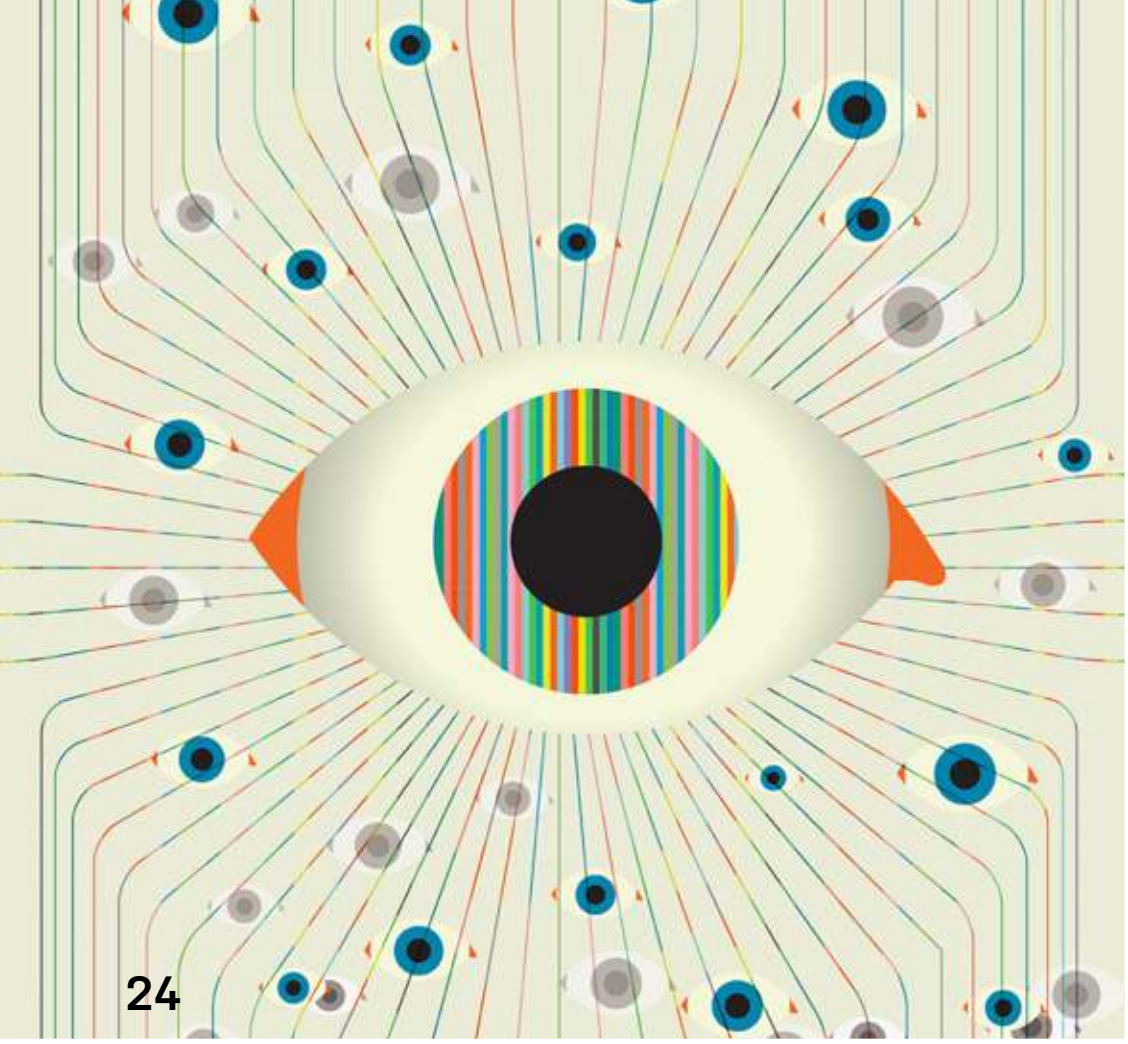
FALL 22

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

What Good Is Science Writing?

Journalism about medicine continues to inform and enlighten. Is anyone paying attention? p30



contents

FALL 2022

STAT

POST-OP

FEATURES

on the cover

Trust in journalism, as with other professions, has reached critical lows. For those who try to bring scientific facts to the public, what does the future hold?
// Illustration by Jim Tsinganos

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®

Founded in 1811, Massachusetts General Hospital is a 1,043-bed academic medical center located in Boston. It is a founding member of Mass General Brigham (formerly Partners HealthCare) and is the original and largest teaching affiliate of Harvard Medical School.

IN SEPTEMBER 2005, Massachusetts General Hospital launched *Proto*, a magazine that took readers to places where innovation was unfolding and introduced fascinating people pushing the boundaries of medicine. The cover story of that inaugural issue looked at pandemics, focusing on H5N1—avian flu—which was then in the crosshairs of the Centers for Disease Control and Prevention. Experts warned of the potential for a deadly global outbreak, "long overdue," and cautioned that failing to prepare for such a pandemic could prove disastrous.

Almost two decades later, and for nearly three years, *Proto* has teemed with stories about the COVID-19 pandemic—its origins, treatment and prevention as well as descriptions of disparities in care and clinician burnout. This issue considers how a vaccine might be made in just 100 days and features an essay from a science writer about the challenges of covering COVID while battling misinformation with science and facts.

Between the bookends of one pandemic that was evaded and another that is devastating and ongoing, *Proto*'s 17-year journey has delivered hundreds of stories about innovation, clinical care, health policy and the indomitable human spirit. Medicine has evolved and advanced, and so has the way it is provided and consumed amid a demand for real-time, at-the-fingertips information. Today, more than 70% of Americans get their health information from the internet and social media.

Mindful of these changes, MGH has made the difficult decision to discontinue publishing *Proto* magazine in its current format. Yet we remain firmly committed to the vision of *Proto*—to provide information from medicine's leading edge, exploring breakthroughs, dissecting controversies and providing a forum for informed debate. The *Proto* website, protomag.com, will continue to house a rich archive of stories, perspectives and images. And given today's vast and growing need for reputable and trusted medical information, we are assessing what form *Proto* can take going forward to fulfill its promise.

We thank our collaborators at Dotdash Meredith for their enthusiasm, creativity and commitment to the vision and mission of *Proto*. We also salute the MGH *Proto* team as well as the dedicated members of our editorial board for their wisdom, expertise and guidance in shaping each issue. Most important, we extend our deepest gratitude to those who have read *Proto* over the years and provided thoughts and feedback. Producing this magazine has been a labor of love and a true privilege.

DAVID F.M. BROWN, M.D.
President
Massachusetts General Hospital

MARCELA DEL CARMEN, M.D., M.P.H.
President
Massachusetts General Physicians Organization

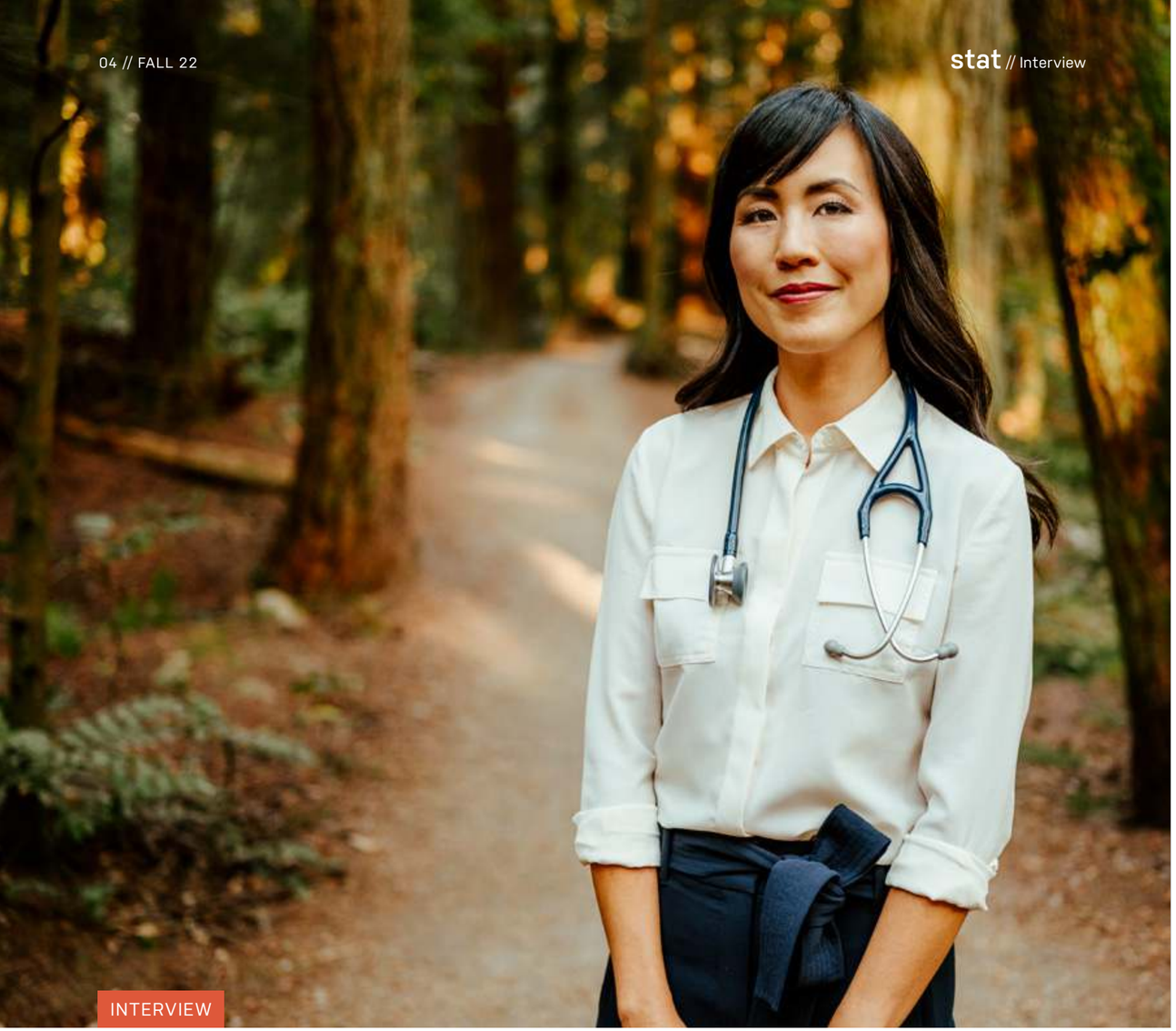
Facebook.com/protomag @ProtoMagazine ProtoEditor@MGH.Harvard.edu

stat

FOCUS

Scientific papers rely on figures—including the graph, butterfly wing and protein diagram pictured here. These particular images, however, allow blind scientists to see data just as well as their sighted peers. The lithophanes can be printed in minutes on a $3,500 printer, with resin that costs less than 50 cents per image. A recent study published in *Science Advances* found that blind participants were able to interpret data from these lithophanes as well as or better than sighted individuals. Blind scientists have, until now, generally relied on braille, screen readers, and tactile models that cannot differentiate the details of many images and datasets. Inventive accommodations such as these are sorely needed. Nearly 9% of graduates awarded doctoral degrees in biomedical sciences report one or more disabilities, according to a 2021 report from the National Science Foundation. Poor workplace accommodations may be one factor in the finding that these scientists are significantly less likely to receive research grants.

VICTOR PRADO



INTERVIEW

The Nature Prescription

Can encounters with nature be healing? Family physician Melissa Lem thinks they should be part of the medical toolkit.

A growing body of evidence suggests that spending time in green spaces can have a range of beneficial effects—improving blood pressure as well as reducing anxiety, depression, rumination and neural activity in brain regions associated with mental illnesses. While the mechanisms are still coming into focus, such findings have, for physicians around the world, sparked interest in prescribing doses of nature.

One leader in "nature prescriptions" is Vancouver physician Melissa Lem, a clinical assistant professor of family practice at the University of British Columbia. She directs Canada's first national nature prescription program, PaRx, which recently partnered with Parks Canada to enable doctors to prescribe national park passes to patients. Since she helped launch the initiative in 2020, the program has attracted some 6,000 physicians—more than 5% of the country's practicing doctors.

OPPOSITE PAGE: KAMIL BIALOUS; THIS PAGE: THE NOUN PROJECT

Q: When did you start thinking about the health benefits of nature?
A: I started "self-medicating" as a child, I think—whenever I felt stressed, I would go to a natural place where I intuitively felt safe. When I moved back to downtown Toronto after working as a rural physician, I experienced nature deficit for the first time. I just felt my stress level increase.

Q: For the patient, what does a nature prescription look like?
A: Based on the latest evidence, our standard recommendation is that patients spend at least two hours a week in nature and at least 20 minutes during each visit. Health care practitioners can then collaborate to refine the prescription based on a patient's interests and abilities as well as what nature is nearby. You can find nature in your community garden, backyard or in a city park. The research shows that patients see health benefits when *they* feel that they've had a meaningful nature expereince.

Q: What's been your own experience prescribing nature to patients?
A: The bulk of patients I would tend to write a formal prescription for are people with mental health concerns. It's usually part of an overall treatment plan; we wouldn't typically withhold medication and prescribe nature first, unless the symptoms are very mild. As with any prescription, the physician should check in and see how patients are doing as time goes on. That provides them with support and also shows them that it's a serious recommendation.

I have to say I was initially a bit nervous about prescribing nature. I thought patients would see me as some out-of-touch, tree-hugging doctor. But every time I've prescribed it, patients nod their heads and say, "You're right, I do feel better when I spend more time outdoors." When a doctor formalizes that in a prescription, patients are more open to doing it. And there's research about exercise prescriptions, showing that when something is written down, it increases a patient's motivation to actually carry it out.

Q: What are the challenges for patients in filling a nature prescription?
A: One is transportation, especially for people who don't live in nature-rich areas. Another issue is time. People are really busy. One good strategy is to substitute outdoor activities for things you typically do indoors. For instance, if you usually go to the gym, do your workout on a trail or in a park. Or if you're going to meet friends at a restaurant, head outside for a picnic instead.

