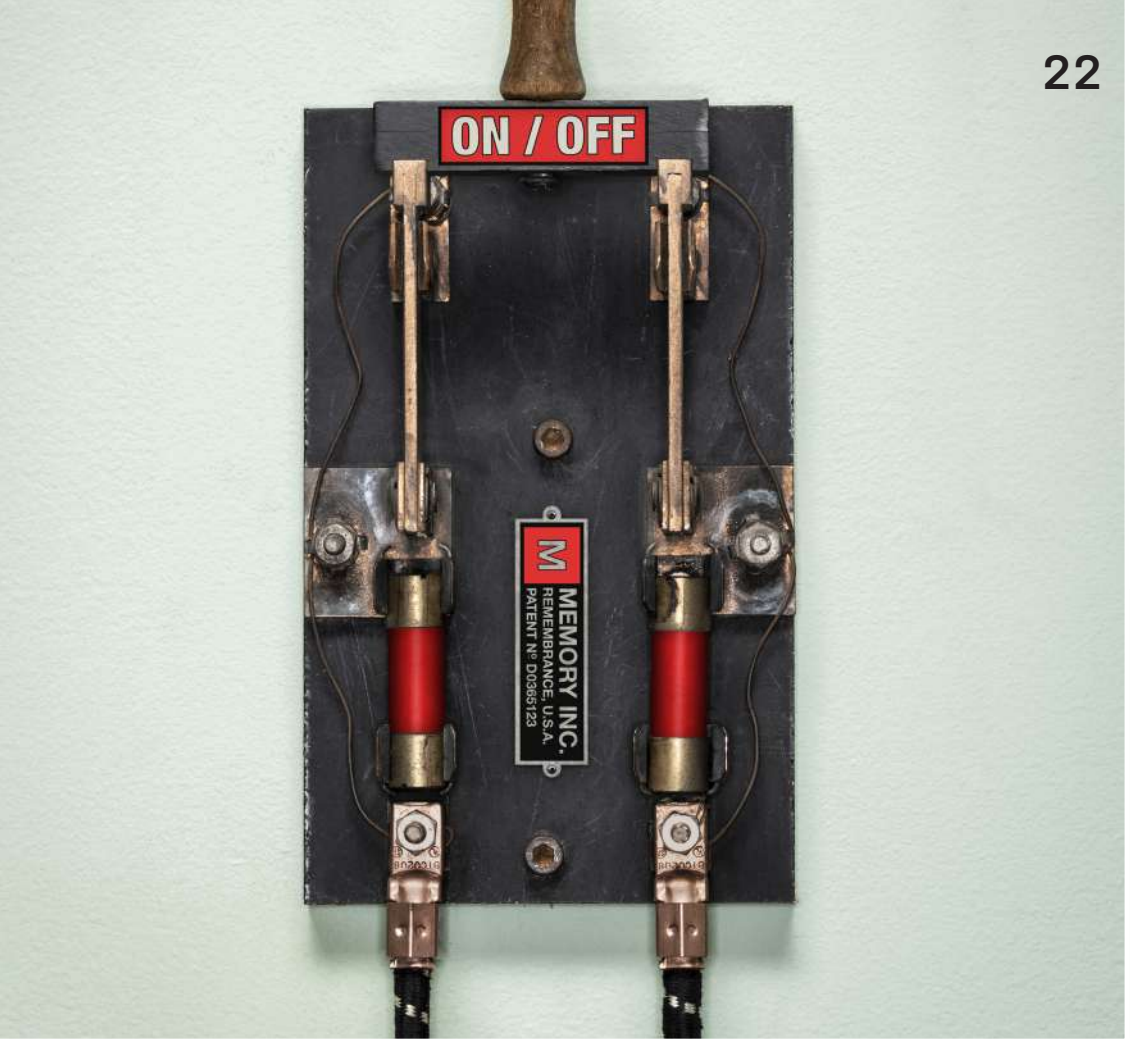
SPRING 19

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

Good Enough?

