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

Early Adversity p18 • Health Care’s Great Resignation p24
The Puzzle of the DGAT Gene p30
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.

contents

STAT

04 Interview
Geneticist Ting Wang explores some of the ideas shaping the Human Pangenoome Project.

06 Infographic
Venomous toads and scorpions are the unlikely sources of new therapies.

10 Milestone
During the Civil War, why did some soldiers die from homesickness?

POST-OP

36 First Person
A medical resident reflects on her calling after a kidney transplant.

FEATURES

12 Where Psychedelic Research Goes Next
A wave of research has put mind-altering drugs back in the spotlight. Learning more about their therapeutic mechanisms may open the doors to clinical use.

18 The Tender Years
Early childhoods marked by adversity—poverty, abuse and violence—lead to adulthoods filled with health problems. New research aims to break that chain.

24 I Quit
Health care faces an unprecedented staffing crisis. What is at the root of the problem, and how can the industry persuade the workforce to stay put?

30 An Errant Gene
A single case of acute diarrhea in Brazil leads to the discovery of a rare disease and insights into the metabolism of fat in the body.

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
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 seek 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.

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 20% 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.

In the U.S., many patients suffering from psychiatric disorders, however, it can be tedious, frustrating and sometimes heartbreaking to seek 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.

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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.

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 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 from Indigenous backgrounds. 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: 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.

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 long-term effort to create a resource to better serve humanity. This and other methods have since become more efficient, but by 2020 they had solved only about 1% of human protein structures.

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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.

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.
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 venoms 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 antithrombotic 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 therapeutic avenues 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.

For example, a recent study demonstrated that microRNAs from sea anemones reduce pain levels.

**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.

**Bufo toads**

Scurried in Florida, where they are considered invasive pests and a threat to pets, bufotoxins 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.

**Scorpions**

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

**Honeybees**

Honeybees venom is brimming with intriguins 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.

**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 belinostatin, derived from the deadly pufferfish, had reduced pain levels.

**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.

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 subspecialties. 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 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.
The Gift of Data

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

BY STEPHEN ORNES

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 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 Maha 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, which must be conducted in the interest of the public good. Some altruists opt in, in their health care data will flow into a central “pool” per the DGA, where registered organizations can access it.

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 nudges to citizens or organizations to become data altruists must also be accompanied by strong assurances that those data will be properly protected, says Kristin Kostic-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.”

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 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, have traditionally been marginalized, says Hamill. “We have a window of opportunity to prevent the spread of monkeypox, and we need to grab it.”

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 magnitudes of COVID-19 testing.

Another challenge is to locate the epicenter of infection. Keleto 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.”

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A Death from Nostalgia

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

BY HANNAH THOMASY

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 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 "bushed excessively in the brain, [and] cannot flow through the invisible tubes of the nerves to make the 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 those deaths be viewed today? Classic nostalgia does seem to share elements with depression and suicidality, 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 twentieth century, doctors found shifts in how it thought about disease—and this is as true today as it was in the past—is shaped by their cultural and historical context.

Today, the lowest research field in medicine looks at the mental health of military personnel. 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 Ukraine, 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 friends with whom you identified with, and homesickness associated with greater symptoms of depression and anxiety. Experts call for addressing not only the physical but mental health—by including homesickness—of those forced to leave their mountainous land.

Proto Spring 2022

MISSED THE LAST ISSUE? All stories from Proto Spring 2022 are available at protomag.com.

SECOND OPINION

Trust and the "Infodemic"

The article "The Trust Crisis" (Spring 2022) described in detail the disintegration of public trust in health care. While this decline has been wide-ranging, it is important to distinguish the distinct domains of trust discussed. (1) that individuals have in their health care providers, who have long been among the most trustworthy professions 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 patients 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.

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 friends with whom you identified with, and homesickness associated with greater symptoms of depression and anxiety. Experts call for addressing not only the physical but mental health—by including homesickness—of those forced to leave their mountainous land.
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.
And the effects are sometimes extraor-
dinary. In small trials, psilocybin, the most-studied psychedelic, has been shown to ameliorate tobacco addiction, alcohol addiction, obsessive-compulsive disor-
der, cancer-related anxiety and depression and treatment-resistant depression. Some patients who have taken the drug report feeling optimistic again after years of crip-
pling depression that conventional treat-
ments didn’t improve. Psilocybin is also being studied as a therapy for myriad other disor-
tugs—and others around the world—might use this understanding to develop better, safer or more accessible substances or treat-
ments. More immediately, uncovering the mechanisms of psychedelic drugs may show who exactly these drugs can help and in what contexts.