Making people feel comfortable and safe in nature is also important. Some people haven't spent much time outdoors because it's not part of the culture they grew up in. The British Columbia Parks Foundation runs an initiative called Healthy By Nature, which gets marginalized groups out into nature. We're working on expanding this nationwide.

Q: What's next for nature prescriptions?
A: There are currently two national nature prescription initiatives worldwide, one in the United States and one in Canada. Other countries have reached out to us for advice on launching something similar. This is a phenomenon I would love to see spread across the world, because prescribing nature isn't only good for humans, it's good for the planet. Research shows that people who are more connected to nature are more likely to engage in pro-environmental behaviors such as recycling and conserving energy. I like to think that every time I write a nature prescription, I'm doing something for the environment.

BY THE NUMBERS

Emojis

75.2

Percentage of emojis on Weibo—often called "Chinese Twitter"—during January 2020 that indicated feelings of sadness about COVID-19. This transitioned to mixed feelings of sadness (54.5%) and anger (45.5%) by March, according to a study in *Psychological Medicine*.

45

Number of medically related emojis recognized by the world's Unicode Standard. In recent *JAMA* commentary, a team trying to introduce 15 more noted the effectiveness of emojis in patient communication.

95%

Amount of agreement between a pain scale based on emoji faces and a numeric pain scale, based on a study published in the same issue of *JAMA*. Though visual systems already exist, emojis may offer a low-cost and universally familiar alternative.

#771714

Hexadecimal color code for a proposed kidney emoji in an *American Journal of Kidney Diseases* editorial. The accurate color and rich physiological detail will make discussions on the renal system more accessible, say the authors.

300,000

Number of views reported in three days on a post about a new vaccine emoji concept. The flexing bicep with a bandage on the deltoid muscle shows strength and removes the need to show a syringe, according to creators from the Task Force for Global Health. The group's goal is to combat vaccine hesitancy.

INFOGRAPHIC

The 100-Day Vaccine

COVID vaccines happened in record time. Could the next be even more rapid?

BY STEPHEN ORNES

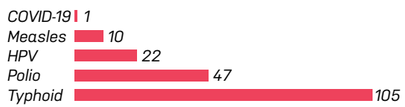
The first vaccine for COVID-19 broke records: Only 342 days passed between the virus being sequenced and an FDA-authorized vaccine. Looking back, researchers now wonder whether it could be done even more quickly.

Speedier vaccine development for COVID would have saved many lives. At 100 days, in April 2020, about 2.3 million people had been infected worldwide. By the time of the first vaccine approval, in December, that number had skyrocketed to 75 million.

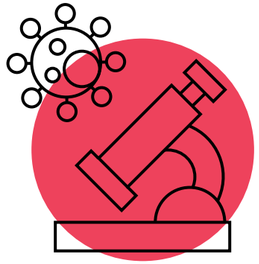
"There's much more we can do," says Melanie Saville, executive director of vaccine research and development at the Coalition for Epidemic Preparedness Innovations, a foundation that focuses on vaccines and other biological countermeasures for epidemic and pandemic diseases. Saville and her colleagues recently published a roundup of ideas showing how streamlining current techniques could shorten the time to only 250 days.

In an emergency, that timeline might be whittled down to just 100 days, as outlined here. "But that has to be in a situation where you have a highly lethal, highly contagious virus," Saville cautions, noting the benefits of a vaccine would have to clearly outweigh increased risks.

Vaccine development times, in years



1 BEFORE



BEFORE THE CLOCK STARTS Rapid response begins before a pandemic with an investment in vaccine technologies and a database of known threats. In the COVID response, years of prior work on viral vector and mRNA vaccine platforms came in handy, as did experience with coronaviruses MERS and SARS.

THE TIME SAVER
A 100-day response would need to supercharge those efforts. Global teams can start building expansive libraries of vaccine prototypes for the 25 or so known viral families, say CEPI researchers. "Some diseases with pandemic potential are already out there," says Saville, and current efforts can begin testing vaccine safety profiles in both animal and human trials.

2

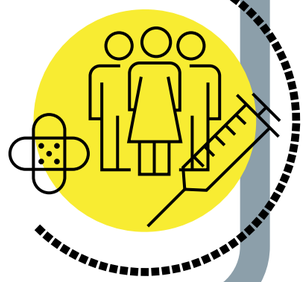
35 DAYS

MAKING THE VAX The first COVID vaccine entered human clinical trials only nine weeks after sequencing. Using the preparation in step one—libraries of pathogenic threats and ready-to-go vaccine platforms—could cut that time almost in half.

THE TIME SAVER
A limiting factor might be the time needed for the biological components of the vaccine to grow. "Ideally you'd have your first batch of material in 30 days, fit to go into humans," says Saville. During this time, researchers can validate and expand preclinical studies. Epidemiologists can predict the most vulnerable areas so that manufacturing facilities are situated conveniently.

3

56 DAYS



CLINICAL TRIALS The fastest COVID vaccine trials took six to seven months—a vast improvement over the historical window of five to seven years. The makers merged some traditional phases of clinical trials and quickly expanded enrollment of trial participants. An even brisker design could cut that window by two-thirds. Immunobridging studies, which use immune response biomarkers as a sign of efficacy, could also move approval forward more quickly.

THE TIME SAVER
Fully merged phase 1 to 3 trials, testing safety and efficacy in one go, could be launched as soon as the vaccine is ready. Adaptive designs that first enroll high-risk patients before expanding to a wider pool of lower-risk patients would enable fast data collection.

4

7 DAYS

APPROVAL In 2019, the U.S. Food and Drug Administration approved Merck's Ebola vaccine in only 15 months. Pfizer-BioNTech's COVID vaccine received emergency use authorization just three weeks after the company submitted data. Vaccine review may be possible in one short week.

THE TIME SAVER
Agencies can review data on a rolling basis. And in advance of a crisis, the establishment of digital benefit-risk models—showing which groups might be authorized to receive a new vaccine at various stages of its rollout—would aid in speedy implementation.

5 AFTER

MANUFACTURING AND ACCESS The key to curbing a pandemic is to get a new vaccine quickly into arms around the world, says Saville. The COVID pandemic exposed faults in the global public health response network. By July 2021, only 1% of people in the world's poorest countries had received a vaccine.

THE TIME SAVER
Saville champions the idea of manufacturing vaccines closer to where outbreaks occur. This is increasingly possible through expanded use of new tech, including mRNA printers and the development of vaccines stable at room temperature. But it will require the collaboration of every nation and the establishment of manufacturing capability in underserved regions.

MSJONESYC

MEDUCATION

I Shall Be True

France is instituting an oath for new scientists. Can it combat fraud?

Starting this fall, new French scientists will be required to take an oath upon receiving their Ph.D.s. They will promise, among other things, to "maintain integrity in my relationship to knowledge, to my methods and to my results." Like the Hippocratic oath sworn by new doctors around the world, the words will not be legally binding. But the French government hopes the oath will nonetheless promote better research ethics.

The move happens in an era when many are pressing for greater integrity in research. A biting 2015 editorial in *The Lancet*, reporting on the reproducibility crisis in biomedicine, maintained that half of the scientific literature "may simply be untrue." Those shaky findings may in part be the result of the pressures on scientific careers, which require a stream of publications in high-impact journals to advance. The pressures to cook results are sometimes irresistible.

More recent scandals—such as a report earlier this year that a seminal Alzheimer's disease paper in *Nature* contained a doctored image—show that the problem exists at all levels of the profession. The consequences can be dire. More than 260 COVID-related papers have been retracted since the start of the pandemic, many for blatant acts of fraud. A third of the studies on ivermectin, for instance, contained mistakes or falsifications.

The idea of an oath to keep scientists on the straight and narrow is not new—philosopher Karl Popper proposed such an oath in 1968. It remains to be seen whether it will have the intended effect.

CSA IMAGES/GETTY IMAGES

UPDATE

Mind the Children

To reduce burnout and retain staff, should hospitals embrace on-site childcare?

BY HANNAH THOMASY

The past few years have been a time of intense stress for many health care workers, and the effects are beginning to show: 40% of nurses and nearly 25% of physicians surveyed have said they expect to leave their practice within the next two years ("I Quit," Summer 2022). Although the causes of burnout are complex, childcare is a frequent worry. Could better options help turn the tide for some?

The question predates the COVID-19 crisis. In one pre-pandemic study, medical center employees who were parents of young children reported that finding and retaining childcare was their biggest source of stress. Another survey found that more than 60% of residents and fellows with children had difficulty arranging childcare.

Rachel Apple, an internist and pediatrician at Vanderbilt University Medical Center in Nashville and lead author of the first study, says she wasn't surprised. "In my own experience, I can't go to work if my children are not safely cared for," Apple says. "So this is something I think about on a daily basis."

The situation got worse during the pandemic, with one study finding that stress about childcare affected more than 20% of *all* health care workers, including some who didn't have children. Worries about childcare were associated with an increased risk of anxiety or depression, burnout and intent to resign.

Elizabeth Harry, an internal medicine specialist, senior medical director of well-being at UCHealth in California and lead author of that study, says that typical childcare arrangements may not be adequate for many in health care. "Our profession cares for people around the clock," she says. "We may need childcare at atypical hours."

Having childcare at work may be one potential solution. Apple's pre-pandemic study found that having children in institution-affiliated childcare reduced employees' childcare-related stress and overall stress levels. And a growing number of hospitals and universities are taking heed. Wellstar Kennestone Hospital in Georgia built a 17-classroom childcare center that also provides care for mildly sick children. Mass General Brigham, which already offered childcare, expanded those services during the pandemic. Many other medical centers, including Stanford University and Vanderbilt University, offer childcare on-site.

"Many more hospitals now want to do on-premises childcare," says Priya Krishnan, chief client and experience officer at the childcare company Bright Horizons. "Conversations about establishing care have increased multifold for us in the past year and a half."

Yet having a place for children at work is still far from the norm at medical centers. According to an Association of American Medical Colleges report, fewer than half of responding institutions provided childcare options prior to the pandemic, and of these, only about 60% had expanded childcare options since the start of the pandemic.

Even when on-site childcare exists, many employees aren't able to use it. About 20% of health center-affiliated childcare locations had waitlists of more than a year, and some are even longer. At the University of Washington, the wait for infant spots can be as long as three years, for example.

Cost is also a major factor. Infant care at academic health care centers is commonly between $200 and $400 per week, while nurses and residents, on average, make about $1,500 and $1,200 per week, respectively.

Despite such barriers, however, offering convenient and affordable childcare not only helps reduce stress for those who have access, but also helps hospitals and other medical facilities attract and retain diverse groups of workers. Providing that core benefit may be a strong draw for women and people of color. Multiple studies have shown that female physicians have more childcare responsibilities than male physicians, and childcare stress is more prevalent in health care workers who are racial minorities.

"If we say we want a diverse workforce, but can't relieve childcare stress for groups that disproportionately experience it, then the system is perpetuating inequities," says Harry. "We need to look at the policies that drive some of these inequities. In this sense, childcare couldn't be more important."

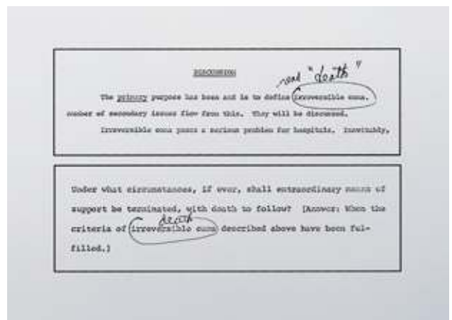
MILESTONE

Living and Dying

The 1968 Harvard criteria for brain death face new inquiries.

BY HANNAH THOMASY

The 1960s were a time to question everything, and in medicine, this included the definition of death. "From ancient times down to the recent past it was clear that, when the respiration and heart stopped, the brain would die in a few minutes," wrote anesthesiologist and medical ethicist Henry Beecher in 1968. But by the time of his writing, things had become much less clear.


DISCUSSION

The primary purpose has been and is to define irreversible coma. Under what circumstances, if ever, shall extraordinary means of support be terminated, with death to follow? [Answer: When the criteria of irreversible coma described above have been fulfilled.]

PHOTO BY DAN SAELINGER

THE HARVARD MEDICAL LIBRARY IN THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE, BOSTON

Beecher, who practiced at Massachusetts General Hospital, had gained the national spotlight for his 1966 paper "Ethics and Clinical Research." It outlined almost two dozen cases in which subjects of medical experiments had been put in grave danger. The paper became a landmark and led to the creation of review boards that would oversee all human experiments.

The task facing Beecher in 1968 was, if possible, even more fraught. Recent advances had dramatically changed the possibilities at then end of life. Improvements in supportive care—especially mechanical ventilation—meant that patients could have their hearts beat indefinitely, "alive" in some new sense of the word, even when their brains were catastrophically damaged.

Making the issue more pressing, organ transplantation capabilities were improving, with the first heart transplant performed a year earlier in South Africa. While physicians were careful not to conflate the two frontiers, a clear indication of when patients had no hope of brain recovery—or were "hopelessly unconscious"—might allow harvesting their organs in an ethical way for patients in need.

To define a permanently nonfunctioning brain, an ad hoc group of men, most with affiliations at Harvard University, was assembled. The group included several neurologists and a transplant physician as well as a lawyer, an ethicist and a public health scholar. Their "Harvard Criteria" outlined the medical characteristics of so-called brain death.

Although mental unresponsiveness was a controversial way to define death at the time, public and legal opinion gradually shifted to accept it. This was cemented in 1981 with the Uniform Determination of Death Act, which established that brain death was accepted as legal death throughout the country.

This statute has held firm, although ethical debates have continued, and one state, New Jersey, allows religious exemptions in defining death. It remains to be seen what will happen as new medical frontiers blur once-established lines.

This past summer, a team at Yale University was able to initiate activity in the brain, heart and kidney cells of a pig an hour after the animal had died. Because of the profound ethical implications of reversing brain death, the researchers used nerve blockers to forestall the possibility. But as medicine progresses, it is perhaps only a matter of time before the lines between life and death must once again be redrawn.