The debate continues over what makes a donor organ acceptable—and who deserves to receive it. p10



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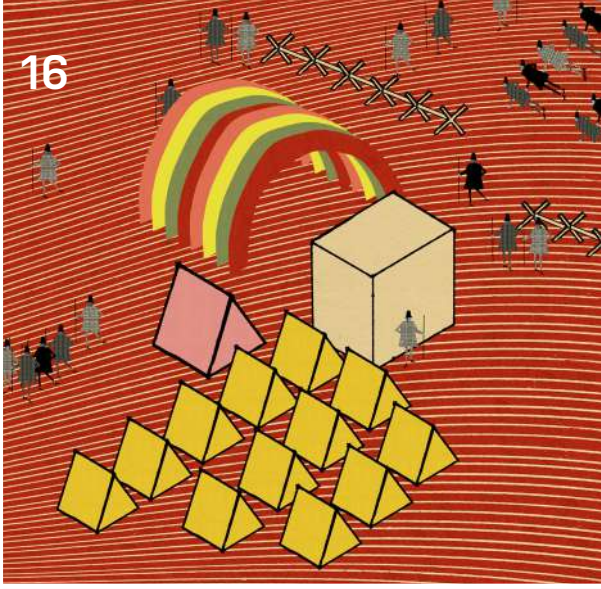

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POST-OP

FEATURES

on the cover

An organ from a donor with HIV or hepatitis C generally goes to waste. But more institutions are considering revisions to transplant guidelines, which could mean more healthy years for organs and recipients alike.
// Photograph by Kyle Bean

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

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Founded in 1811, Massachusetts General Hospital is a 1,000-bed academic medical center located in Boston. It is a founding member of Partners HealthCare and is the original and largest teaching affiliate of Harvard Medical School.

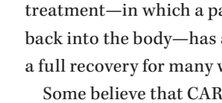
CAR T CELL THERAPY HAS BEEN called transformative and a "miracle," and has garnered as much excitement as any cancer breakthrough in recent memory. The treatment—in which a patient's immune cells are removed, reengineered and placed back into the body—has a success rate as high as 90% in some blood cancers, offering a full recovery for many who had given up hope.

Some believe that CAR T can be pushed even further. In "The Solid Tumor Barrier," *Proto* explores efforts to marshal this therapy beyond blood cancers to solid tumors, which make up the vast majority of cancer cases. Marcela Maus, director of cellular immunotherapy at Massachusetts General Cancer Center, is working both on ways to target solid tumors with greater precision and on reducing the considerable costs of CAR T manufacture, which remain a major obstacle.

If successful, these efforts will present a revolution not only in cancer treatment but in care delivery. Immunotherapies such as CAR T therapy don't come off the shelf, ready to use. Each treatment must be personalized to the patient, a labor-intensive process that calls for close work between many divisions of the hospital. Patients often remain on site for weeks to be monitored. In 2020 Massachusetts General Hospital aims to break ground on a building that will house six floors of new inpatient beds, with a focus on cancer and cardiac care, in part to be ready for the future in which moving patients through this and other processes will be far more common.

The first generation of this therapy is also not without complications. About three-quarters of the people who receive CAR T experience side effects, often severe and sometimes fatal. To understand these effects and set new standards in their treatment, MGH created a Severe Immunotherapy Complications Service. This pioneering team of 41 doctors and researchers from 22 areas of the hospital both treats these off-target effects and discovers ways to keep them from happening, in part by identifying which patients might be genetically disposed toward them.

The fight against cancer has many fronts, and the end is not likely to come soon. But we must prepare to press every advantage. As CAR T moves forward, the health care field must prepare not only for its vast promise to cure but also for its new and complex demands.



PETER L. SLAVIN, M.D.
President
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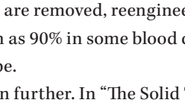

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GREG WHITE

stat

FOCUS

Donated Blood is carefully filtered, processed and screened before it reaches a patient. Keeping this supply safe is critical, but it doesn't come cheaply. A recent study in the *Annals of Internal Medicine* estimated that testing donated blood for the Zika virus—a step taken in all 50 states after the outbreak in 2015—cost an astounding $5.3 million for each single unit of blood that eventually tested positive. While the U.S. Food and Drug Administration mandates universal testing for certain pathogens, such as HIV and syphilis, adding others to the list has to balance costs and priorities.

The latest target for blood screening is *Babesia microti*, a parasite transmitted by the deer tick. The vast majority of infected people infected have no symptoms, but those with depressed immune systems—such as organ transplant patients, who also require a great deal of transfused blood—can die from it. In recent years, *B. microti* has been a leading cause of infection-related death from transfusions, and last year the FDA approved the first test to screen for the parasite in donated blood. In May it recommended that all donations be tested in 14 northeastern states and Washington, D.C.