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

Researchers will need to figure out how these drugs bring about their positive effects. Only three or four hours in humans, there seem to be effects that can persist weeks or even months.”

director of the MGH Center for the Neurosci-
ence of Psychedelics. Yet the data came from a phase 2 trial, with only 233 patients, and roll-
ing the project out to a phase 3 deployment, with the difficulty of working with controlled substances, can make gathering insights much more difficult. In one recent psilocy-
bin 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 Sharmiren Ghaznavi, associate professor of psychiatry at Harvard University. Unintended 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 trips,” which can also 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 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 bind-
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tive 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
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 formed Roskies and Doss 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 afterward. Changes in other brain networks could also be important. Psychodicals 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 psychodicals, 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 away 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 how much of the change is driven by the drug’s psychopharmacological properties. Indeed, multiple studies have shown correlations between subjective experiences during a trip and long-term benefits as measured by changes in neuroplasticity. In an ongoing study, Christopher Nicholas, a clinical psychologist at the University of Alabama at Birmingham, found 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 a balanced way. And to avoid the temptation to fall into one extreme or the other. Those and other issues will have to be addressed as the scientific understanding of this concept unfolds. ‘I think we’re still in the first inning here,’ says Haggerty. ‘How do we make those 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 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. 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. Psychodicals that produce a shorter “trip” such as 5-MeO-DMT, might also help enabling psychedelics to unrealistically positive expectations. “It appears that there’s genuine promise for psychodicals to be effective treatments for some mental disorders,” says Haggerty. “But 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.

Patients need specially trained therapists to prepare them for the experience.
Adversity in early childhood too often equals poor health later. Now researchers are looking for ways to change the equation.

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

director of Child and Adolescent Psychiatry at the University of Maryland School of Medicine. “Those circumstances can make grieving traumatic in itself!”

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 developmentally, 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-founder 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 under- or overreact, 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 especially 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. “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. “Environmental 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 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 experienced at different ages when the adversity happened and how 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 pathogen or environment, but others may persist and cause long-term health problems,” she says.

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, tasting 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 20% a low response 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 the health outcomes that we were concerned with—respiratory disease, injuries, mental disorders, behavioral disorders,” he says.

Highly reactive kids who grew up in most stressful environments 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
early trauma: building supportive families, 667 mothers and their 11-year-old children can American youth growing up in rural and academic trajectory of low-income Afri-
program for improving the psychological with Gene Brody, professor of human devel-
Greg Miller at Northwestern teamed up
perhaps through adulthood. believes that improving the environment of
says, "were the most responsive and sensitive
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by failing to invest in children's health, we are
“Association of Childhood Adversity with Morbidity and Mortality in US Adults,” by
“Leveraging the Biology of Adversity and Resilience to Transform Pediatric Practice,”
"We focus on their goals, not ours," says Stol-
them find safe housing and stay in school. Staff
hospital-based violence intervention program called Healing Hurt
"The literature suggests there is a reopening of susceptibility to positive interventions during adolescence."• • •
At the University of Maryland Children's Hospital in Baltimore, clinicians expect the children who are admitted to have suffered a
"80% of our kids have had layers upon layers of
At the University of Maryland Children's Hospital in Baltimore, clinicians expect the children who are admitted to have suffered a
"At age one, toddlers in the intervention
from the effects of childhood adversity.
"Our findings tell us we need to continue until the children are four
\$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 Medi-
"We hedge, saying that we don't really know yet 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
"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.
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 Bregan, director of nursing practice at...
in the exodus. Long hours, hostile patients and safety concerns aren’t the only factors driving the exodus. While the burnout crisis predated the pandemic, the past two years have been the final exacerbator. 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, says, “Understanding 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 understaffed 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 experience of 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 moving “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.

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In January 2022 the Biden-Harris administration announced a $20 billion plan to pay higher wages and bonuses for frontline 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.

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

The findings of

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.

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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 Paulo, 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
in Depth • Clinical Research

In July 2011, Daly emailed Farese about 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. 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 DGAT2 inhibition, it appears that you would be able to make fat in the body and vice versa. That would be fundamentally exciting," says Farese. "But it could also be exciting from a therapeutic standpoint. With DGAT2 inhibition, it appears that you would be able to make fat in the body and vice versa.

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. Eliahsr had been fed formula through a feeding tube, 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

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 experimen
tal compounds that blocked or inhibited DGAT1 as potential treatments for obesity, elevated triglycerides and other conditions.

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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 drop
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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 whites born 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 have this gene mutation, compared with perhaps one in 100 among the general population. So the parents took their twins 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 an aversion to eating, and Rishai 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 Farre 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 Farre 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, who is in the University 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.

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 Farese and Tobias Walther in the lab at the Harvard School of Public Health to develop a simple blood test that could detect the DGAT1 mutation more quickly. Early detection and treatment enabled a child to be 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.

A little girl, like Eliashiv in Brazil and Rishai and Kian in London, is fortunate enough to have a treatment for the condition. As with most rare diseases, families and children with DGAT1 deficiency struggle to find resources. Harland Winter credits the DGAT1A DOSSIER with “the world’s largest user-driven effort to identify a treatment, developing early diagnosis and, after only 10 years, becoming one of the most active hubs 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., 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.
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 hyper-competitive, 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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