POLICY

The Medic Reinvented

Can medical AI on the battlefield make sound decisions about who lives or dies?

BY ADAM BLUESTEIN

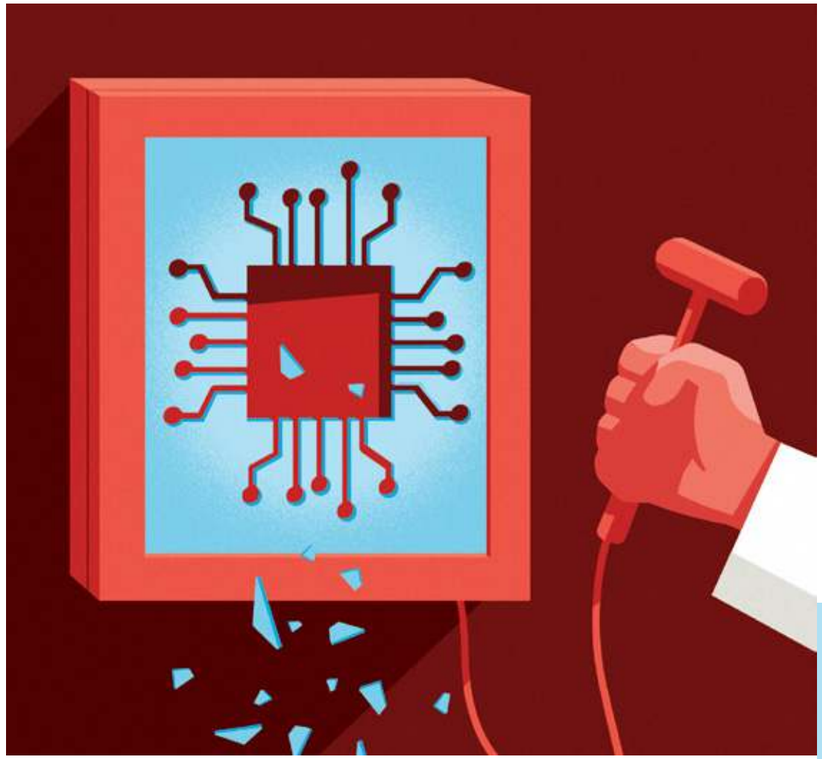


ILLUSTRATION BY CHRIS GASH

In the fog of war, medical decisions come quick and hot. Someone must be on hand to assess injuries and make rapid decisions about who to treat and in what order, who should be evacuated and—in worst-case scenarios—who can't be saved. Could the best person for this job be an autonomous artificial intelligence?

DARPA—the U.S. military's research and development arm—recently called on experts in industry and academia to collaborate on a new decision-making tool that is "human off the loop"—in other words, completely autonomous. The In the Moment (ITM) project will focus first on small-unit battlefield triage but then will also aim to manage mass-casualty events.

The goal for ITM is to examine "foundational questions" about this type of technology, including how to build an algorithm that humans can learn to trust with decisions of life and death, according to program manager Matt Turek. "We picked triage because it's challenging," he says. "It forces us to deal with difficult decisions, where humans often disagree about the right approach."

A central requirement will be to demonstrate that a system reliably produces "right" answers, in which algorithms' answers compare favorably to those of human decision-makers. But there is also an opportunity for deeper questions. "Subject matter experts are going to disagree," says Turek. So determining which humans should serve as models, and why, becomes a research frontier. "Studies have shown that when people evaluate which humans to trust, integrity and perceived benevolence are essential," says Turek. Can such qualities be embedded into a machine?

> Triage is a task machine learning is well suited to.

The trust riddle aside, the In the Moment AIs must also reliably assess health and possible outcomes for a range of wounded soldiers. In that regard, many solutions will most likely build on existing health care projects. Autonomous risk prediction has been under development for more than a decade, says Michael R. Pinsky, a professor of critical care medicine at the University of Pittsburgh School of Medicine and a senior advisor in its Center for Military Medicine Research. Pinsky is a principal investigator and co-investigator in multiple federally funded projects developing tools that can foresee health outcomes in acute-care settings with startling clarity.

Triage is a form of prediction based on a body of previous data, which is a task machine learning is very well suited to, Pinsky says. A project looking at emergency department patients who go into cardiac arrest, for instance, would explore medical records to find clear patterns. One current project, which uses only heart rate and other vital signs to predict which ER patients will remain stable, is right 80% of the time. "That's better than you can do with any human method," says Pinsky.

A collaboration among Massachusetts General Hospital, MIT and Leiden University Medical Center in the Netherlands has produced another proof-of-concept tool in autonomous triage. Trained on a database of patients with gunshot wounds, the AI can assess a new shooting victim, accurately identify whether that person might soon go into shock and predict the need for massive transfusions or major surgery with a "high degree of certainty."

But not all AI tools are transparent in how they make decisions. Many are "black boxes"—that is, the logic of their predictions can't be explained in a way that humans will understand. That might be all right for some uses, says Sara Gerke, assistant professor of law at Penn State Dickinson Law, who studies ethical and legal issues in health care AI. But for decisions about organ transplants or in traumatic injury triage—in which one person might have to die so that another can live—"you really want to have an interpretable model," Gerke says.

If such a triage tool is to be eventually rolled out to military teams, the ethical groundwork must be rock solid, she says. Research shows that "automation bias"—in which humans just follow what AI wants them to do—can be particularly common in emergency situations. Even if DARPA does its job, however, and the battlefield triage tool proves able to come up with reliable answers, the military will need to contend with weighty questions involving implementation. "For instance, if you use this tool, are you required to follow its decisions, even if you don't agree with them?" asks Gerke.

Turek acknowledges that the ITM project is full of such "cross-disciplinary challenges." He hopes it will bring together perspectives from both the Department of Defense and civilians of many stripes. Submissions are currently under review, and Turek expects to offer contracts to winning teams for work that will begin in early 2023. But ITM performing teams will have the opportunity to publish their research without any restrictions. "We can't fund a lot of teams, but we want to share results with a large research community," he says.

SECOND OPINION

A Time to Catch Up

The article "Where Psychedelic Research Goes Next" provides an informative synthesis of the rapidly developing field investigating currently illicit psychedelic drugs for therapeutic potential. After years of dormancy, the science is still catching up to elucidate just how psychedelic therapies can be used and how they work.

For now, a great deal of uncertainty remains around the directions in which this new psychedelic renaissance might take us. For many patients, psychedelics may lead to new and powerful forms of therapy that could accelerate the path toward recovery. However, it is critical to highlight they are not a panacea or miracle cure and will not work for everyone nor ameliorate the urgent sociocultural crises we now face. For scientists, psychedelics provide a fascinating tool for better understanding not only the mind and brain, but probing long-standing philosophical issues like the nature of creativity, spirituality and consciousness. For the broader public, my hope is that wider access to psychedelics could lead many to a renewed sense of meaning and purpose, reinvigorate collaborative efforts to better society and help move us collectively toward the possibility of a world reimagined.

Albert Garcia-Romeu, Ph.D. // Center for Psychedelic and Consciousness Research, Johns Hopkins University School of Medicine

Beyond Duality

The article "Where Psychedelic Research Goes Next" provides a timely overview of serious academic research into the effects of psychedelic drugs. Working with psychedelics forces clinical researchers into realms that are, for many, outside of their medical-model comfort zone, like dealing with philosophical issues of the mind-body relationship. Intuitive "folk psychology" is inherently dualist; it takes hard work to avoid the intuition that brain processes and mental processes unfold on separate planes. This tendency feeds the question, prominent in the field, of whether psychedelic effects are "just" pharmacological effects or whether psychological processes are critical for therapeutic benefit.

The fact that therapeutic change is associated with biological processes does not make the accompanying psychological phenomena any less remarkable. And the observation that self-reported psychedelic experiences predict therapeutic improvement does not make neurobiological effects irrelevant or uninteresting. Rather, these fascinating associations across levels of analysis give us a glimpse into connections between brain and mind, and a new opportunity to understand them.

Christopher Pettinger, M.D., Ph.D. // Deputy Chair for Translational Research, Department of Psychiatry, Yale University School of Medicine

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

Be Nice

ACTS OF RUDENESS ARE ON THE RISE IN MEDICINE. CAN A CIVILITY PUSH LEAD TO A HEALTHIER WORKPLACE?

It seemed like a minor incident. Peckish between cases, a top physician at a major health system grabbed an apple from a table in the hospital's breakroom. But to the nurse who expected to eat the fruit, this was one insult too many. "Dr. Smith" often did things to rub people the wrong way. He was routinely condescending and once barked at a nurse, in front of a patient, to stop asking stupid questions. So this time, the owner of the pilfered apple filed a formal complaint.

Smith thought what he'd done was trivial. Yet the nurse's choice to escalate the encounter—a matter for the hospital's review and possible censure—is emblematic of a turning point in attitudes toward the much larger problem of small indignities, a souring of good behavior among doctors, nurses and other health care workers. The problem of incivility is pervasive and can compromise performance and safety. "We're here to take care of people, and we forget to take care of each other," says Linda Groah, a nurse and chief executive officer of the Association of periOperative Registered Nurses (AORN), one of several national nursing organizations working to raise awareness of the problem.

In many walks of life, rudeness is on the rise. Anger and toxicity are hallmarks of social media platforms. Research shows that rude behavior spreads like a virus, not only through people who experience it but also through those who witness it, and recent polls suggest most Americans believe incivility has risen to crisis levels. It's a particular problem in the workplace, where three out of four employees report they experience rudeness on the job at least once a week.

But health care may be a hot zone for bad behavior, with verbal abuse and physical threats from colleagues and patients, ratcheted up during the COVID-19 pandemic, now at record highs. Small-scale irritants—eye-rolling, demeaning comments, gossip and a lack of cooperation—contribute to a general climate of disrespect and can lead to angry outbursts, verbal abuse and bullying. Soon, behavior may escalate to a

By **LINDA KESLAR** + Illustrations by **GARY TAXALI**

level where it has legal consequences, with formal complaints for harassment, discrimination and even physical violence. Last May, a female surgeon filed a lawsuit accusing NewYork-Presbyterian/Columbia University Irving Medical Center of tolerating a "toxic culture of gender discrimination."

Incivility within medical teams can have dire results for other workers as well as patients. It may take the focus away from essential tasks, leading to medical errors and substandard care. It also drives employees to leave their jobs during these days of rampant workforce turnover. "Now people across medicine have changing expectations about civility and improving how we should be treated," says Jo Shapiro, associate professor of otolaryngology–head and neck surgery at Harvard Medical School. But reforming ingrained patterns of behavior, one colleague at a time, won't happen quickly.

The word civility is derived from *civilis*, Latin for "the state of being a citizen." Daniel Buccino, assistant professor in the department of psychiatry and behavioral sciences at Johns Hopkins Medicine in Baltimore, describes it as an essential part of the social contract, a "benevolent awareness, a sense of respect for oneself and others."

Buccino heads the Johns Hopkins Civility Initiative, founded in 1997 by the late P.M. Forni, a professor of early Italian literature and author of *Choosing Civility: The Twenty-Five Rules of Considerate Conduct*. For more than two decades, the initiative has been researching the place of civility in society and has sought to encourage its practice. Yet although the idea of civility continues to resonate, Buccino says, in practice it has been on the decline for many years. "There's so much more emphasis on individualistic pursuits and success than on what we might achieve collectively," he says. Add the stress of the pandemic and the anonymity of the internet, and the erosion of kindness and consideration seems inevitable. "The prevalence of incivility and disrespect in the workplace has spiked," says Christine Porath, associate professor at Georgetown University's McDonough School of Business, who has studied uncivil behavior in nearly two dozen industries, including health care.

In Porath's research, health care ranks as one of the least civil industries, with its unique stresses triggering unkind and disruptive behavior. Moreover, medicine has long been built around a rigid, male-dominated hierarchy that tolerates brusque behavior from the physicians on top—at the expense of those who aren't male and aren't doctors. "The culture of uncivil behavior in health care didn't happen by mistake," says Stephen Paskoff, chief executive officer of Employment Learning Innovations, an Atlanta consulting firm that helps organizations create civil environments.

"This is a health care culture in which mentors traditionally abuse trainees on every level," says Kit Bredimus, chief nursing officer at Midland Memorial Hospital, a teaching hospital in West Texas. "The old methodology was 'tear you down to build you up.'" But many younger students and

trainees now refuse to accept that approach. Younger surgical nurses, says AORN's Linda Groah, show little tolerance toward the behavior their older peers have endured, and many are choosing the exit door. "They can't believe the things mentors have told them they may have to put up with," she says. "Their response is, 'No, I don't.'"

Many physicians, lulled by an abusive status quo, don't even realize they're part of the problem. "A surgeon told me recently that until he received some very frank feedback, he had no idea most people thought he was a jerk," says Porath. "He was treating residents the way he'd been trained." There's also a persistent star system in medicine, in which the bad behavior of rainmakers is tolerated. "Physicians who are big revenue generators are given a pass when it comes to offensive behavior," says an internist at a Pennsylvania hospital.

In national surveys conducted in 2003, 2013 and last year, the Institute for Safe Medical Practices asked health workers about disrespectful behavior and workplace intimidation. Respondents through the years have cited incidents of being demeaned by fellow workers. But in the more recent surveys, workers have noted a rising proportion of insults targeting race, religion and gender, and they've reported more and more disrespect happening online, through emails and in virtual meetings. Reports of physical assaults have also doubled since 2013.

A 2022 Medscape survey of 1,500 physicians found that more than 80% said they had witnessed bullying and harassment by other doctors. Offenders were mostly male and in their 40s, and respondents identified oversized egos as a frequent source of trouble. But this awareness of the problem went only so far, with 85% of those surveyed saying their own conduct hadn't contributed to the problem.

Emerging statistics about burgeoning workplace incivility almost certainly understate the problem because so much bad behavior goes unreported. "We encourage people to report incidents of rudeness and bullying, but even today there exists a power gradient that often prevents reporting," says Diane Colgan, a physician at Johns Hopkins Medicine-Suburban Hospital in Bethesda.