INTERVIEW

Homegrown

Kayse Shrum is launching the first U.S. medical school affiliated with a Native American tribe—part of a strategy to train doctors where they're needed most.

BY DAVID NOONAN

SHEVAUN WILLIAMS FOR *PROTO*

Kayse Shrum, president of Oklahoma State University Center for Health Sciences, didn't start to think about a career in medicine until she was in college. Growing up in Coweta, Oklahoma, a town with a population of fewer than 10,000, Shrum had pictured herself in one of the careers held by people she knew in her community. She didn't dream of being a physician simply because there weren't many around.

Encouraged by a professor, Shrum applied to medical school, earned a doctor of osteopathic medicine degree and embarked on a journey that took her through programs at Harvard and Stanford. Along the way she worked to raise awareness of medicine as a career option among Oklahoma's rural and Native American young people.

Most recently that effort has culminated in the creation of the nation's first tribally affiliated medical school. The Oklahoma State University College of Osteopathic Medicine at the Cherokee Nation, located in Tahlequah, is scheduled to open with its first class of 50 students in 2020.

Q: How did the partnership with the Cherokee Nation come about?
A: We have been partnering with the Cherokee Nation for more than a decade to train primary care doctors for rural Oklahoma. The Cherokee Nation has allowed our students to do rotations there, and many of our graduates practice at the Cherokee Nation. During Chief Bill John Baker's two terms as principal chief, he has made improving the health outcomes of the Cherokee people a top priority for his administration. It's invested hundreds of millions in building new clinics and renovating existing ones and is also currently working on building an outpatient health facility.

If you look at national statistics, 0.5% of students across the United States in osteopathic and allopathic medical schools are Native American. At OSU, in the past three years, 12% to 18% of our medical students have been Native American. So the Cherokee Nation looks at us and says, "They're dedicated to recruiting and training more Native Americans in medicine and we're dedicated to improving the health of the Cherokee people. So let's work together in this shared vision."

Q: What are the issues facing rural Oklahoma?
A: Oklahoma has traditionally ranked pretty low in most health outcomes, in part because of the shortage of primary care physicians—in some counties, there is not a single one. The federal government considers all but one county in Oklahoma to be a health-professional shortage area. We have very high rates of preventable death, cardiovascular disease, diabetes and obesity.

In Stilwell, which is inside the Cherokee Nation's jurisdictional area and about 30 minutes away from where our new medical school will be, life expectancy is 56.3 years. That's the lowest in the United States, and it's on par with sub-Saharan countries such as Uganda and Mozambique. When I met with my team several years ago, I said we need to look at what we can do to not be in the bottom 20% in health outcomes. We have made some tremendous gains over the years, but we need to do more. Growing our own rural doctors in partnership with the Cherokee Nation is a step in the right direction that will have meaningful health impacts on rural Oklahomans for years to come.

Q: How will a medical school help?
A: A few factors govern where people practice in the prime of their careers: where they grew up, where they did their undergraduate work, what their medical school focused on, and, of course, where they did their residency training.

We've done some studies on our residency programs and how they affect longer-term career decisions. When our graduates train in an urban area, 80% of them stay within a 100-mile radius of where they did their residencies. We also have seven rural residency programs, some of which are funded by the federal Health Resources and Services Agency. These federal grants have allowed us to set up residency programs in smaller rural communities, which is great. Those doctors tend to stay in those areas to practice.

What's really interesting is that the more rural the area where residents train, the higher the retention rate. If you start a rural residency program close to an urban area, urban health systems start recruiting them out. When it comes to the more rural areas, those students are choosing to go there and there's a desire to stay and serve in these communities. You stay, you build relationships and you make a difference. We hope that our new medical school in Tahlequah will do just that.

BY THE NUMBERS

Gutta Percha

200

Years since William Montgomerie noticed that gum from trees of the genus *Palaquium* was firm when cool but could be molded when hot. As Singapore's first surgeon, he wrote to the Medical Board of Calcutta that it might be a "valuable substitute" for materials used in splints and other custom medical devices.

30

Grains of gutta percha that could be mixed with benzene and rubber to form a thin liquid. When it dried, it created an airtight seal on the skin. By 1848 a similar product marketed as Traumaticine was used to protect open wounds and treat skin conditions as varied as eczema, psoriasis and ringworm.

