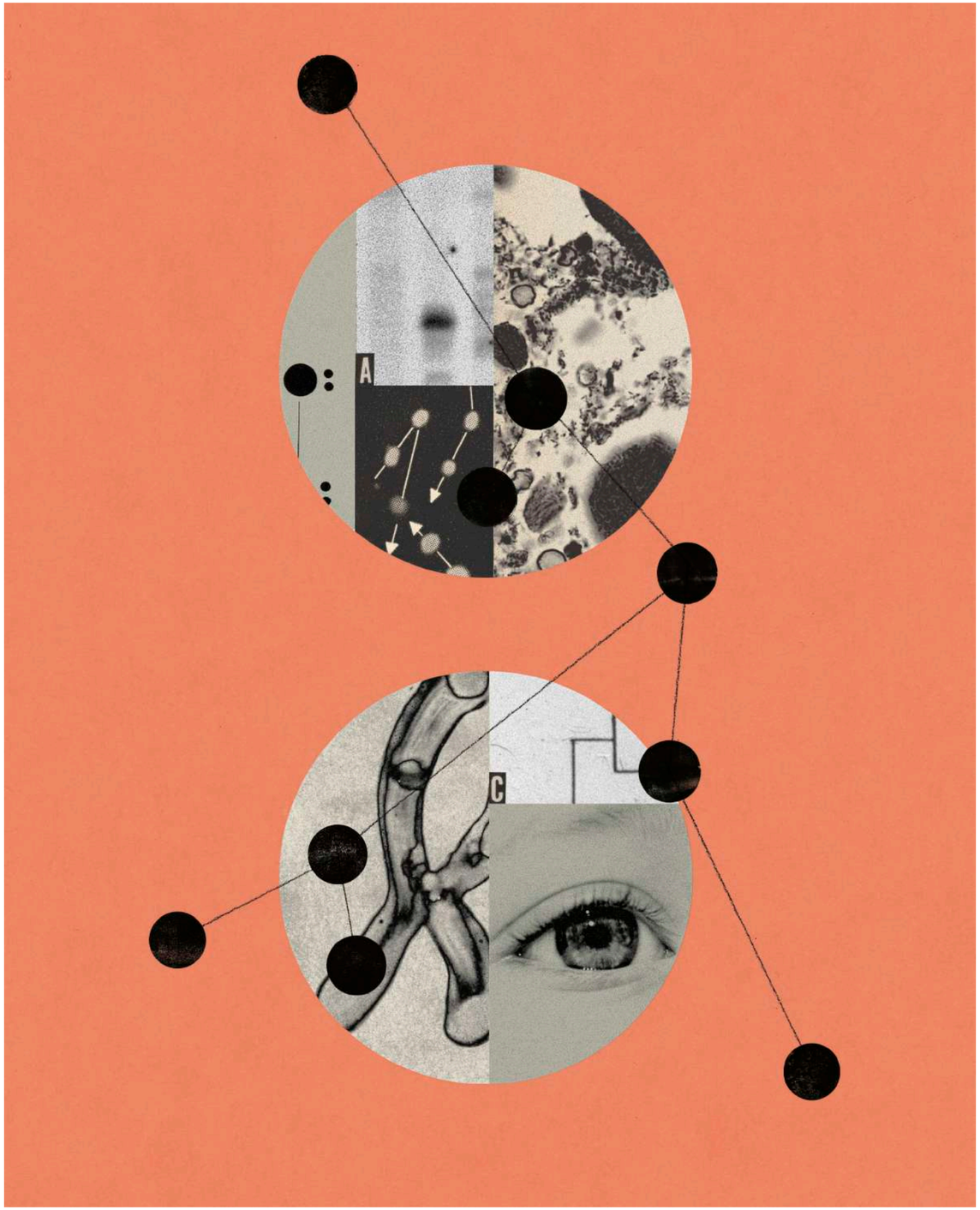
But job changes like hers, even when clinicians and others stay with the same employer, do little to relieve the pressures of the great resignation. Black's hospital continues to deal with a nursing shortage, she says, and it has struggled to fill open positions in the department she left. "Morale is really low," she says.

DOSSIER

Allinforhealthcare.org. This online hub sponsored by a coalition of health care organizations contains action steps, practical tips and resources to support organizations looking to create programs for health care worker well-being.