Incivility within medical teams can have dire results for other workers as well as patients.

Physicians also tend to resist reporting their colleagues, she says, "no matter how egregious their behavior may be."

Long-standing efforts to address workplace violence and other high-level behavioral problems are now being adapted to encompass rudeness. For example, The Joint Commission, an accrediting organization, last year updated 15-year-old requirements for hospitals to now include a broader definition of workplace violence that encompasses any disruptive or potentially harmful behavior, including verbal aggression and attempts to humiliate, sabotage or intimidate fellow workers.

Rudeness, often thought to be at the bottom of the scale of bad behavior, is increasingly being studied for the harm it can cause. A 2015 study published in *Pediatrics* showed how rudeness may sabotage cognitive processing and weaken team collaboration. It's a pervasive issue in perioperative care, and in one survey, 98% of clinicians said they had witnessed disruptive behavior in the past year, which in a 2019 study in *BMJ Quality & Safety* was found to interfere with clinical performance. In a trial that included dozens of surgical teams at multiple institutions, anesthesiology residents exposed to rudeness showed decreased vigilance, communication and teamwork, and scored lower on every measure compared to simulations in which a surgeon was polite.

Other research suggests rudeness can amplify "anchoring bias," the tendency to base decisions solely on the first piece of information received in a situation. Prior analyses have shown that anchoring is by far the most common cognitive error in medical diagnoses, and a study last year in the *Journal of Applied Psychology* showed that anesthesiology residents interrupted by rudeness from another physician were more likely to stick to an initial, anchored diagnosis, ignoring evidence that it was wrong.

Several doctor and nursing groups are now trying to raise the bar on civil behavior. Last March, the American College of Cardiology (ACC) issued a policy document on building respect, civility and inclusion in the cardiovascular workplace, and in October 2021 AORN and two other nursing organizations—the American Association of Nurse Anesthesiology and American Society of PeriAnesthesia Nurses—released a position statement on the need for workplace civility. Both documents urged health care organizations to adopt comprehensive policies. The ACC wants to see better awareness of the importance and prevalence of incivility, as well as clear repercussions for physicians and others who fall short. And although the problems of sexual harassment, discrimination and bullying are priorities for the group, the need to address more subtle forms of disrespectful behavior also became apparent during the project's nearly two-year development, says Pamela Douglas, a cardiologist and professor of medicine at Duke University School of Medicine who helped write the document.

One institutional response to growing incivility is to make it easier to report. More than 180 U.S. health care systems (and dozens outside the country) have adopted the Co-Worker Observation Reporting System. Developed by Vanderbilt University's Center for Patient and Professional Advocacy (CPPA), the program compiles complaints electronically, processes the data and sends back reports to participating institutions. It has accrued data on some 100,000 physicians and advanced practice professionals, says Gerald Hickson, a physician and a founder of the CPPA. Complaints have been made against doctors of all ages, and 93% of reports involve acts of disrespect rather than bullying, sexual harassment or physical threats.

In a model developed by CPPA, consequences increase as the number of reported incidents rises. The actions of Dr. Smith, who stole the apple, are described in a paper published in *The Joint Commission Journal on Quality and Patient Safety*. Following CPPA guidelines, Smith was notified of the nurse's complaint and invited to discuss the incident over a cup of coffee with a trained physician mentor. Normally, the coffee meet-up is sufficient, Hickson says. But a fraction of offenders tend to account for a large number of complaints, and their misconduct may require escalating interventions. Smith was also required to have a performance evaluation, including a physical and mental health assessment, and his service chief met with him monthly to monitor his performance and see whether he needed additional support, such as coaching, or even disciplinary action.

"This wasn't just about a pilfered apple, but rather one of many signals of a human in trouble," Hickson says. Sometimes bad behavior is triggered by a heavy workload or other situational factors, but it can often be traced to personal issues, such as addiction, family problems or an inability to handle stress. "The goal of our work is to maximize the probability that the people having trouble can receive support, treatment or whatever else may be needed to help them remain as a productive part of a medical team."

But sometimes behavior remains toxic, and hospital leaders need to rethink their tolerance even for star performers. As hospitals implement escalating interventions, habitual offenders will sometimes be fired or leave. But even then, about a fifth of the time, a fired physician will show up at another CPPA partner hospital and again appear in the reporting system. "We see people go from site to site and create problems in the new environment," Hickson says.

Some health systems are now rolling out campaigns that emphasize civil behavior as an organizational priority. But tackling incivility requires a sustained commitment, says Stephen Paskoff of Employment Learning Innovations. "The problem isn't a lack of policies and rules—everyone has those," he says. The challenge is implementation.

At Texas's Midland Memorial Health, that has meant taking the long view in a campaign now in its eighth year. The facility has implemented a checklist of strategies to improve working relationships. These include a new mission statement and an employee pledge to refrain from complaining, bullying, gossiping and engaging in other toxic emotional behaviors.

The pledge is displayed on posters throughout the hospital, along with a "Civil Proclamation" declaring that incivility and a list of other disruptive behaviors won't be tolerated. All 2,200 employees have been required to complete one or two days of training.

Although the pandemic brought an uptick in disruptive incidents, the civility initiative seems to be helping, says chief nursing officer Kit Bredimus. "Part of our push has been to get employees to bring up these issues, document them and know that we are actually addressing them," he says. The results of employee surveys have been largely positive, he says, and Midland Memorial is the only hospital in its West Texas area that hasn't had to resort to sign-up bonuses to draw in potential nurses in a highly competitive market.

In 2016, at UMass Memorial Health, the largest health system in central Massachusetts, the results of an employee engagement survey made clear that many of the staff didn't feel respected. A grassroots group of clinicians and staff then pushed for changes that eventually spread to the system's two other community hospitals and to multiple clinics. More than 5,000 employees participated in a survey about respect, which in turn served as raw data for a civility campaign. It was based around what organizers dubbed the six standards of respect, which include listening, being kind, being responsive and being a team player.

The health system's leaders used the six standards as a starting point for a system-wide overhaul. It included rewriting the employee code of conduct and launching training workshops for the system's 17,000 employees. Now, a manager feedback program gives employees a tool to suggest how managers can improve how they demonstrate respect, and UMass Memorial is updating its workplace violence reporting system. "We still have a way to go, but we're doing a much better job of addressing disruptive behaviors," says Tod Wiesman, UMass Memorial interim chief human resources officer. So far, the campaign has led to higher scores on patient satisfaction and employee engagement survey items about respect.

In 2019, MGH launched a program called Know the Line to prevent abusive workplace conduct, and the program has since been adopted across the Mass General Brigham system, providing a common language and approach for all organizations. Know the Line attempts to standardize training, content and reporting for culture and behavior, says Christine Pierga, vice president, employee relations and labor strategy. "We wanted something comprehensive to address the climate of the organization in a way that was educational and supportive, and not primarily disciplinary," Pierga says. "We want people to have a way to interact with each other in a less confrontational way. We want to create an opportunity for a pause or a reflection when someone's behavior doesn't conform to expectations, a moment that can lead the conversation in a better direction."

Sometimes behavior remains toxic, and hospital leaders need to rethink their tolerance even for star performers.

People can learn civility on the job, says Georgetown's Christine Porath, and the benefits are clear. Her research shows that employees considered to be civil were more likely to be consulted for information and twice as likely to be seen as leaders, and nearly three out of four survey respondents said they would work harder for someone who treated them with respect. Organizations that have reformed their policies have begun to move the needle. "The number one thing that people seem to want is the sense of feeling valued," she says. "They want respect."

DOSSIER

***Mastering Civility: A Manifesto for the Workplace*, by Christine Porath, Balance, 2016.** Porath's rigorous research shows what incivility is costing leaders and organizations and offers practical suggestions for building a more productive work culture.

"2022 American College of Cardiology Health Policy Statement on Building Respect, Civility and Inclusion in the Cardiovascular Workplace," by Pamela S. Douglas et al., *Journal of the American College of Cardiology*, May 2022. A comprehensive report on the range and consequences of uncivil behaviors in the cardiovascular workplace, as well as strategies for improvement.

PROP STYLING BY ARIANA SALVATO

PRESCRIPTION: THIN

WEIGHT LOSS STRATEGIES HAVE ALWAYS PUT DIET AND EXERCISE CENTER STAGE. CAN TWO NEW DRUGS CHANGE THE MEDICAL MINDSET ABOUT OBESITY?

By **Anita Slomski**
Photographs by **Jamie Chung**

Sarah's story is familiar in a country where more than 40% of adults and a fifth of children have obesity. At school, she was bullied for her weight and, starting in her teens, dreaded getting weighed by doctors because they were always critical. At age 26, she had bariatric surgery—yet after dropping 80 pounds, her weight returned. Year after year passed with cycles of strict dieting and trials of various anti-obesity medications. "The weight always came back," says Sarah, who asks that her real name not be used.

Last fall, Sarah's care team, including obesity specialist Fatima Cody Stanford, a physician at Massachusetts General Hospital's Weight Center, recommended that Sarah try a new drug, semaglutide. "I knew within the first week that it was going to work," says Sarah, now 46. "Without trying, I was eating less than what I normally did, but I didn't feel hungry or deprived." Within a year, she had lost 63 pounds. And although only time will tell whether the weight stays off, for now she feels as if "the battle is over" and she can get on with her life.

Treating people with anti-obesity drugs isn't new. Historically, however, most indicated medications have proved ineffective, dangerous or both—between 1964 and 2009, 25 of these compounds were withdrawn from the U.S. market because of serious side effects, including psychiatric problems, cardiotoxicity, and drug misuse and dependence. Bariatric surgery works better, but the screening requirements can be prohibitive, most people don't want it and weight loss after the procedure isn't always permanent.

New treatment semaglutide—approved in 2017 by the U.S. Food and Drug Administration to treat type 2 diabetes and in 2021 for weight loss—and a second drug, tirzepatide, which received the Fast Track designation from the FDA for obesity treatment this past October, could improve on that record dramatically. Like most anti-obesity drugs, they target parts of the brain that control appetite. These medications get there in a novel way, mimicking naturally occurring hormones to help prevent overeating. In recent studies, patients taking semaglutide lost an average of about 15% of their total weight, and those taking tirzepatide for diabetes reported losing 15% to 21%.

"After years and years of trying, we can finally replicate the efficacy of bariatric surgery with medication," says Louis Aronne, director of the Comprehensive Weight Control Center at Weill Cornell Medicine in New York City and an investigator on the tirzepatide trial. Yet optimism for a safe, attractive treatment for obesity—a condition that is estimated to cost the United States nearly $200 billion annually and underlies rising rates of heart disease, diabetes, cancer and many other conditions—is tempered by the barriers these new drugs face.

Although better tolerated than their predecessors, semaglutide and tirzepatide can have significant side effects. Both need to be taken forever. Most pressingly, they are covered by only a handful of health insurance plans, and semaglutide's $1,557-per-month cost is well beyond most household budgets. For these and other reasons, most physicians have been reluctant to prescribe anti-obesity drugs of the current or past generations. According to Stanford, only 1% of patients with obesity received a prescription for obesity management drugs from 2011 to 2016, in part because of the drugs' price.

Moreover, obesity specialists note a persistent knowledge gap about how best to treat the condition. "Many physicians still believe that people with obesity need to eat less and exercise more, which is completely wrong," says Stanford, who notes that it wasn't until 2013 that the American Medical Association finally recognized obesity as a chronic disease.

"Obesity is where diabetes was 30 years ago, when clinicians would tell patients to stop eating sugar," says W. Timothy Garvey, director of the Diabetes Research Center and senior scientist at the Nutrition Obesity Research Center at the University of Alabama at Birmingham. "Many physicians don't believe that obesity should be treated medically, so they blame the patient for overeating and not exercising. In turn, patients blame themselves."

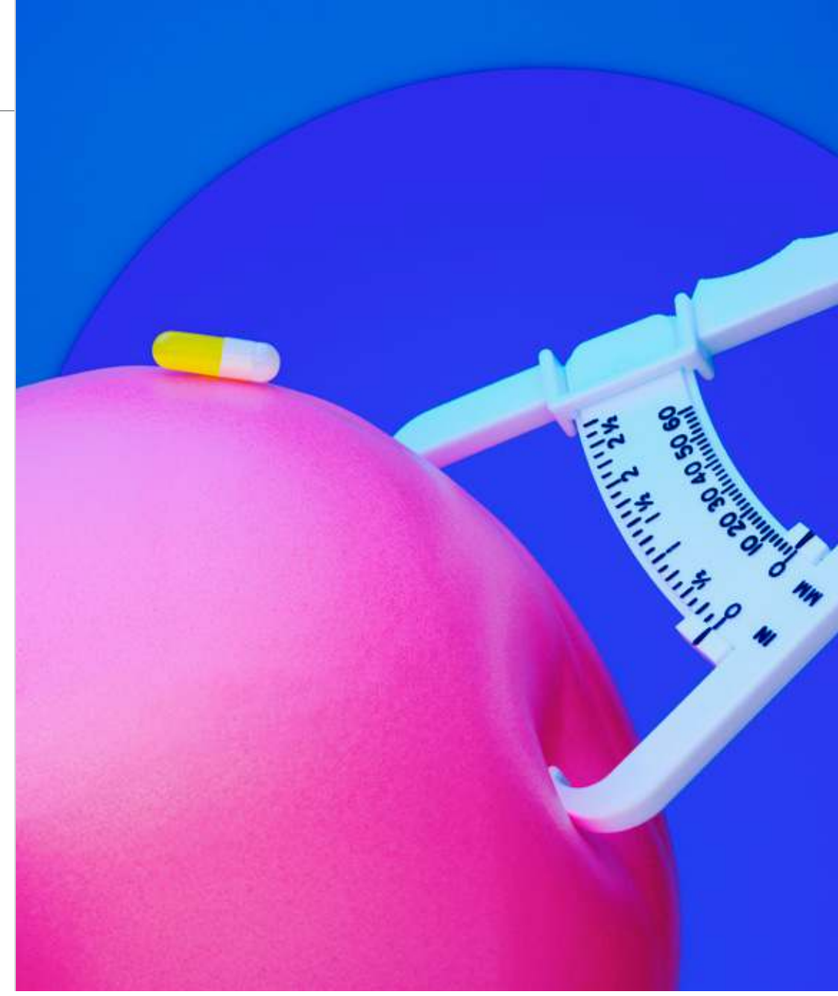
"WE CAN FINALLY REPLICATE THE EFFICACY OF BARIATRIC SURGERY WITH MEDICATION."