2

Tubes made of gutta percha in the first binaural stethoscope, which allowed physicians to listen with both ears. It debuted at the Great Exhibition in London in 1851.

25

Nautical miles of the first undersea cable, in 1851, made possible by a waterproof coating of gutta percha. For physicians at the time, it opened another means of communication—speaking tubes that connected their front doors to their bedrooms, allowing them to communicate with midnight visitors without getting out of bed.

96

Percent of modern root canal procedures that use gutta percha to fill the space left by removed tissue, a process introduced in the 1840s. It is one of the material's only current uses. Researchers at UCLA are now working to embed dental gutta percha with nanostructural and antibiotic materials.

INFOGRAPHIC

The New Anatomy

Parts of the body are constantly being proposed or discovered. Where do they come from?

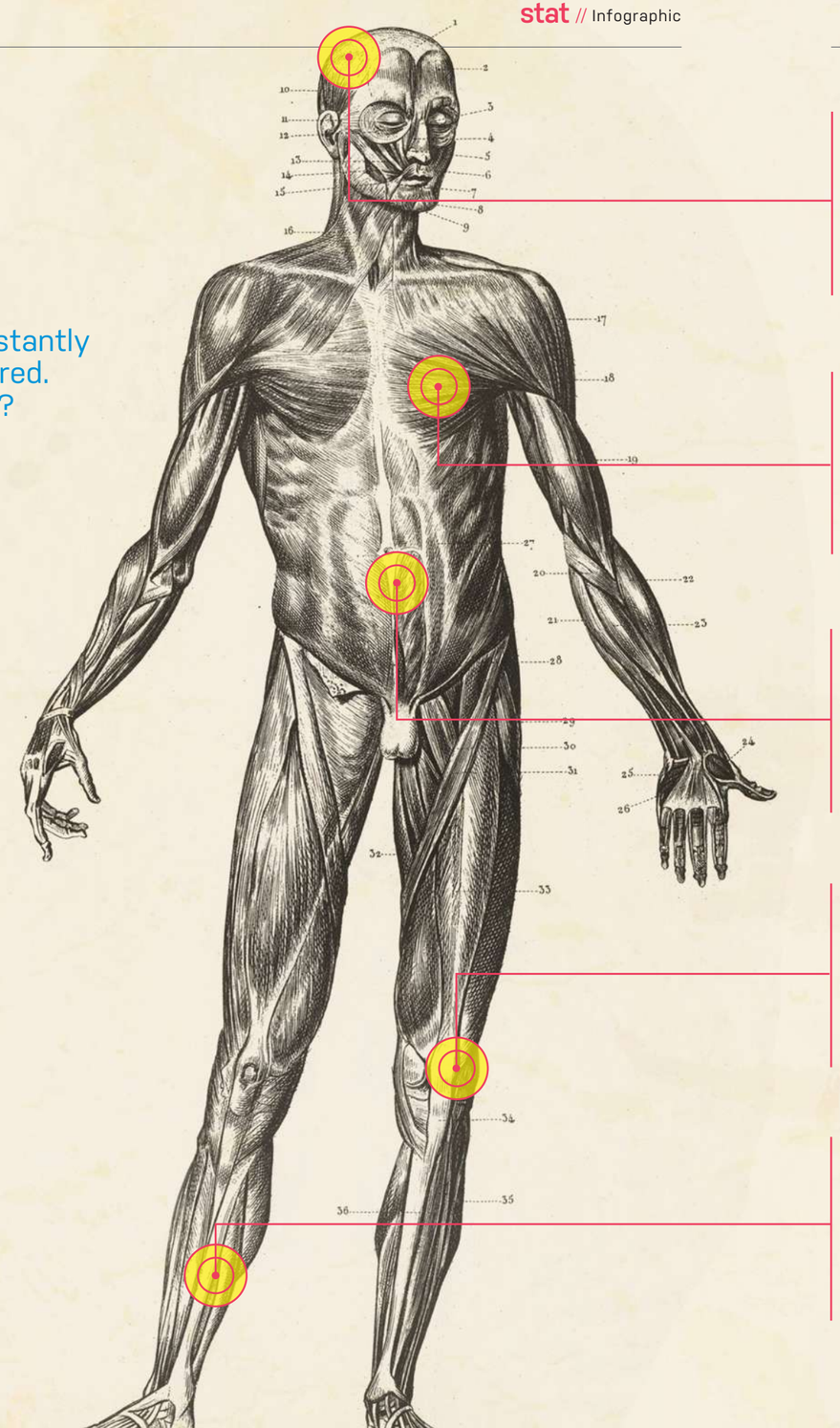
BY NAOMI ELSTER

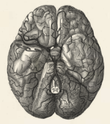
Susan Standring has been the editor in chief of the 39th, 40th and 41st editions of *Gray's Anatomy*, the venerable tome on the human body. She is now at work on the 42nd. "Hippocrates said that anatomy is the basic discourse of medicine," she says, "and like any medical discourse, it is ongoing."