"COVID-Related Stress and Work Intentions in a Sample of US Health Care Workers," by Christine Sinsky et al., *Mayo Clinic Proceedings*, December 2021. The findings of this American Medical Association-sponsored study revealed a workforce intent not only on cutting back their hours but also on leaving their current jobs.

"The Evolving Role of the Chief Wellness Officer in the Management of Crises by Health Care Systems: Lessons from the COVID-19 Pandemic," by Kirk Brower et al., *NEJM Catalyst Innovations in Care Delivery*, April 2021. The authors explore the role of the CWO at nine organizations in the midst of the pandemic.



An Errant Gene

A rare disease, now treatable thanks to a valiant international effort, offers a window into the metabolism of fat.

By Timothy Gower //
Illustrations by Mike McQuade

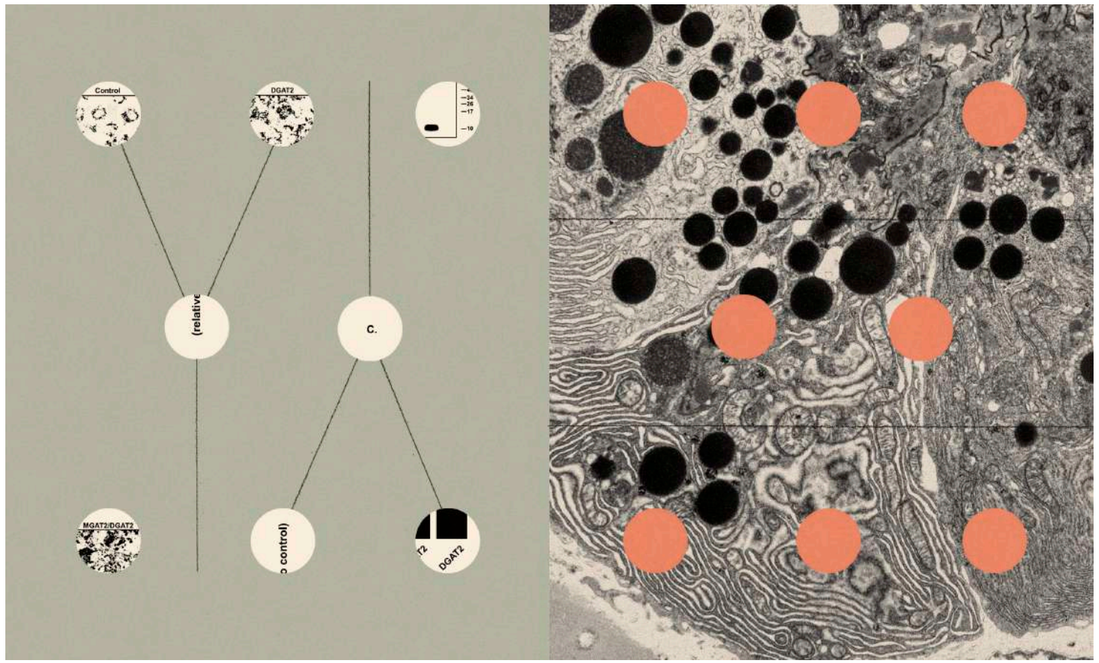
Harland Winter, a pediatric gastroenterologist at Massachusetts General Hospital, clearly remembers the day in 2010 when he received an email from Mauro Toporovski, a pediatrician in Sao Paolo, Brazil. Toporovski sought Winter's advice about an infant girl named Nechama who had a mysterious case of severe, intractable diarrhea. Although Toporovski had tried switching her from breast milk and cow's milk formula to soy-based formula, the diarrhea persisted. Tests showed that Nechama was losing a significant amount of protein in her stool.

To find the cause of the baby's gastrointestinal distress, Toporovski had run every exam he could think of, including a screening for congenital diarrhea disorders, which are relatively rare. He consulted with several colleagues in Brazil and beyond, including Winter. But no one could figure out what was wrong with the child.

When Nechama was 17 months old and still hospitalized, she acquired a serious infection, most likely because her immune system was weakened by malnutrition. She developed sepsis, possibly related to the catheter she needed for nutrition, and died.

A month later, Nechama's mother was pregnant. Toporovski offered congratulations, but he was worried that the little girl's diarrhea might have had a genetic cause, a mutation that the new sibling could also inherit. "I hoped that it was just one case, and that the other baby would survive and be healthy," says Toporovski. But after a trouble-free pregnancy, the woman gave birth to a boy, Eliashiv—and he also developed severe diarrhea. "It was exactly the same disease," says Toporovski.