Losing weight through diet and exercise—and keeping the weight off—can be next to impossible for some people with obesity. According to a theory accepted in many quarters, the body has a defended fat mass set point—a fat mass that the brain, hormones and metabolism "want" that person to have. The basic equation for losing weight—to expend more calories than you take in—can indeed lead to significant weight reduction. Yet because the body's fat mass set point doesn't recalibrate to the lower weight, body and brain connive to regain the lost pounds.

Environmental as well as genetic factors affect fat mass set point. Today most Americans have a fat mass set point that's higher than ever before, thanks to a combination of pressures. These include readily available, highly processed foods; chronic sleep deprivation; an increase in stress levels; less need for physical activity; and social lives that revolve around food. Nearly three-quarters of the U.S. population is now considered to be overweight or to have obesity.

People with obesity can also have the additional problem of a siren's chorus of hormones being released from the gastrointestinal tract when they eat, nudging the pounds back on. "When people with obesity lose weight, there's an increase in hormones that make you eat more, while the hormones that make you eat less go down," says Stanford. "The combined effect is that the brain is driving you back to a certain equilibrium of body fat mass—and that equilibrium is set much higher in people with obesity."

Brain inflammation may also help explain why people with obesity have abnormally high fat mass set points. "Adults don't grow additional fat cells," says W. Scott Butsch, director of obesity medicine in the Bariatric and Metabolic Institute at the Cleveland Clinic. "Rather, their existing fat cells expand when they gain weight and contract when they lose it." When a fat cell expands, that increases inflammation in the body and, in some studies, in the hypothalamus, which centrally controls body weight. The chronic low-grade inflammation may disrupt the brain architecture that regulates the body fat mass set point.



Genetics also plays a major role. "If your parents have obesity, there is a 50% to 85% likelihood that you will too, regardless of your diet quality, activity level and stress management," says Stanford.

What obesity is not, however, is a behavioral disorder. "Just as people with diabetes cannot will their blood sugars to be normal, people with obesity cannot will their bodies to carry less fat," says Ania Jastreboff, director of weight management and obesity prevention at Yale Stress Center and lead investigator of the tirzepatide trial. Yet this attitude of weight loss as a matter of will has pervaded culture and the thinking of many physicians.

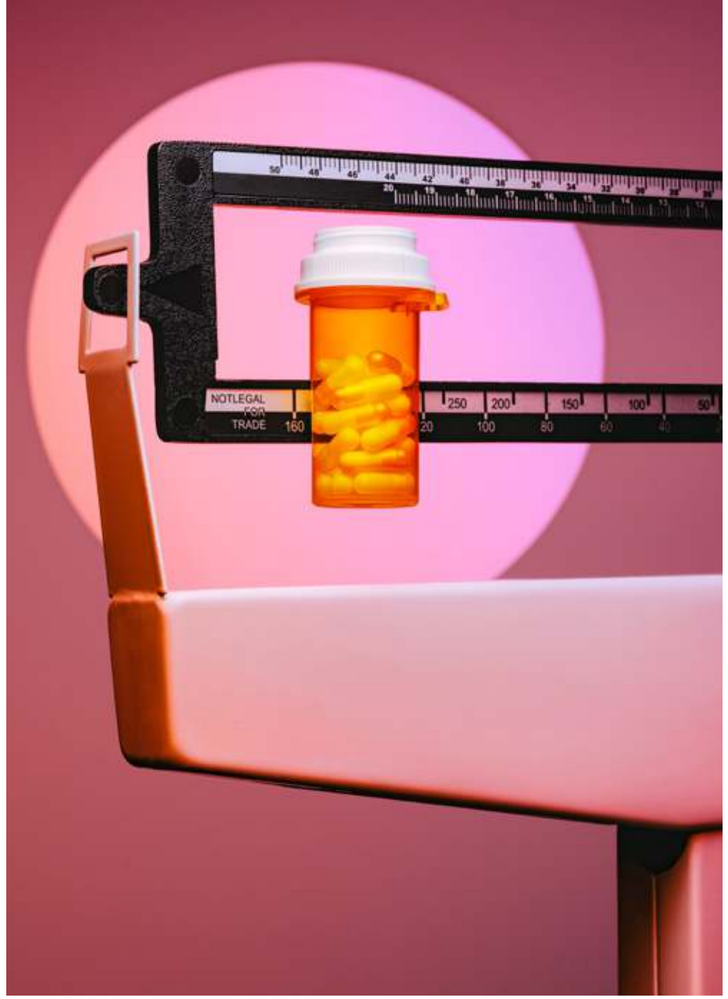
Earlier anti-obesity drugs did little to inspire confidence that obesity could be successfully treated—or that medical treatment was appropriate. Over many decades, more and more such medications were withdrawn from the market for safety reasons, which only reinforced clinicians' bias that overeating and personal behavior were the real problem, says Butsch.

One of the first weight-loss drugs was phentermine, approved in 1959 by the FDA, which continues to be the most widely prescribed drug to treat obesity. Phentermine is thought to suppress appetite by increasing the levels of the neurotransmitter norepinephrine in the hypothalamus. But it's indicated only for short-term use—no more than three months—because if taken for longer periods and at higher doses, it can cause anxiety, rapid heart rate and high blood pressure.

In 1973, fenfluramine was introduced as an anti-obesity drug, and for years it was paired with phentermine to create the wildly popular fen-phen, a cocktail that produced substantial weight loss. But fenfluramine, too, was approved only for short-term use, and it was withdrawn in 1997 after it was found to stimulate the growth of muscle cells in the heart, leading to heart-valve damage and pulmonary hypertension. Another appetite-suppressing drug, sibutramine, was also associated with major cardiovascular problems, including stroke and heart attack, and was taken off the market in 2010. The most recent anti-obesity drug to be withdrawn was lorcaserin, pulled in 2020 because of cancer risks.

It wasn't until 2012 that reasonably safe, effective anti-obesity drugs came on the market. People who took Qsymia, a combination of phentermine and the migraine medication topiramate, lost an average of 8% to 10% of their body weight. Contrave, which combines naltrexone, used to treat alcohol and opioid dependency, and bupropion, an antidepressant and smoking-cessation drug, results in an average loss of 5% to 7% of body weight.

The new drugs, semaglutide and tirzepatide, contain a glucagon-like peptide-1 (GLP-1) receptor agonist, which mimics a hormone secreted in the intestines during eating that signals when a person is full and should stop eating. The GLP-1 receptor agonists reinforce that signal and help suppress appetite in people with obesity. "We think these medications help the brain reset the defended fat mass set point, resulting in people eating less," says Jastreboff. "Often, they feel full earlier and don't go back for seconds."



Tirzepatide also targets a second receptor with another human gut hormone—glucose-dependent insulinotropic polypeptide (GIP). That additional target may explain why it tends to result in greater weight reduction than semaglutide.

Changes in GLP-1 are also responsible for weight loss after bariatric surgery. "The surgery alters the speed at which food passes through the stomach, and that changes the hormonal milieu and causes people to have much higher levels of GLP-1 after they eat compared with people who haven't had surgery," says Judith Korner, director of the Metabolic and Weight Control Center at NewYork Presbyterian/Columbia University Medical Center in New York.

A precursor to the new drugs, exenatide, was approved by the FDA in 2005 to treat type 2 diabetes. Also a GLP-1 receptor agonist, exenatide improved insulin secretion from the pancreas and regulated blood sugar. But it also had an unexpected benefit—significant weight loss—and that discovery led drugmakers to explore the potential of GLP-1 drugs to help people lose weight, says Samuel Klein, director of the Center for Human Nutrition at Washington University School of Medicine. In 2014, liraglutide, a daily injection, became the first GLP-1 receptor agonist approved for treating obesity.

Both semaglutide and tirzepatide are marketed for type 2 diabetes treatment—semaglutide at a lower dose than when prescribed for weight loss. But for reasons that aren't yet known, people who have diabetes and take the drugs tend to lose fewer pounds than those who don't have the disease. "That just underscores the importance of treating obesity early—before people develop type 2 diabetes or other weight-related diseases," says Jastreboff. "If we can help someone lose a significant amount of weight, we can treat the root cause of or main contributor to diabetes."

Louis Aronne at Weill Cornell Medicine points out that well over 2 million people have taken GLP-1 receptor agonists since they were first approved for treating type 2 diabetes. That's a substantial number to observe for side effects, and those patients have suffered few serious issues. Yet the phase 3 trial of semaglutide for obesity, which ran for 68 weeks and included nearly 2,000 adults, raised a few short-term side effects. Three out of four people taking the drug had gastrointestinal problems—nausea, diarrhea, vomiting, constipation—compared with half of those in the placebo group. More serious problems, including cardiovascular or liver disorders, were reported by 10% of the semaglutide group and just over 6% of the placebo group.

Sarah recalls feeling nauseous when she started taking semaglutide, but this side effect has since abated. Others reported needing to learn to eat more slowly and pay attention to feelings of fullness—and they sometimes vomit because their stomachs don't empty as quickly as before. People who take the new drugs, which they inject at home, start on a low dose that is increased gradually over 17 weeks. "The GI side effects of semaglutide and tirzepatide usually occur as we're escalating the dose," says Jastreboff. "When people get their maintenance, those problems lessen and, most often, resolve."

People who have regained weight after bariatric surgery may also be candidates for semaglutide and tirzepatide. "Our research shows that the use of anti-obesity medications can get people who've had surgery back to their lowest weight or even below that," Aronne says.

Other drugs now being developed show promise for helping people lose even more weight. A recent article in *Nature* listed 26 compounds being evaluated in human trials. One combines semaglutide with an analog of amylin, a hormone secreted by the islet cells of the pancreas that delays gastric emptying after eating and suppresses glucagon, a hormone that stimulates glucose production. In a phase 1 trial, the amylin analog and semaglutide resulted in greater weight loss—up to 17% of body weight—than semaglutide alone. Other early trials are evaluating the effectiveness of GLP-1 agonists in concert with two additional compounds. "Combining a GLP-1 recptor agonist at a lower dose with one or two other compounds can reduce the gastrointestinal side effects associated with high-dose GLP-1 therapy," says Klein. "Many other chronic diseases, such as hypertension and diabetes, are treated with combinations of medications. So this is the future of effective obesity management."

Yet even as these drugs work their way through the pipeline, several structural issues may restrict the widespread use of even existing drugs. For one, semaglutide and tirzepatide aren't yet approved to treat children and younger adolescents, although obesity specialists stress the importance of helping young people overcome obesity, in particular as a way to head off type 2 diabetes. Trials on young people are underway, and in the meantime, some physicians say they're comfortable prescribing the drugs off-label to kids.

Another problem is that extreme weight loss, whether from bariatric surgery or medications, also results in loss of muscle mass and bone density. Exercise can help counteract that loss, but researchers are also investigating pharmaceutical fixes. In a trial of bimagrumab, a monoclonal antibody, people with type 2 diabetes lost about 21% of total body fat but had a nearly 4% increase in lean muscle mass.

Still, the lack of insurance coverage remains one of the biggest obstacles—and one of the most frustrating to obesity specialists. "It's a travesty that insurers will pay for 10 medications people take for weight-related conditions but they won't cover the treatment that could help prevent those diseases," says Korner.

"BIAS IS THE CULPRIT THAT PREVENTS OPTIMAL CARE OF THIS DISEASE."

The Treat and Reduce Obesity Act, which has ongoing bipartisan support in Congress, was first introduced in 2013 and would require Medicare to cover FDA-approved anti-obesity medications. Yet each year it has fallen short of the votes needed to pass, in part because of bias and misunderstanding about obesity, says Joe Nadglowski, president and CEO of the Obesity Action Coalition. "Too many people still think obesity is a condition of personal fault, not a complex chronic disease requiring treatments like counseling, medications and surgery," he says. One sign that attitudes may be changing, however, is an announcement from the federal Office of Personnel Management that, beginning in 2023, anti-obesity medications will be covered for federal employees.

For widespread use of the drugs, though, primary care physicians will need to become more willing to prescribe them. Anti-obesity medications won't be used effectively and sufficiently unless primary care physicians are engaged in obesity treatment, say obesity experts. And a 15-minute appointment isn't enough to manage the complex disease of obesity.

Moreover, no medication, however effective, can banish the unfair notion—from society, physicians and patients themselves—that obesity is a lifestyle choice. "Weight bias prevents patients from being informed, engaged and empowered. And it keeps clinicians from acquiring the training to provide anti-obesity interventions," says Garvey. "Bias is the culprit that prevents optimal care of this disease."

DOSSIER

"Treatment of Obesity: Pharmacotherapy Trends of Office-Based Visits in the United States from 2011 to 2016," by Mechelle D. Claridy et al., *Mayo Clinic Proceedings*, December 2021. The authors document that only 1% of people with obesity who visited physicians received anti-obesity medication.

"Once-Weekly Semaglutide in Adults With Overweight or Obesity," by John P. H. Wilding et al., *New England Journal of Medicine*, March 2021. This pivotal trial showed that weight loss from medical treatment can rival bariatric surgery and led to FDA approval of semaglutide for obesity.

"Describing the Weight-Reduced State: Physiology, Behavior, and Interventions," by Louis J. Aronne et al., *Obesity*, April 2021. The authors describe the effects of behavioral factors, exercise and drug therapy in maintaining weight loss long term.

The People Who Never Were

Machine learning can create fake medical images and histories that look real. They may transform research.