It may seem curious that something as well studied as the body should harbor uncharted territory. Yet every age has managed to make discoveries, Standring says. In the sixteenth century, which she describes as "the Golden Age of anatomy," anatomists at the University of Padua in Italy corrected errors in anatomical texts that had been used for centuries.

In 1784 the German writer Goethe announced that he had found a previously unknown bone in the jaw—the intermaxillary—though two others, a few years earlier, had each discovered it independently. The passage of the Anatomy Act of 1832 eased restrictions on human dissection in the United Kingdom, opening the doors to further progress in clinical medicine, such as the first imprint of *Gray's Anatomy* in 1858.

The latest discoveries come as the result of advances in technology, Standring says. Robotic and laparoscopic surgery, for instance, allow surgeons to explore parts of the body that had previously been difficult to access in living subjects. And advances in medical imaging—which resulted in three of the five discoveries to the right—allow researchers to see living tissues in high resolution. "The recent progress has been extraordinary," she says, "and I don't see an end in sight."

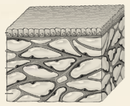




MENINGEAL LYMPHATIC SYSTEM

What it is: An elaborate network of lymph vessels in the brain

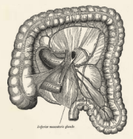
How it was discovered: These vessels lie alongside much larger blood vessels, and are quite literally in their shadow. A team at the National Institutes of Health used advanced MRI imaging to see them for the first time, and published the images in *eLIFE* in October 2017.



INTERSTITIUM

What it is: A layer of fluid-filled pockets in a web of collagen that surrounds organs like bubble wrap

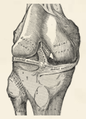
How it was discovered: Cells are normally drained of fluid for microscopy, making this tissue elusive. But researchers discovered it using a technique called confocal laser endomicroscopy. Their 2018 paper sparked debate about whether the interstitium should be counted as a new organ.



MESENTERY

What it is: A protective lining around the intestines

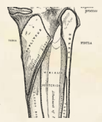
How it was discovered: Anatomists thought the tissue that connects the intestines to the abdomen was most likely composed of separate sections or compartments. But surgeon J. Calvin Coffey recently concluded, after years of study, that it is a single continuous tissue.



FABELLA

What it is: A small bone in a tendon behind the knee

How it was discovered: A 2019 study by Imperial College London researchers found that fabellae, once uncommon, are somehow making a comeback. The bone was only present in 11.2% of the population 100 years ago, yet 39% of people have it now, an increase they attribute to nutrition and lifestyle changes.



TRANS-CORTICAL VESSELS

What it is: A set of blood vessels connecting bone marrow with the bone surface

How it was discovered: In 2019 a team in Germany treated mouse bones with a chemical to make them transparent, then watched as tiny red blood vessels trickled across the shaft of long bone. TCVs transport blood both to and from the heart via veins and arteries.

POLICY WATCH

A More Ethical "Fingerprint"

Should law enforcement have broad access to public genetic data?

BY LINDA KESLAR

Thirty years ago, federal and state governments began to construct the first national genetic database for criminal investigations. It would contain the genetic signatures of people who had been arrested or convicted of a crime, and be calculated from only 13 locations on "junk DNA," which contained no medically important information.

That goal of protecting genetic privacy—and broadly keeping medical data out of law enforcement's hands—has been all but forgotten in recent years. Police now routinely turn instead to public genetic databases, where everyday people share a broad range of personal genomic information. This method allows authorities to track down suspects or their relatives, and has helped them close nearly two dozen cold cases, including the capture of the Golden State Killer in 2018.

"Catching dangerous criminals is a good thing, but privacy is also important," says Natalie Ram, a professor at the University of Baltimore School of Law. Many are concerned about overreach, as unrestrained access to genetic data could be used to pursue even minor criminals, she says, or allow the genetic surveillance of targeted population groups.