Winter agreed that the diarrhea probably had a genetic cause, and to help identify it, he consulted Mark Daly, the founding chief of the MGH Analytic and Translational Genetics Unit, launched in 2010 by the department of medicine to connect clinical researchers at the hospital with the burgeoning world of genomic medicine. "Genome sequencing was then still in its very early



days," says Daly, who had recently begun using the technology to conduct clinical research with colleagues at the Broad Institute of MIT and Harvard. "We were building new tools in real time."

One of those tools was whole-exome sequencing, a process that scans the exome, the 1% or so of the human genome that carries the code for making proteins. Most known gene mutations associated with diseases occur in these regions. Daly recommended using this process to search for a potential genetic cause of the syndrome that had killed Nechama.

Winter requested blood specimens from Eliashiv, both parents, an older brother who had never developed chronic diarrhea and several other relatives. He was also able to get a sample of Nechama's blood, preserved from birth in the form of a "blood spot," a tiny amount of blood taken from a newborn's heel for routine screening and collected on special paper.

Daly, working with Christine Stevens, now an associate director of scientific projects at the Broad, oversaw extraction and sequencing of DNA from the blood specimens. They discovered that each parent had one normal version (or allele) of a gene called DGAT1, as well as a mutant allele that suggested they were missing a segment known as exon 8. Someone who has both a normal and a mutant version of an allele—making that person *heterozygous*, in scientific terms—shouldn't have problems, because the normal gene is able to provide code for making an essential protein. Babies, however, receive one allele from each parent, and Nechama and Eliashiv were both *homozygous* for the DGAT1 mutation—each child had inherited two copies of the mutant gene.

This was compelling evidence that the DGAT1 mutation might be behind the children's life-threatening diarrhea. But the researchers needed to know more—about the role of a normal DGAT1 gene, and why its absence might make babies so sick. The search for answers led Winter, Daly and the others to a laboratory 3,000 miles away, where other scientists were already working to solve the mystery of DGAT1—a mutation that not only caused the rare illness but seemed to play a critical role in the way that the body metabolizes fat.

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Physician Robert Farese Jr., in his laboratory at the Gladstone Institutes at the University of California, San Francisco, had focused much of his research on cellular lipid metabolism, and in 1998, Farese and his colleagues identified a gene that produces diacylglycerol O-acyltransferase, or DGAT. It's an enzyme that converts fatty acids from food into triglycerides, a form of fat stored by the body in lipid droplets to produce energy. A short time later, collaborating with a biotechnology partner, Farese's lab discovered a second form of DGAT. The researchers first found it in plants but then discovered it was present in humans, too. Two genes, DGAT1 and DGAT2, carried the code for these enzymes.

Farese and his colleagues observed that mice bred not to have the DGAT1 gene—and thus not producing the DGAT1 enzyme—had remarkable qualities. "Those mice looked amazing," says Farese. "They were thin, didn't get obese and lived 25% longer than other mice." The mice also seemed impervious to metabolic conditions such as diabetes and nonalcoholic fatty liver disease, a condition that affects about one in four U.S. adults. For those involved in the research, as well as the pharmaceutical industry, this discovery looked like a breakthrough that could have far-reaching implications. Being able to replicate those effects in people could improve health and save millions of lives. Several companies began to develop and test experimental compounds that blocked or inhibited DGAT1 as potential treatments for obesity, elevated triglycerides and other conditions.

> Mice bred not to have the DGAT1 gene had remarkable qualities.

In July 2011, Daly emailed Farese to say that the whole-exome sequencing of Nechama and her family had identified a mutation in DGAT1 that appeared to be linked to severe diarrhea in children. By then, Farese had established a joint lab with biochemist Tobias Walther, which they would transfer to the Harvard T.H. Chan School of Public Health in 2014. Farese, Walther and their team produced a clone of the DGAT1 mutation Daly had discovered and tested it in the lab. "We found that there was a total loss of DGAT activity," says Farese. That explained why babies who lacked the DGAT1 enzyme developed gastrointestinal distress. Without enzymes to make triglycerides that can be stored in lipid droplets, fatty acids from food build up in the intestine "and wreak havoc," says Farese. The accumulation of these detergent-like compounds damages cell membranes and promotes cell death, resulting not only in diarrhea, vomiting and other GI symptoms, but also dangerous loss of protein in the stool. That was also the reason that those DGAT1-blocking drugs, developed with high hopes for treating obesity and other metabolic conditions, haven't worked in people. While it's not clear why mice without DGAT1 avoid the problems that are so debilitating in people, Farese suspects it may be because mice, unlike humans, also make DGAT2 in their intestines, and that related enzymes can serve as a back-up mechanism for turning fatty acids into triglycerides.