During his keynote lecture at a 2022 conference on medical images, Alex Frangi projected scans of the vasculature of two brains. Although the luminous tangle of blood vessels appeared to be all but identical in the two images, even to this audience of medical and computer science experts, only one image depicted a real human. The other had been created by a computer algorithm, mimicking what might be captured from a real patient through magnetic resonance angiography.

"I asked, which of these is real and which is synthetic?" says Frangi, who directs the Center for Computational Imaging and Simulation Technologies in Biomedicine at Leeds University in the United Kingdom. "It's very, very difficult to tell."

The creation of a brain image real enough to fool experts was far from an academic curiosity. Rather, it is central to a flourishing new field of synthetic data, which could change the way patients are diagnosed, how clinical trials are conducted and especially how artificial intelligence–driven tools—an arsenal proliferating across the medical landscape—are trained and perform.

AI tools require vast amounts of data to train their algorithms, and health care produces that data in torrential quantities. But health systems and other guardians of data are reluctant to share that information, in large part because of privacy concerns. It has also, historically, been extremely difficult for researchers to put most of that data to use.

Synthetic data, used to produce fake brains and other not-quite-real medical artifacts, can help solve that problem, giving researchers access to potentially unlimited numbers of images and histories they can use to train AI models, which in turn can diagnose illnesses, or model and predict how diseases such as COVID-19 affect populations. Another exciting use of synthetic data is taking off in the pharmaceutical industry, where "digital twins"—made-up subjects in clinical trials' control arms—reduce the need for real humans.

In some of these cases, the manufactured data is purely numerical, providing the statistical parameters that make up a unique health profile. In other cases, it is visual, approximating scans, photos or other medical imaging. Yet the aim for most synthetic data is the same—to create exquisitely accurate models representing human subjects to further science while keeping people out of harm's way. The possibilities of that approach, and its limits, are only beginning to emerge.

By Laurie Clarke **Illustrations by John Hersey**

The implications of the medical sector's data gap came into harsh relief during the COVID pandemic. In theory, a disease that has infected more than 600 million people globally would create a robust data trail, one equal to training AI in some of the key needs for pandemic management: spotting the signs of COVID in patients and building models that help predict the spread and impact of the disease.

But multiple studies examining the flurry of COVID AI models came to the same conclusion: They were ineffectual in the fight against the virus. A large review published in *Nature Machine Intelligence* combed through hundreds of deep-learning models trained on chest X-rays, chest computer tomography scans and other medical images to diagnose COVID or predict patient risk. After closely examining 62 of these tools, the authors concluded that because of a high risk for bias or other methodological flaws, not one was fit for clinical use. Another review, published in *The BMJ*, which examined models using any type of clinical input data (not just medical imaging), reached a similarly dim view of hundreds of newly minted diagnostic and prognostic tools for COVID.

Deep-learning algorithms hone their proficiency on an astronomical number of records, which must be clean and neatly labeled. Yet with COVID, deep wells of data that met the needed criteria—substantive, freely accessible and well formatted—have proved almost impossible to come by. Privacy rules have thrown up another barrier.

There's also the laborious process of preparing the data. "If you're trying to identify cancers in the lungs, for example, you need someone to manually annotate those images indicating the pixels that correspond to cancer," says Frangi. This makes collecting medical images costly and tedious, requiring the participation of radiologists as well as AI experts.

Without extensive reserves of meticulous patient records, the resulting AI model can be unpredictable or incomplete. For example, several research groups used chest scans of children not infected with COVID-19 to teach algorithms what non-COVID cases looked like. But instead of learning to identify who did or did not have COVID, the AI tools learned to identify children.

At the heart of the issue was "not having access to the desired data, or having data that were not suitably formatted or documented," according to a 2021 report from the Alan Turing Institute, the United Kingdom's national center for data science and AI.

Yet even AI trained on images that *are* clean and neatly labeled may still face challenges in the field. In 2020, Google Health researchers tried out an AI diagnostic tool for diabetic retinopathy, a condition that affects people with diabetes and can cause blindness. In the laboratory, the tool worked with a data set of eye photographs and achieved 90% accuracy in diagnosing the condition. But in the real-world setting of 11 clinics in Thailand, the deep-learning system's shortcomings became apparent. It frequently didn't know what to make of photos of patients' eyes snapped in poor lighting conditions and wasn't able to make a diagnosis.

Synthetic data might help with many of these issues. By generating records that are in line with real human examples, it can produce an ample, well-annotated training database that may avoid privacy concerns. And synthetic data engines can be calibrated to produce a wider array of examples that reflect what AI tools are likely to encounter when meeting real-life data in the wild.

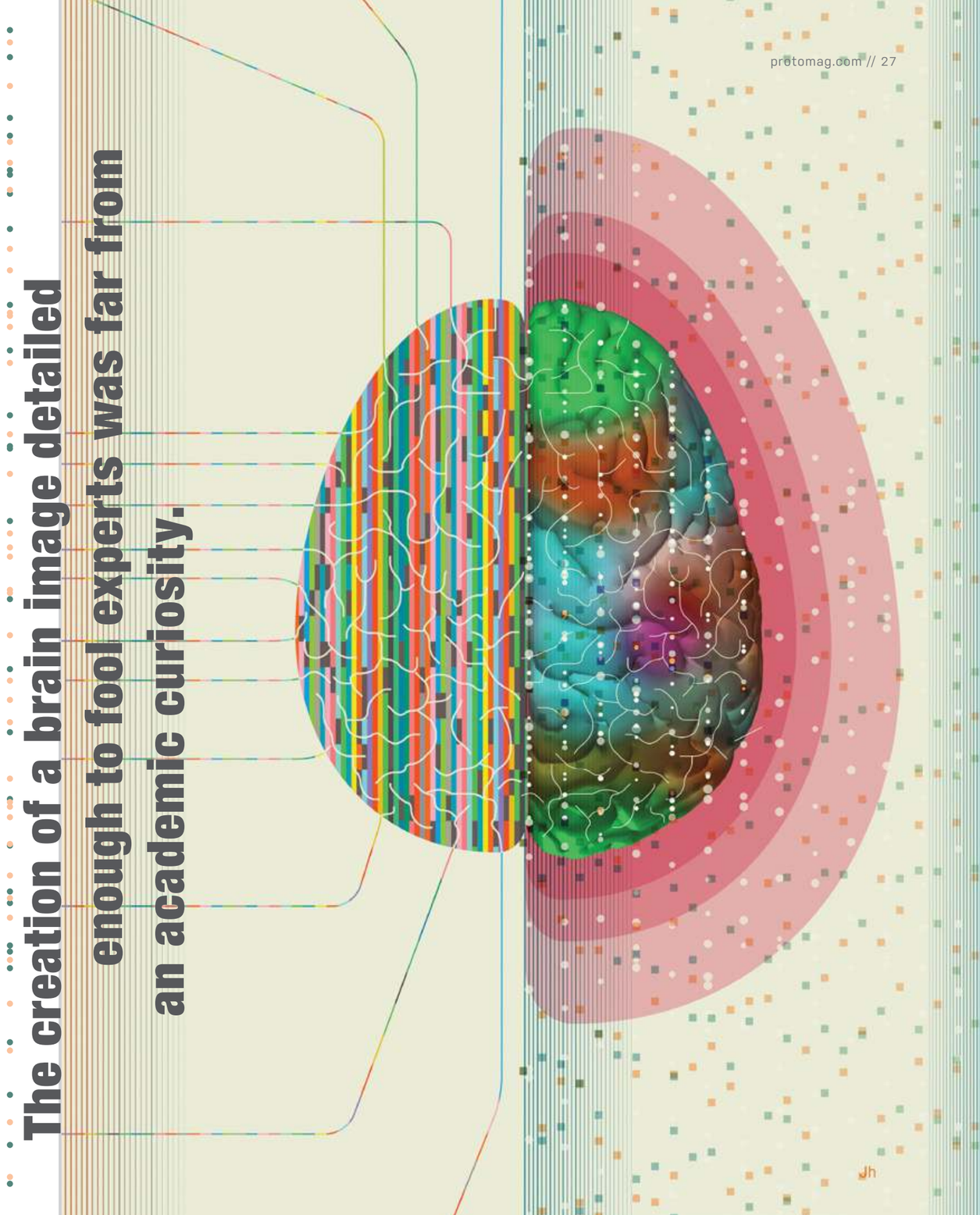
To produce synthetic data or images, a model known as a generative adversarial network, or GAN, is often used. As a first step, the GAN works with a deep set of real images and learns to produce data that is statistically similar. A neural network called a generator creates outputs—for example, photos of artificial faces—that are as realistic as possible. A second network, called the discriminator, compares those generated images with real examples in the training data and tries to decide whether they are genuine or fake. Based on that feedback, the generator tweaks its parameters for creating new images, continuing until the discriminator can no longer tell the difference between real and artificial.

Synthetic data generated in this way can produce more training images with greater variation, including examples on the margins of clarity that mirror real-world data. While the GAN approach is relatively new, researchers have already used it to create photorealistic synthetic data for skin lesions, pathology slides and chest X-rays. Early in the pandemic, a study carried out by researchers from the Maharaja Agrasen Institute of Technology in New Delhi created synthetic chest X-ray images of COVID-19 patients to supplement a scarce set of real radiographic images. They found that adding the synthetic images increased a diagnostic AI's ability to detect patients who had COVID.

• • • •

Philip Payne, founding director of the Institute for Informatics at Washington University in St. Louis, led a team that created what he believes to be the largest synthetic medical data set ever assembled. The set was based on data in the National COVID Cohort Collaborative (N3C), which pooled patient-level data representing 13 million patients from 72 institutions. The synthetic data mirrors the characteristics of the original subjects, but because of the way the set was created, its records do not correspond exactly to any real patients.

The techniques the researchers used represent one approach to using patient data sets without running into privacy concerns. The usual way to share patient records for research is to "de-identify" the patients, removing characteristics such as names, phone numbers and birth dates that could be used to pin down a person's identity. The Health Insurance Portability and Accountability Act, or HIPAA, includes a privacy rule that spells out many of these requirements. Some regulations were temporarily lifted during the pandemic, and sources such as the Open COVID-19 Data Curation Group, which collated international patient-level



de-identified data, emerged. But health care teams are trained to protect their patients, and invitations to contribute patients' data to national efforts met resistance, even when oversight was relaxed. "Combining data can create a lot of anxiety for the stewards or owners of that data," Payne says.

Researchers needed elements of real patient data—neighborhoods in a city where COVID infection was highest, for example, or the dates when an infection had peaked. But ersatz records that mirrored the situation accurately might work just as well as the real thing. To create the N3C data set, Payne's team partnered with Israeli startup MDClone on a computational approach that takes detailed information—not only geographic information but also medical data including body mass index, kidney function and blood pressure—from the records of real patients. "You create new synthetic patients that are replicas of the source patients," Payne says. "The individual measurements, while not identical, don't have statistically significant differences."

Payne's team was excited by the prospect that this huge, national data set would enable the research team to undertake "really big, predictive analytics projects—such as trying to ascertain which COVID patients are at risk of requiring ventilator support and who is going to get very severe disease," he says. "Researchers would have enough data to really be able to answer those questions."

Two studies, in the *Journal of the American Informatics Association* and the *Journal of Medical Internet Research*, confirmed that the synthetic data provided an accurate representation of the real patients on which they were based. But Payne and his team also wanted to assess whether the fake data effectively maintained the privacy of patients. So researchers looked for data in the public domain involving the patients from whom the synthetic data was derived. This included demographic data, census data, voting records, information about what foods people bought in grocery stores and financial data. They then tried to combine that information with the fake data to re-identify particular patients. According to Payne, the synthetic data did a better job than normal methods of de-identification to reduce the chance that someone could be re-identified.

The N3C data set of actual patients has already been used by researchers, for instance in probing which factors may predict the development of long COVID, or why some immunocompromised patients experience breakthrough infections after vaccination. The synthetic data based on the NC3 can be used to answer similar questions.

Payne believes the work with COVID-19 could lead to a much broader use of synthetic data. "We've seen how data-sharing is the lifeblood of a rapid, agile public health response," he says. "Synthetic data is at the forefront of being able to do that while managing privacy and confidentiality."

Synthetic data may also revolutionize how new drugs and medical devices are developed, which typically requires testing first in the lab, then on animals and finally on people in at least three phases of clinical trials. The process can take as long as 15 years and may cost hundreds of millions of dollars, says Alex Frangi at Leeds University. Much of that expense goes for recruiting and supporting trial subjects. "Digital twins"—computationally derived versions of human subjects—are showing promise for populating trials' control arms and could speed research, control costs and let more patients try experimental medicines.

Suppose you want to run a clinical trial involving 2,000 people, says Charles Fisher, co-founder and CEO of Unlearn.AI, a trial-design company pioneering the use of digital twins. Ordinarily, that would mean recruiting 1,000 patients for the experimental arm and 1,000 for the control arm. Unlearn uses computational modeling to deploy human trial subjects more efficiently—say, with 1,500 patients receiving the experimental treatment and just 500 getting the control, with synthetic versions of patients used to bolster the control group. "We can't completely eliminate real human control groups, but we can make them smaller," says Fisher, a biophysicist and a former data scientist for Pfizer.

Unlearn uses control arms of previous clinical trials and observational studies to create an AI model that is appropriate to the disease under investigation. It then collects relevant health information for all of the patients in the new trial. For patients with Huntington's disease, for example, that might include not only general health data but also results from tests such as the Unified Huntington's Disease Rating Scale–Total Motor Score.

The model then derives a digital twin by simulating how the real patient, assigned to the trial's experimental arm, would likely have fared if they had been in the control arm. One trial subject effectively becomes two, with the investigators gathering data on what actually happens when the person receives the experimental treatment, and Unlearn's model predicting what *would* have happened if that subject had received the control treatment. The difference is taken as a measure of effectiveness for the new drug or device. "We're not imagining the medical records of some hypothetical person," says Fisher. "We're actually predicting the future medical records of a specific person."