Ram and her colleagues have called for new legislation to limit these kinds of searches. Meanwhile, researchers from Vanderbilt University in Nashville, Tennessee, have proposed a more radical solution—a universal genetic forensic database. This deliberately provocative argument, published in Science in November 2018, suggested that a master database of all U.S. citizens' DNA, stripped of all but the barest signifiers, would at least prevent further intrusions by law enforcement into medical records and other confidential sources.

Another approach would be to enact a law similar to the Health Insurance Protection and Portability Act, which shields patient records from public access. The new statute could be designed to specifically protect genetic information. Sally Greenberg, executive director of the National Consumers League, has been meeting with members of Congress to promote such a firewall between the data that law enforcement agencies compile and the data contained in consumer DNA databases. "What we're seeing now is the one being added to the other," Greenberg says. "That shouldn't happen."

MEDUCATION

Higher Education

Medical marijuana has swept the country, but physicians aren't trained how to use it.

BY ANITA SLOMSKI

CHRIS GASH

The use of cannabis as a therapeutic drug is now legal in 33 states and the District of Columbia. Yet patients who ask physicians whether marijuana can help them are often met with anything but an informed response. For their part, physicians complain about a lack of information about what medical cannabis can do and what role they are supposed to be playing.

While laws have been changing, medical school curricula have not. In a 2017 study published in *Drug and Alcohol Dependence*, researchers at Washington University School of Medicine in St. Louis found that only 9% of U.S. medical schools included medical marijuana in the curriculum. And 85% of the 258 residents and fellows surveyed said they had not received any education about therapeutic cannabis at medical schools or in residency programs.

"In medical school, we learn about marijuana as an illicit drug, similar to how we learn about other illicit drugs like heroin and cocaine," says Anastasia Evanoff, first author of the 2017 study and a fourth-year medical student at Washington University School of Medicine. "We're taught the pharmacokinetics of marijuana in the body. But we never learn how to prescribe it."

Part of the problem is that physicians aren't technically *allowed* to prescribe cannabis, which the U.S. Drug Enforcement Administration still considers an illegal drug. They can simply "recommend" it if a patient has a health condition on the state's approved list. But without a prescribing system, such recommendations can be ignored, and physicians have no say in what their patients receive at official dispensaries.

"It's medical malpractice to have 20-something-year-old 'budtenders'—employees of the dispensaries—making decisions about strains and doses of medical cannabis," says internist and emergency physician Jordan Tishler, president of the Association of Cannabis Specialists. "We have to change this to the real practice of medicine before medical schools or residency programs will consider making medical cannabis part of medical education."

Rigor is lacking in other areas, too. Clinical trials have demonstrated that cannabis can alleviate nausea and vomiting from cancer chemotherapy; provide relief from chronic pain and from pain related to cancer, neuropathy and multiple sclerosis; and may help treat epilepsy, glaucoma, post-traumatic stress disorder and Crohn's disease. But because cannabis is a Schedule I drug—hence illegal—additional trials that could substantiate these and other medicinal claims are notoriously challenging to conduct. While state legislatures have been persuaded to make medical marijuana available, medical schools have so far been reluctant to add this field of study to an already overloaded curriculum.

"Medical schools teach the solid fundamentals of medicine, and we're impeded in our knowledge of medical marijuana because of the regulatory issues surrounding it," says Laura Jean Bierut, professor of psychiatry at Washington University School of Medicine. She is the former member of the National Advisory Council on Drug Abuse and co-researcher—with daughter Anastasia Evanoff—on the doctors-in-training and medical marijuana study.

The Association of American Medical Colleges agrees: "U.S. medical education is grounded in evidence-based science. The academic medicine community eagerly awaits the results of research studies currently underway that are examining the efficacy and safety of medicinal cannabis," writes Alison Whelan, chief medical education officer of AAMC, in a statement for *Proto*.

Pharmacists, on the other hand, seem more willing to embrace the reality of medical marijuana. Sixty-two percent of U.S. pharmacy schools have already added medical cannabis to the curriculum—and 23% of schools planned to make it part of the curriculum within the year, according to new research from the University of Pittsburgh School of Pharmacy. "Student pharmacists must be prepared to care for patients using marijuana either alone or in combination with prescribed medications, over-the-counter products, and supplements," write the researchers.