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The emerging understanding of how and why DGAT1 deficiency led to GI symptoms meant there might be a straightforward solution for people with the mutation—simply reduce fat in their diet. Eliashiv had been fed formula through a vein, which bypassed the gut and kept him alive. But when he was placed on a fat-restricted diet, his diarrhea soon eased. He gained weight and was discharged, and today, he's a healthy 10-year-old. It's only

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A Key to the Body's Fat?

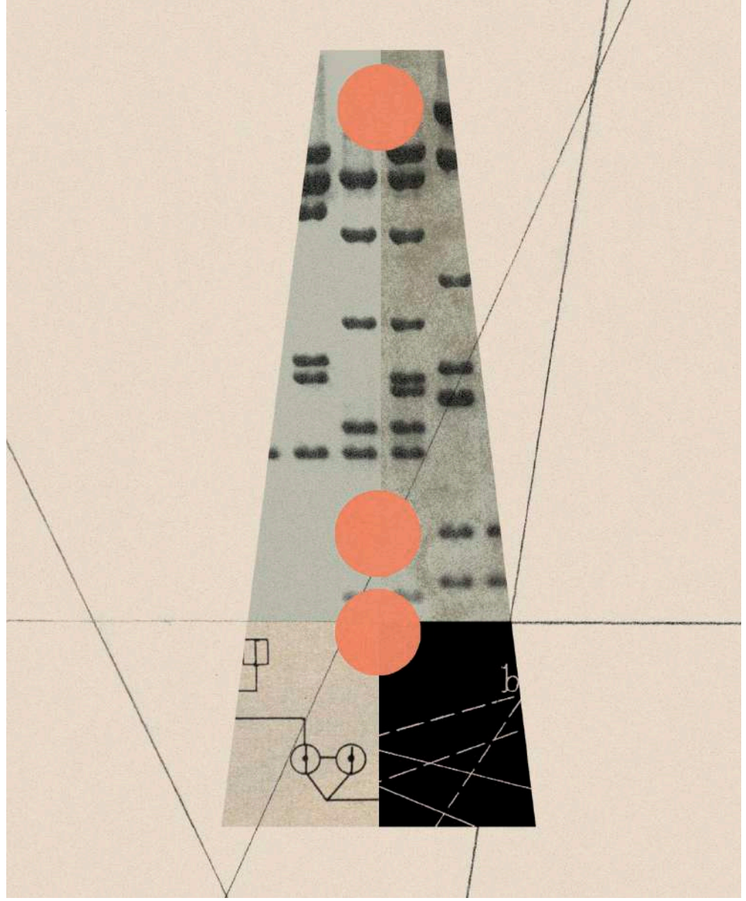
The role of DGAT2 comes into focus.

Robert Farese Jr., who helped pioneer research into the enzymes DGAT1 and DGAT2, and Tobias Walther are probing the mysteries of lipid droplet biology at their joint laboratory at the Harvard T.H. Chan School of Public Health. Some of that work has focused on DGAT2. It turns out to be essential for making triglycerides, which provide storage for most fat in the body. Farese and Walther recently made an intriguing discovery in animal studies. "When you block DGAT2, you shut down not only production of triglycerides but also lipid synthesis in general," Farese says.

The scientists theorize that the body may have a feedback loop, wherein the amount of fat stored influences how much fat is made, and vice versa. "That would be fundamentally exciting to understand," says Farese. "But it could also be exciting from a therapeutic standpoint. With a DGAT2 inhibitor, it appears that you not only block triglyceride synthesis; you also shut down the production of new fat. That could be quite an effective drug."

The most promising use of such a therapy would be to treat nonalcoholic fatty liver disease, which affects about one in four Americans and can lead to liver failure. A drug that blocks DGAT2 synthesis is currently in development. In a randomized trial, patients who received the experimental drug experienced a rapid and large drop in liver fat, compared with no change in patients who got placebo shots.