To gauge the accuracy of the model, it also projects the synthetic control group's response and compares that to real-world responses in the human control group. If there's a discrepancy between the two, the model can be adjusted. Using this method means researchers are able to assign a larger proportion of total subjects to the experimental arm while using fewer real patients as controls.

Major pharmaceutical companies are beginning to show interest in experimenting with virtual patients in trials. Unlearn has signed up for a multi-year collaboration with Merck KGaA, Germany, to accelerate late-stage clinical trials in immunology and perhaps other therapeutic areas.

Unlearn has received a regulatory qualification from the European Medicines Agency that describes the applicability of its approach for phase 2 and phase 3 clinical trials. The U.S. Food and Drug Administration may also be open to such trials. In 2020, it approved a new indication for a drug for atrial fibrillation patients based on this kind of trial data.

One trial subject effectively becomes two.

But many questions about synthetic data remain to be resolved. One problem is that there is not yet any regulatory framework for developing AI models, says Faisal Mahmood, associate professor of pathology at Harvard Medical School. Another issue is to what extent clinicians will actually adopt AI tools trained by synthetic data. Mahmood notes a reluctance on the part of clinicians to use the 200 "software as a medical device" products already approved by the FDA, mostly because those tools tend to require changing well established and commonly used clinical workflows. "It will take a fundamental redesign of clinical workflows in order for AI to have a role," he says.

In the meantime, those who believe artificial data could have a broad impact are working to refine their models. Working on one disease at a time, Unlearn is looking at how to create digital twins for clinical trials for treating such diseases as Alzheimer's and rheumatoid arthritis. The ultimate goal is to have one model that works for everyone, Fisher says, "with the ability to simulate any person's future health outcomes under treatment A, B or C."

To accomplish that, and to explore other frontiers for the use of synthetic data, will require overcoming technological challenges. Better machine learning algorithms, faster computers and more and better data will help speed progress. For now, the quality of medical data lags far behind data in other industries. But synthetic data research demonstrates how much can be done even with substandard data—raising hopes for a future in which ever more sophisticated efforts might finally crack medicine's persistent data problem and help revolutionize medical AI.

DOSSIER

"Synthetic data in machine learning for medicine and healthcare," by Richard J. Chen et al., *Nature Biomedical Engineering*, June 2021. The authors chart the growth of the synthetic data frontier in medicine, noting the method's current limitations and potential regulatory hurdles as it gains wider adoption.

"The National COVID Cohort Collaborative: Analyses of Original and Computationally Derived Electronic Health Record Data," by Randi Foraker et al., *The Journal of Medical Internet Research*, October 2021. A synthetically derived national COVID-19 data set is run through a handful of use cases and is shown to successfully mimic data results from the real world.

WHAT GOOD IS SCIENCE WRITING?

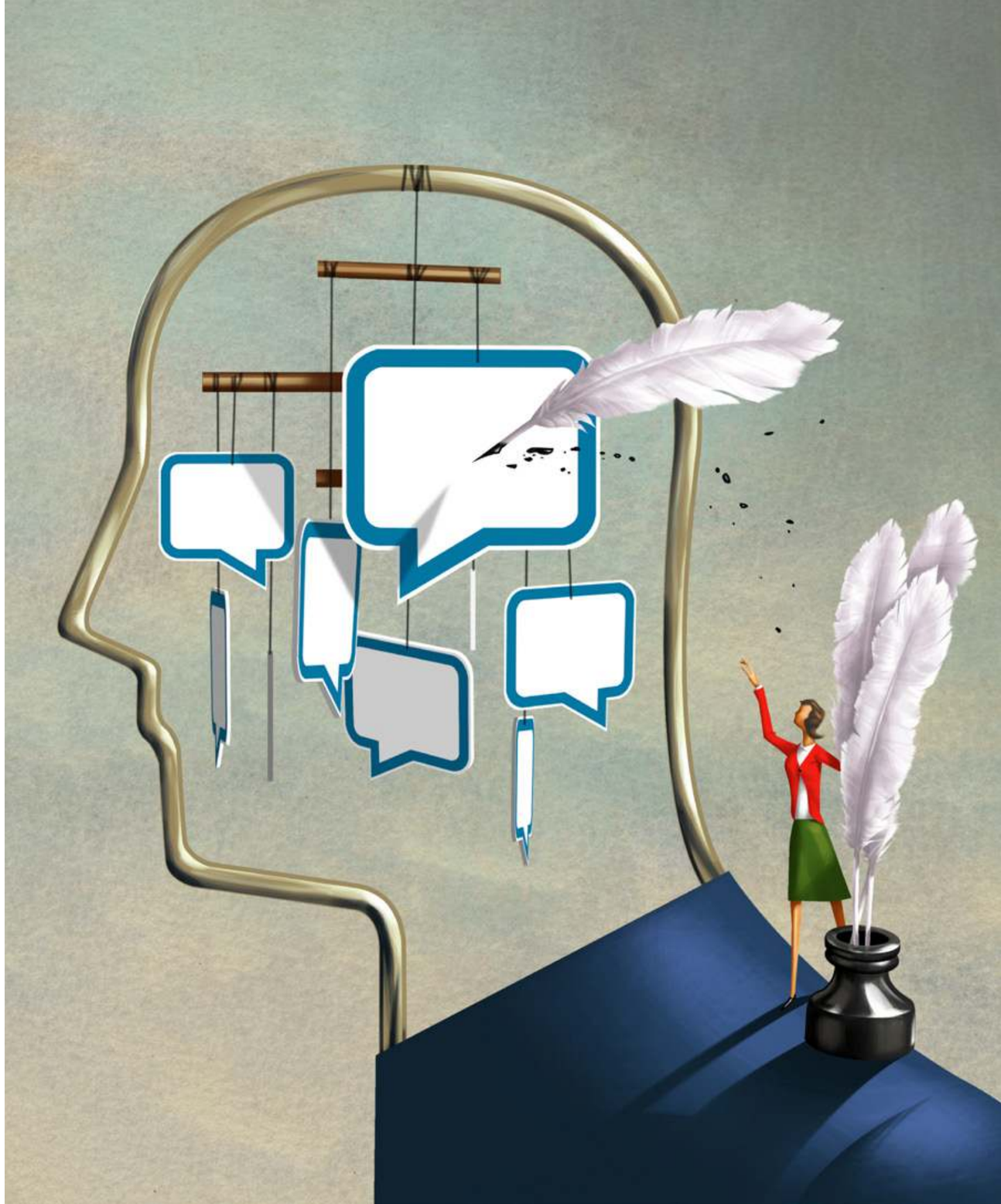
Public skepticism has cast a shadow over medicine and those who report on it. Yet for both professions, the mission continues.

When the World Health Organization declared COVID-19 a pandemic in March 2020, my profession moved to center stage. Science reporters like me had spent our careers helping people make sense of the world of research and medicine, and suddenly we faced a story that had the undivided attention of a global audience. It was all hands on deck. As medical professionals ran their own gauntlet of long hours and uncertainty, we also felt a sense of purpose and preparation for a role that would be tough and sometimes thankless in the months ahead.

Science writers are trained to understand complex facts, map out what's known and what remains uncertain, and make all of it digestible for readers. "Science reporters help people understand reality in a way that captures the best knowledge of the moment," says *Scientific American* editor-in-chief Laura Helmuth. As the pandemic took hold, our work was essential in helping a wide swath of the nonscientist public, including policymakers, grasp what was happening so that they could make informed decisions.

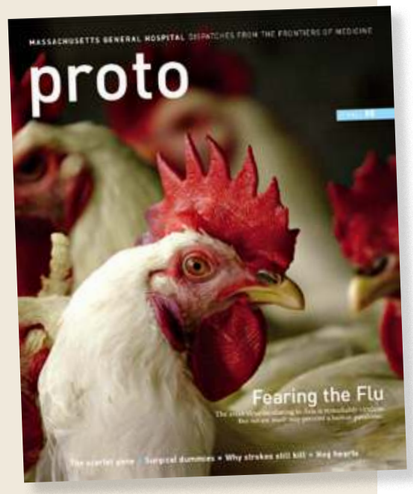
Our profession aims to help society navigate complex issues where science plays a role. It didn't start with the pandemic, nor will it stop there. As the climate crisis hits home in the form of fires, floods and global heat waves, for instance, science reporters are tasked with explaining the forces behind these catastrophes without shortchanging

By CHRISTIE ASCHWANDEN /// Illustrations by JIM TSINGANOS



THE PANDEMIC THAT WASN'T

Public conversations about transmissibility, vaccines and risk got a trial run in Proto*'s launch issue.*



For medical journalists, 2005 was the year of the avian flu. The highly lethal virus was believed to have killed more than 100 million birds, and in instances where it hopped over to human hosts, the flu killed six out of 10 people who were known to have contracted it. As the public tried to gauge their personal level of threat—some researchers had predicted human deaths in the millions—they were met with journalistic takes that, in many cases, were light on the risks and mechanisms of transmission and heavy on voices predicting the worst.

It was in this environment that *Proto* launched its fall 2005 debut issue. The magazine's first cover feature did not dismiss the possibility of H5N1 developing into a pandemic, but focused instead on the events that could realistically trigger a public health disaster. The piece explored the "antigenic drift" that creates new viral threats, as well as the specifics of H5N1 and its interaction with human hosts. For instance, the virus at that time had not been seen to colonize the human upper respiratory tract—a sign that, in its current form, both bird-to-animal transmission and human-to-human transmission remained unlikely.

In a foreshadowing of the COVID-19 pandemic, the article also highlighted the dangers of wet markets, places where live animals are sold for human consumption, calling them "the ideal conditions for viral evolution."

This model of reporting on infectious disease, focusing on scientific questions and debates, would serve as the first training for *Proto*'s coverage of the COVID-19 pandemic nearly two decades later. The outbreak—which in the end resulted in a few hundred deaths globally—would also serve as a wake-up call for pandemic preparedness and the need for new vaccine models.

the complexities and unanswered questions that researchers continue to grapple with.

Yet just when the need for good science writing is greater than ever, it is increasingly under attack. The explosion of social media, with its ecosystems of alternative news and disinformation, has made the public skeptical about, if not openly hostile to, the very notion of scientific fact and those who present it. As every species of medical fact has been questioned, so too have the writers faithfully trying to present those facts.

Across the journalistic profession—just as in public health—many of us have tried to trace what has gone wrong over the past few years. In the pandemic's early days, as scientists raced to learn about an entirely new virus, questions arose much faster than answers could be delivered. Hungry for guidance, people snapped up simplistic half-truths, which the purveyors of misinformation were only too happy to supply. Science writers were then, as always, working out the trickier outlines of the facts—which are nearly always complicated, unsettled and slow to come into focus. It was perhaps not surprising which option the public gravitated to. "We're in the middle of an epic battle between sense and nonsense," says Helmuth.

When science writers publish their work, the response to even the most well-researched, articulately delivered pieces is likely to be mixed. In 2021, I wrote a story for *Nature* explaining the complex science of herd immunity, when a sufficient proportion of the population becomes immune to an infectious disease, either through vaccination or exposure, so that it fades away for lack of new hosts. My story explained why scientists had come to see herd immunity as an unreachable goal for COVID-19. Some readers thanked me for providing a path through a difficult, confusing topic, and the piece became the journal's most-read news story of the year. Yet others wrongly pointed to the story as evidence supporting what they already believed—that vaccines didn't work.

Sometimes the most important thing a science writer can do is harness the firehose of information into a cohesive narrative. Ed Yong, a science writer at *The Atlantic*, won a Pulitzer Prize for his reporting on COVID-19. "Ed's coverage has been meaningful for a lot of people," says Daniel Engber, senior editor at *The Atlantic*. What made some of his most influential stories so important, Engber says, wasn't that he was always breaking news. It was that he provided a trusted voice that could help make sense of a confusing time. "There is real value in being able to frame things for people and deliver the information with clarity and authority," Engber says. "That's something in particular that science journalists can do."

When science writing does break through, it often does so by "telling" science in ways the human brain can more easily process. Narrative storytelling, for instance, sometimes does a better job of helping people grasp complex scientific information, a finding borne out by research into how public health agencies can convey the importance of vaccines. Where data can be cold, human stories can connect.

One very public lesson from the past few years has been how difficult it is to convey findings when there is conflict or disagreement among researchers. Yet this has always been part of the beat. In 2014, I wrote in *Proto* about the challenges of treating a breast condition called ductal carcinoma in situ. Emerging evidence suggested that this precancerous condition was being overtreated, with women receiving aggressive therapy they didn't need, but experts disagreed about the extent of the problem and how to address it. The best way I have found to report on conflicting points of view is to look for where consensus exists, explain the questions at stake and lay out the points of contention. But even when I do that, readers will sometimes take a balanced article and weaponize it on behalf of their own point of view.

Another recent lesson has been the importance—both to medicine and to the public—of questioning powerful voices. Around Thanksgiving in 2020, as people considered whether it was safe to gather with their families for the holiday, many state officials advised against it, asserting that small gatherings were driving this phase of the pandemic. But *New York Times* science and global health reporter Apoorva Mandavilli wasn't convinced that small gatherings were the biggest problem. Statistics released by most states showed that it was primarily

THE PERSONAL AND THE POLITICAL

In 2016, pediatric gender transition had not been widely covered. That would dramatically change.

Transgender identities are a pediatric issue, with two out of three transgender adults saying they first experienced gender dysphoria in childhood. The average age for having those feelings was 8. Over the past few years, the topic of medical treatment for these children has become a fraught—and politically embattled—conversation.

As of October 2022, more than a dozen state legislatures have proposed or enacted laws to limit gender-affirming medical care and penalize those who offer it. In Alabama, for instance, providing puberty blockers, hormones or medical procedures to those under 19 is now a felony punishable by up to 10 years in prison.

In 2016, national debates about transgender people had been confined to bathroom laws and participation in sports and the military. *Proto* was one of the first publications to explore the medical dimensions of gender dysphoria for youth. Nodding to politics but largely sidestepping these discussions, the article explored the evolving and incomplete landscape of research, as well as the conversations about these patients happening among endocrinologists and psychiatrists—all with an eye to giving these kids happy and well-adjusted lives.