> "We're impeded in our knowledge of medical marijuana because of regulatory issues."

The opioid crisis may offer a more pressing reason to study the applications of medical cannabis. Research has suggested that patients may switch to cannabis as an alternative to opioids for chronic pain. One study found that daily doses of prescribed opioids declined by 14.4% per year in Medicare recipients when medical marijuana dispensaries opened. And a new study of patients with an average age of 81 found that nearly one-third reduced their opioid medications after using medical cannabis and experiencing relief from pain, sleep problems, neuropathy and anxiety. Last year, two Harvard medical students published an essay in *STAT*, a health-oriented news website, calling for medical schools to teach medical marijuana as a "public health imperative" to help with the opioid crisis.

When the shift does come, says Laura Bierut, it is likely to come from doctors in training, who will push to put more information about medical cannabis on the curricula. "All physicians should get training on medical marijuana," she says, "but just as often happens with other innovations and new technology, young physicians will likely take the lead in teaching older physicians."

SECOND OPINION

Mitigating Health Care Violence

An emergency room is a dangerous place—ask any emergency nurse or physician. The pervasiveness of violence in health care settings can be attributed to several causes, as outlined in "When Healers Get Hurt" (Winter 2019). They include the reactive nature of security measures, high volume, long wait times and inadequate staffing. Regardless of cause, available literature suggests that nurses will leave a violent environment, leading to predictable shortages and detrimental effects on patient care.

Critical to the identification and mitigation of violence in health care settings is data to guide interventions that are appropriate to the setting. Violence prevention is not a one-size-fits-all process. Reporting incidents of violence in health care settings, however, is fraught. There are roadblocks in terms of complicated reporting processes, an absence of policies to allow for thorough reporting, and passive or active resistance on the part of health care institutions that discourage nurses and other health care workers from reporting.

Research suggests that a multipronged approach is necessary, including better training for the early recognition of potentially violent patients and of de-escalation techniques. These interventions should be guided by data, so first steps for any organization should include a simple and streamlined reporting process that provides the right people with the data they need to make a difference.

Lisa A. Wolf // Director, Institute for Emergency Nursing Research, Emergency Nurses Assn., Schaumburg, Illinois

Better Controlling STDs

"Danger in the Sheets" (Winter 2019) discusses the rise of sexually transmitted diseases (STDs) in the United States and mentions perhaps the most significant barrier in the first sentence: Disentangling our predisposition to mix "moral judgment with medical solutions." This is key to more effective STD control.

The majority of treatable STDs often lack symptoms, so those infected aren't always aware of their condition. As a result, broad-scale screening is the most effective way to identify STDs.

But how do we get from here to there? Patients need to advocate for their own sexual health by demanding better, affordable and accessible testing. And health care providers need to treat sexual health screening how they used to treat Pap testing—as an annual event that maintains patient health with no implied judgment. Parents should also encourage their children to adopt healthy, routine vaccination and screening behaviors. When we start to consider STDs in the same light as we consider the flu, strep throat or virtually any other infectious disease, we will begin to see a revolution in the success of STD control efforts.

Barbara Van Der Pol // President, American Sexually Transmitted Diseases Association, Durham, North Carolina

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

MISSED THE LAST ISSUE?
All stories from *Proto*, Winter 2019, are available at protomag.com.

RETHINKING THE PERFECT ORGAN

The critical shortage of organs isn't going away. Revising the current guidelines about who should be a donor—and who should be a recipient—might save lives.

By Anita Slomski // Art by Kyle Bean

At 74, Stephen Farrell was the second oldest person to receive a heart transplant at Massachusetts General Hospital—and among the first to receive a heart infected with hepatitis C (HCV). It was offered to Farrell in April 2018, and came with the certainty that he would be exposed to the virus. Farrell had been waiting three years for a new heart, and he reasoned that this one was better than the alternative—the ventricular assist device that he relied on to keep his own heart beating. He decided to go through with the surgery, and before long he was able to carry his own clubs through a full game of golf for the first time in nearly a decade. Now he also walks his dog every day and has returned to his position as sweeper on his curling team. As for the HCV, Farrell got the first dose of a curative therapy on his way to the operating room, and there is no sign of the disease now. "It turned out to be a great heart," he says.