Farese and Walther also continue to study other aspects of the basic biology of lipid droplets, and working with colleagues at the Broad Institute of Harvard and MIT, they recently unveiled the Lipid Droplet Knowledge Portal (lipiddroplet.org), an open-source repository for research on the genomics and proteomics of these complex, critically important structures.



when he consumes dietary fat, says Toporovski, that the diarrhea comes back.

In 2012, the team of clinicians and scientists who linked the DGAT1 mutation to congenital diarrhea reported their findings in the *Journal of Clinical Investigation* (*JCI*). The paper noted that although the mutation is extremely rare, it had been found in at least seven members of a family of Ashkenazi Jewish ancestry—Nechama and Eliashiv, who were homozygous for the DGAT1 mutation, as well as their older sister, parents and two grandparents, who carried only one copy of the defective gene and were unaffected.

Most Ashkenazi Jews are descended from a relatively small population in Eastern Europe, and many choose to marry within their faith and community, increasing the chance that a child might inherit a disease-causing gene mutation from both parents. Conditions such as Tay-Sachs disease, Gaucher disease and others are more common among Ashkenazi Jews because of this kind of genetic concentration, and most babies known to have been born with the DGAT1 mutation have had Ashkenazi Jewish ancestry, says Daly. He estimates that one to two of every 100,000 children born in this community are homozygous for the defective gene, compared with perhaps one in 100 million worldwide.

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Although most children diagnosed with DGAT1 deficiency have the same mutation in the DGAT1 gene—the one that causes a "skip" of exon 8—physicians and researchers have found that there are other mutations in the same gene that can also cause problems. One of those came to light in 2012 in London. Twin boys, Rishaan and Kiaan, developed diarrhea and vomiting immediately after birth, landing them in intensive care for three weeks before they were sent home. But their GI distress didn't respond to treatment and the boys were in and out of hospitals for the next two years as they got sicker and sicker. Their doctors didn't expect them to live.

So the parents took their sons to Columbia University Medical Center in New York City, where doctors initially suspected they had mitochondrial disease. When tests proved that theory wrong, geneticists at Columbia suggested that DGAT1 deficiency might be the cause and proposed performing whole exome sequencing for the twins and their parents.

Both boys had developed an aversion to eating, and Rishaan was so ill he couldn't stand. His father brought him to Boston Children's Hospital, and Winter at MGH was consulted. "At that time, DGAT1 deficiency had been identified only in children of Ashkenazi Jewish descent," says Nina Gluchowski, who was a pediatric gastroenterology fellow at Children's when the boy arrived and went on to work in the Farese and Walther lab. "We didn't know whether it was even possible that other children might be affected by the same condition," as the family is of Indian ancestry.

Sequencing revealed, however, that the twins were homozygous for a DGAT1 mutation that was different than the gene variant found in Ashkenazi Jewish children. Yet this mutation, too, seemed likely to cause GI distress, and Rishaan was immediately placed on intravenous feeding. Two days later, as his father sat next to his hospital bed eating steamed edamame, the boy reached over, snatched a handful of the soybeans and gobbled them. "He didn't stop eating for two weeks," says Rishi, whose son craved egg whites, more edamame and other foods. "It was like a miracle."

The family soon returned to London, and the twins were put on a diet of foods such as plain chicken, rice, potatoes and edamame. Today, they're energetic 10-year-olds who excel in school and love sports. Gluchowski worked with Farese and Walther in the lab at the Harvard School of Public Health to determine how this mutation functioned. It turns out that, unlike the mutation in the Ashkenazi children, this mutation allowed both boys to tolerate a modest amount of fat in their diets, apparently because the novel DGAT1 mutation they were born with causes only partial loss of the DGAT1 enzyme. "We now know that DGAT1 deficiency seems to be more of a spectrum of disease," says Gluchowski, now at the University of Vermont Medical Center. She notes that some children with the deficiency can tolerate up to 10% of calories from fat. What's more, children born without the ability to make adequate amounts of the DGAT1 enzyme may compensate by ramping up activity in their DGAT2 genes, according to one theory.

> Winter saw the need for a simple blood test that could detect the DGAT1 mutation.