The frontier was and remains complex, and it includes the ongoing question of how best to accommodate young patients who go through various gender identities before adulthood. With no apparent biomarkers, the general consensus was—and remains—to listen to the patients. Coverage of this frontier continues to be sensitive, but with a focus on the growing body of peer-reviewed research—and more informed voices on the front lines of gender-affirming care—the hope is that medical consensus, told well, can trump politics.

religious services, indoor dining and sporting events that were spreading the contagion, Mandavilli says.

Despite that evidence, however, a Midwestern governor issued an executive order prohibiting people from different households gathering indoors or even outdoors, although it was clear by then that being outdoors greatly reduced the chances of spreading COVID-19. Yet the order allowed places of worship and wedding venues to have as many as 250 people inside. This guidance didn't square with the evidence, and Mandavilli said so. Yet she caught grief from some researchers for parts of her piece. The story is going to encourage people to go out to parties, some told her, and one prominent scientist tweeted simply, "Do better, @nytimes." But Mandavilli stood firm. "As journalists, it's our job to push back when messaging from experts doesn't align with the evidence," she says.

This responsibility also extends to fact-checking members of the medical field who might be speaking outside of their field or expertise or have conflicts of interest, says Amy Maxmen, a winner of the Victor Cohn Prize for Excellence in Medical Science Reporting in 2021. Some doctors with no training in infectious diseases have nevertheless felt free to opine on how COVID-19 spreads, what drugs should be used to treat it and whether vaccines have any value. The problem extends beyond medicine, as a leader of the movement to deny human-made climate change was an esteemed physicist commenting on science far outside his field.

In looking at medicine, science reporters also must watch for flawed methods and dubious data. In April 2020, for example, former BuzzFeed science reporter Stephanie Lee began looking into a study that gave antibody tests to residents of Santa Clara County, California. At the time, such tests were being used to show whether a person may have been infected by COVID-19, and the results of the study, which was not peer-reviewed at the time, seemed to show that the new coronavirus had already infected many more people than previously believed. The study authors, which included prominent researchers from Stanford University, used those results to argue that the death rate from the new virus was far lower than public health experts were saying. Lee dug into critiques of the study by other scientists and found serious flaws in its methodology. She eventually uncovered damning evidence that the study had received funding from a prominent airline owner who had a vested interest in promoting research that could help end pandemic shutdowns.

Scientific American recently highlighted another important role for science reporting when it revised its mission statement to state that in addition to "sharing trustworthy knowledge" and "enhancing our understanding of the world," it is also committed to "advancing social justice." Helmuth says this updated mission means, for example, covering health disparities and the effects of racism on the impact of the pandemic, and bringing inclusivity and equity to the publication's science coverage.

For many polarizing political issues, media coverage often tends to focus on what people believe or what their values are, Helmuth says. But science can also probe underlying factors that may affect those issues, and science reporters can bring these bodies of evidence to light and help people understand them. Consider the current claims that allowing gender-conforming care for transgender kids is akin to child abuse, and critics' insistence that these children will later wish they hadn't received the care. "The science is absolutely the opposite," Helmuth says. Research shows that denying children gender-conforming care is dangerous and can lead to an increased risk of suicide. In contrast, "providing care that's appropriate to their age and their gender expression is actually a really good way to turn them into well-adjusted, happy people," she says.

Over the past few years, science reporting—like medicine itself—has received a drubbing. Many in our field are burned out. For those who remain, it is important to remember why we are here: Science reporting helps us to see the world as it really is. While those with dubious agendas and misinformation will never be truly stopped, we must believe that reality will assert itself in the end. It is the slow, steady job of science writers to bring that reality into view—even when the news is unwelcome.

"THIS WILL CHANGE EVERYTHING"

Medical innovations are cause for excitement. Voices of skepticism are also critical to invite in.

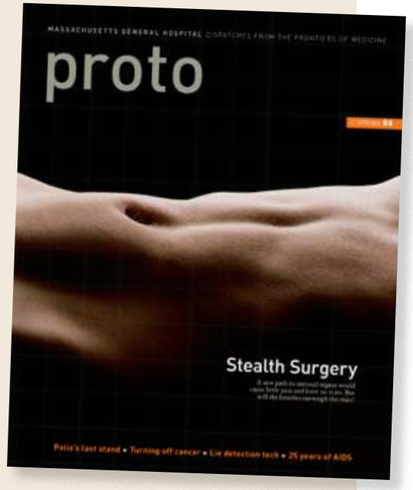
With the hindsight of almost two decades in print, it is clear that not every transformative innovation *Proto* covered will live up to its promise. That messy progress of science is also worth reporting on.

In 2006, *Proto* turned its attention to NOTES—natural orifice translumenal endoscopic surgery. Surgeons would access abdominal organs through natural orifices, such as the mouth or anus, instead of making an incision in the muscles of the abdominal wall, which can account for much of in-hospital recovery time. A major paper showing the success of such surgeries in pigs had been published in 2004, and by 2006 the procedure was discussed as a potential boon for humans. The process would build on the success of endoscopic techniques and theoretically create fewer scars and complications.

While the story cited those who hailed NOTES as a leap in minimally invasive surgery, it also documented several informed objections—a practice built into *Proto*'s innovation coverage. Some commented that NOTES offered few advantages over laparoscopy, which was itself quickly advancing, and often committed the questionable practice of puncturing the stomach wall.

The first human instance of this surgery occurred in 2007, when a team in New York removed a patient's gallbladder through her vaginal wall. Since then, however, the procedure has not been widely adopted.

In 2021, *Proto* interviewed neuroscientist Nicholas Holmes about the need for researchers to create "an honest list of disappointments"—a catalog of their ideas that haven't been borne out by time. For Holmes, frankness about the indirect and sometimes disappointing byways of science is the only way to build trust with the public.



AN INSTITUTION LOOKS INWARD

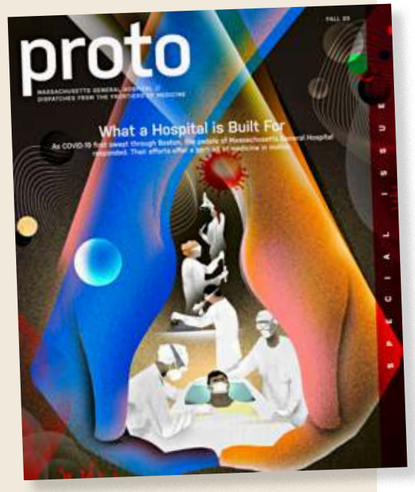
The COVID-19 pandemic drives Proto *to devote an issue to its parent hospital.*

Massachusetts General Hospital created *Proto* with a wide ambit: The magazine would cover innovations in medicine wherever they happened. Although the largest hospital-based research program in the country had plenty of stories within its own walls, *Proto* would instead follow the sweep of innovation in a more holistic way, tracing ideas through the wider community of physicians and scientists.

This journalistic model was novel. *Proto* wouldn't be a house publication, but neither would it be editorially independent. An editorial board drawn from across MGH would help to brainstorm ideas and occasionally review them. Stories about distant innovations would sometimes elicit insights from hospital staff, and stories that started at MGH often branched out as researchers pointed journalists to colleagues and collaborators from around the world.

In the first months of the COVID-19 pandemic, however, it became apparent that one of the great medical stories of the day was happening on the home front. As victims of the virus began to fill up beds at MGH, the hospital was mounting one of the nation's most multi-faceted responses to the pandemic.

The special issue looked at the Ragon Institute's work on the frontiers of vaccine development, at efforts to decontaminate respirators that were in short supply, at early clinical trials for remdesivir and the evolution of clinical practices such as proning that were shown to prolong life.



Relationships that had been built up over decades meant that *Proto* was on the very front lines of the hospital's pandemic response. It showed how exploring novel collaborations between scientists and journalists can bear fruit in a time of crisis.

FIRST PERSON

Kissed

BY KRISTEN FRENCH

One evening, my 84-year-old mother went to the dining hall of her senior residence and noticed a lanky man with a white mane. He was sitting all alone at one of the tables. "Are you waiting for anyone?" she asked him sweetly.

Over the next few hours, I received a flurry of photo texts from my mother's caregiver, Maria. Two figures leaning into one another at the dining table. The two of them walking down a garden path in dappled twilight. And later, their heads bowed together, silhouetted against the glow of a movie screen in the facility's small theater. A romance had blossomed.

My father had passed away two years before, and my mother had been craving male attention ever since. David quickly became my mother's first new boyfriend in more than 50 years.

In those first days, my mother talked a lot about how much she loved to kiss David. They had found a secret spot where they could smooch. There turned out to be other upsides. Within a week, my mother, who has Parkinson's, suddenly seemed sharper. Her sentences were more linear and connected to the world around her, and her memory was more lucid. She walked with greater confidence, too, each step forward like a tiny conquest rather than a timid retreat. The difference even showed up on a cognitive test administered by her neurologist—it was as though six months of dramatic cognitive decline had been erased, she said.

Was romance the medicine my mom really needed? Since her diagnosis in 2014, it had been hard not to see the emotional component in the progression of her condition. Her cognition declined sharply after my father's death, and again when she moved out of her home into a retirement community in 2021.

Yet love, as it often does, brought thorns as well as roses. I soon found out that David encouraged my mother to refuse her meds and to ditch her walker, which she needs for balance. He urged her to get rid of her Foley catheter so that they could have sex. He sometimes barked at her to hurry up or made fun of other residents with ailments and disabilities, an attitude that led my mother to have anxiety attacks and debilitating stomach pains.

David also insulted the caregivers and made them wait outside my mother's room when he visited. I began trying to set some boundaries with him, for her safety, but while David made promises, he ignored every one of them. Eventually, he was called out by the resident services manager and required to stop visiting my mother's apartment. He promptly dropped contact with her.

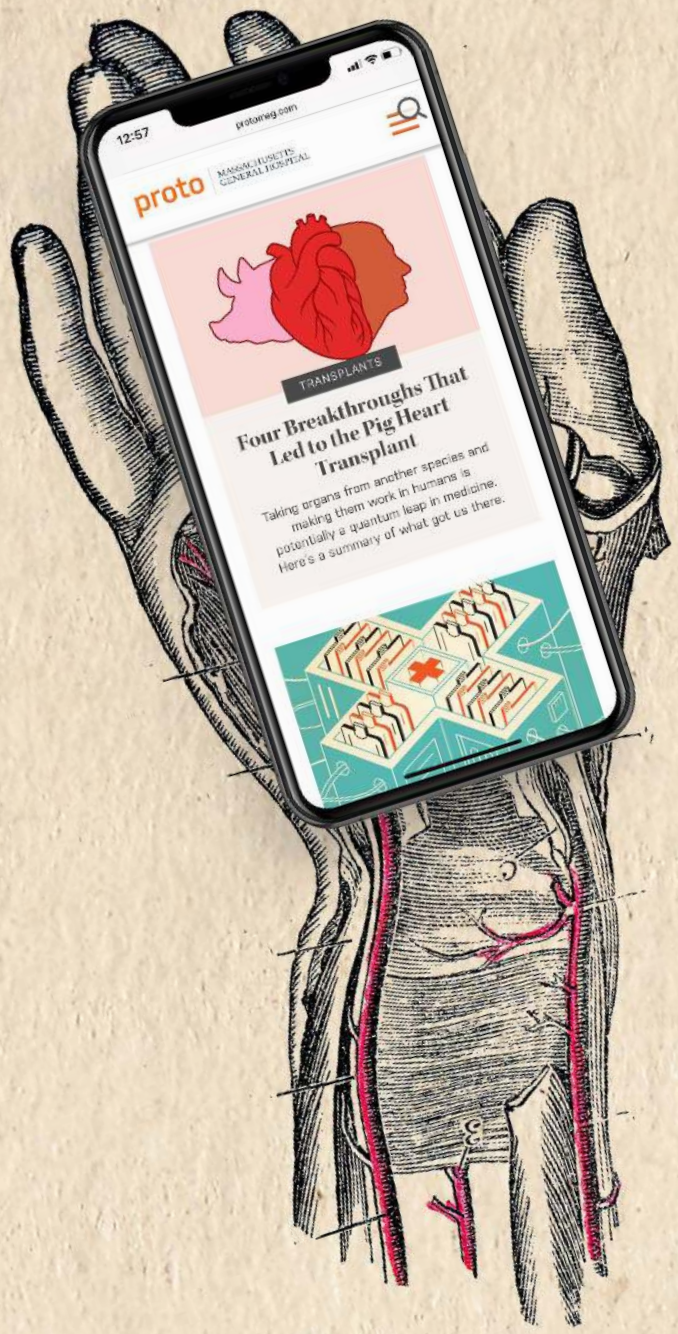
Within a week, it was as if my mother's life force had been strangled out of her. She couldn't get out of bed or her chair without a lot of help. She needed a wheelchair to travel any distance. Her voice became a whisper. The cause was obvious, but I had a hard time understanding how heartbreak could lead to such a profound response. The neurologist was puzzled by her sudden regression until I mentioned the saga of the boyfriend. "Ah," she said, her eyes getting big. "When we get to this age, the connection between the emotional and the physical can be dramatic."

Over the following month, my mother slowly regained her strength and her cognition recovered somewhat. But the effects of that first fire, which lit her up and put her in such good health, have not returned.

I had not expected my mother's romantic life to play a part in my adult caregiving, but it is just one more wrinkle in the reversal of our roles. One day I decided to ask her: Were those kisses in their hidden nook worth all the trouble? She tells me that, overall, she believes she is better off without David, but she has no regrets.

VICTOR PRADO

Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114



The Future Is Here

Innovation moves quickly in the field of medicine. **Follow** *Proto* to explore those frontiers as they emerge.

Sign up for the newsletter and find back issues at ProtoMag.com.

Discover the *Proto* podcast on iTunes and Stitcher.

ProtoMag.com
@ProtoMagazine
Facebook.com/ProtoMag
Proto.Magazine