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DGAT1 deficiency is a rare disease, and what scientists have learned about DGAT1 mutations has been crucial in helping a small number of children born with the gene variants. Since first working with Mauro Toporovski in Brazil, Winter has treated or consulted on many cases of congenital diarrhea linked to DGAT1 mutations. But most of these cases were discovered only after babies had already gone through months or years of extreme, life-threatening distress. The whole exome sequencing needed to confirm a diagnosis could take up to two months to produce results. Early on, Winter saw the need for a simple blood test that could detect the DGAT1 mutation more quickly.

He turned to the Laboratory for Molecular Medicine at Mass General Brigham (then Partners HealthCare) to develop one. The scientists there developed an assay that can determine within a few days whether a baby has the Ashkenazi mutation. (Blood panels that screen for multiple DGAT1 mutations are now also available.) This assay would enable early diagnosis and make possible the prevention of severe manifestations of DGAT1 deficiency.

In 2021, Winter heard from a mother who had a child with the DGAT1 mutation. She said that she was pregnant again and asked for his help in case the new child developed the same problem. Indeed, a baby girl, born in January 2022, had mild symptoms while being fed breast milk. When the assay for the DGAT1 mutation quickly confirmed that she was homozygous for the Ashkenazi gene variant, the parents brought the baby, then just eight days old, to MGH. Clinical nutrition specialist Jill Israelite oversaw her feeding of a special formula without fat, which was developed by Peri Milman at Hadassah Hospital in Jerusalem. The baby's condition improved enough during the first week for her to be transferred to Columbia Medical Center, closer to the family's home. She was discharged a few weeks later and is now faring well on a special fat-free infant formula with intravenous fat supplementation. Early detection and treatment enabled her to avoid the severe diarrhea and protein loss caused by a deficiency in DGAT1.

That little girl, like Eliashiv in Brazil and Rishaan and Kiaan in London, is fortunate in finding a treatment for the condition. As with most rare diseases, families and children with DGAT1 deficiency struggle to find resources. Harland Winter credits the advances in discovering this new disease, identifying a treatment, developing early diagnosis and, after only 10 years, being able to prevent symptoms to "the efforts of health care providers, scientists and parents who worked together to improve the lives of children," he says.

DOSSIER

DGAT1.org The website, created by Harland Winter and his colleagues, serves as both a primer and support group for families and caregivers of children with DGAT1 deficiency and was founded by the parents (Rishi and Milan Khosla) of twins born with the condition.

"DGAT1 Mutation Is Linked to a Congenital Diarrheal Disorder," by Joel T. Haas et al. *The Journal of Clinical Investigation*, December 2012. The first report on the extremely rare gene mutation links the condition to severe diarrhea and other symptoms in newborns.

"An Introduction to Lipid Droplets," by Robert Farese Jr., and Tobias Walther. In this three-part iBiology.com podcast, two Harvard scientists and leading experts on DGAT1 explain how the body uses this enzyme and other factors to make fat.

FIRST PERSON

The Missing Peace

BY MEERA THAKKAR

I reviewed the patient's chart. She was postpartum day 1 after an uncomplicated delivery with minimal blood loss. Everything seemed routine. Then the bolded COVID status caught my eye—positive.

I tensed up. At this point my dread was less about my own safety than what had to happen next: I would need to ask another overworked, bone-tired resident to take on the risk of this patient, because I couldn't.

In my third year of medical school I got the diagnosis: focal segmental glomerulosclerosis, a syndrome that affects the kidneys. One of mine was performing at 60% and the other at 40%. Armed with a student's zeal for the case study that had become my own body, I had researched the consults, specialists and procedures that would need to happen. I set them in motion.

By the middle of my residency, the inevitable occurred: end stage renal disease. The options were either dialysis or a transplant. My family stepped up to test for organ compatibility and my heart sank when my little sister was the match. She was in the middle of her own medical school training in Chicago, and the timing would be as bad for her as it was for me.

We both knew the score. In the hypercompetitive, pressure-cooker atmosphere of medical training, the physical health of the provider comes last. Physical limits aren't supposed to exist, and if they do, you are definitely not supposed to make them known. The years leading to practice are a grueling marathon.

After the transplant, my sister and I decided to recover together. We lived in the same house for the first time since we were teenagers. I studied and processed data when I could for research I was helping to conduct. My sister also hustled to fill her schedule, taking virtual courses while bedridden.

Something happened during those four months. The weight of school lifted. Our whole adult lives, we had faced the cascading pressures of med school—getting in, surviving the MCAT and STEP 1, matching for residency. Now, we occasionally watched Harry Potter movies and ate my mother's food. In the middle of chaos, we got a glimpse of what work-life balance tasted like, and it was wonderful.

After I recovered, I went into the wards to continue my residency, and my body couldn't have been less suited to the time and place. With my immune system suppressed to keep from rejecting the new kidney, I didn't have the ability to fight new infections. And by this time, hospitals were hotbeds of the new COVID-19 virus, with the vaccine still a distant hope.

I didn't want anything to keep me from becoming a doctor. I did everything possible to carry on with the job. But there was a hitch every time I had a patient with COVID-19.

The worst of it was having to ask a fellow resident to cover. I hated putting someone else in harm's way to save myself. Besides, not seeing patients went against everything we were taught, that medicine is about the person who needs help, not you.

Time and again I was tempted to sidestep the glares and the guilt and just take the risk. But how could I take care of others if I got sick?

I turned around and signaled to my co-resident down the hall. "I'm sorry, can you..." I said, holding out the chart to a haggard looking resident. Shockingly, she smiled and said, "Sure."

I want to be a good physician. But I also want to remember those four months in recovery, and those first months back in the hospital. They taught me something about my physical and mental limits. Our bodies do exist, and they also need care. It shouldn't take an organ donation to teach me this, but finally learning the importance of self-care was the silver lining my awful first COVID summer.

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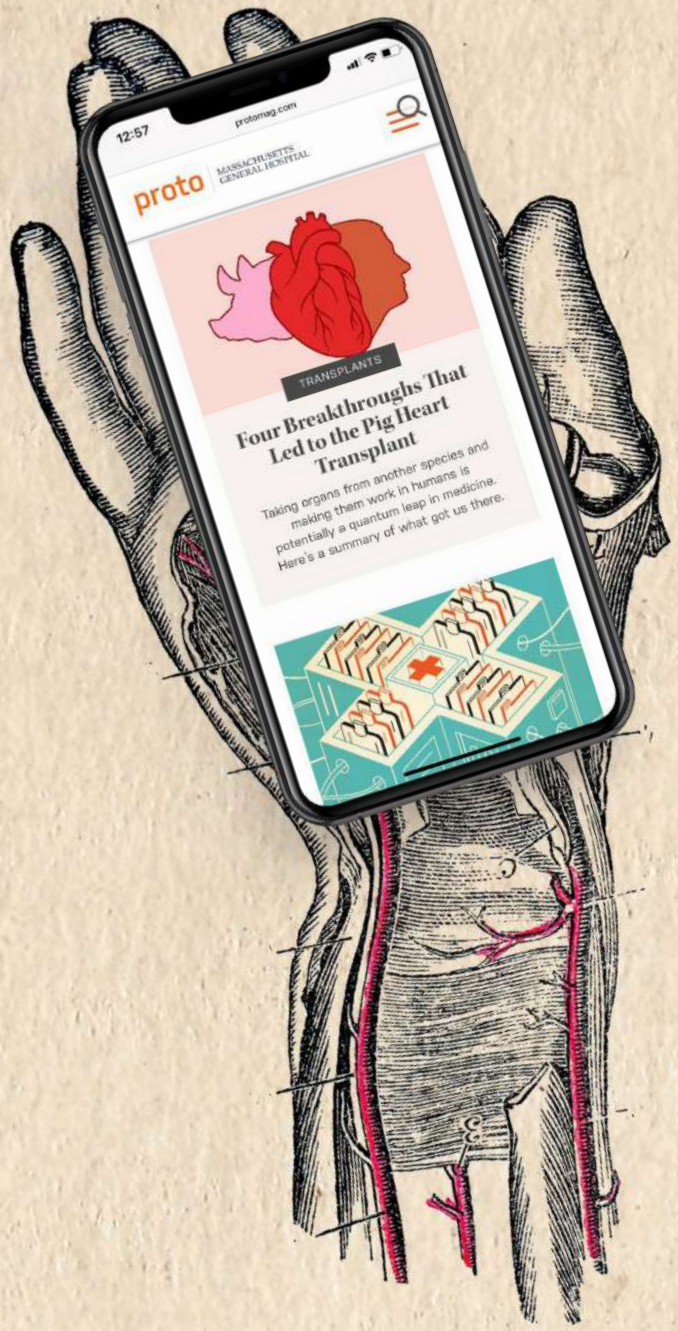

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