Just a few years ago, that heart would have gone to waste or perhaps been transplanted into someone whose own organs were failing because of advanced HCV. Farrell might well have died before getting a transplant—the fate of 5,000 patients in the United States in 2018 who never received the organs they needed. Waiting lists for hearts, lungs, kidneys and livers now contain more than 110,000 people, and hospitals are working against the clock to find healthy, suitable matches.

One solution may be to review the rules for organ transplants and bring them in line with changing clinical realities. Now that HCV has an effective cure, organs from donors with the virus can be transplanted into any willing recipient. "We have such a critical shortage of organs that we need to find new solutions, including intentionally giving patients an infection along with a new organ," says surgeon Julie Heimbach, chair of the division of transplantation surgery at Mayo Clinic in Rochester, Minn. Another surprising candidate may be organs from donors infected with HIV—an infection that's manageable though not yet curable. More than a million people in the United States are now estimated to be living with the virus and may be candidates for organs that are also HIV positive.

On the other side of the donor-recipient equation, rethinking current guidelines also expands those who may be candidates to receive a new organ. Several conditions—obesity, alcoholism and certain kinds of drug use among them—often lead to failing organs, but people who have these conditions have generally been considered poor candidates to draw on the scarce supply of new organs. Yet increasing evidence shows that some of these patients do very well after transplant surgery, which can mean the difference between years of suffering and a chance to thrive.

These and other changes are upending longstanding approaches to which organs can be transplanted and who should receive them. "There has been a sea change in how we think about allocating organs today," says Joren Madsen, the cardiac surgeon who directs the transplant center at MGH. "By broadening the criteria for what constitutes an acceptable organ, patients who need organs the most will now have a greater chance of getting them."

Until recently people living with HCV were in the queue waiting for transplants. The condition slowly destroys the liver through a progression to cirrhosis, an irreversible scarring, or to liver cancer.

Treatments have existed since shortly after the disease was discovered in 1989. But they had a success rate of less than 50% and required weekly injections with side effects that included depression and anxiety. As a result, many avoided or abandoned them.

That situation changed in 2014 with the arrival of antivirals that could directly attack the virus, curing up to 98% of HCV infections. The new therapy not only reduces the need for liver transplants in these patients, but it has also meant that organs from HCV-infected donors, which had been discarded, can now be used for transplants more broadly. "We transplant organs with other viruses all the time—glandular fever virus and cytomegalovirus, for instance, which you have for life and require treatment after transplant," says Cameron Wolfe, associate professor of medicine at Duke University School of Medicine. "With thousands of people on organ waiting lists, it's egregious not to use high-quality organs from donors with hepatitis C."

Transplanting those organs into HCV-negative candidates is not yet standard practice. But all 30 kidney transplant recipients of HCV donor organs in pilot trials at Johns Hopkins and the University of Pennsylvania were cured of HCV, and outcomes for those patients at one year were just as good as for those who received HCV-negative kidneys. In addition, a study published in *The New England Journal of Medicine* in April 2019 looked at 44 patients who received hepatitis C–infected hearts or lungs. Researchers found that the transplants were safe and that the transmitted HCV was eradicated with a four-week course of treatment post-transplant. "If people run into any problems with a transplant, they tend to happen within the first year," says Wolfe, who believes these early results are likely to hold up, encouraging wider use of HCV-infected organs.

All told there have been just over 100 HCV-positive organs transplanted into uninfected U.S. patients in the published literature, estimates Christine Durand, transplant researcher and associate professor of medicine at Johns Hopkins Medicine. "HCV-infected organs may provide an additional 500 to 1,000 kidneys annually, and they could make a big impact in liver, lung and heart transplantation, too," she says. "Wait times may drop from years to months for candidates willing to accept these organs." And while a recent survey of Chicago patients waiting for transplants showed many were reluctant to take an HCV-infected organ, 46% of people *were* willing, says Raymond Chung, medical director of the liver transplant program at MGH, who conducted the study.

Some who argue for using organs with HCV want to go a step further and advocate wider use of organs from "increased risk" donors. The federal government requires that label when a donor was recently in prison, had a sexually transmitted disease in the past year or was a sex worker, an intravenous drug user or a man who had sex with men. Such situations and behavior statistically correlate with higher rates of HCV, hepatitis B and HIV infection. About one in four deceased organ donors falls into one or more of those categories—and though "increased risk" organs can be used if a recipient consents, a large proportion end up being declined.

Yet the donor may not have had any of those infections, and now, with better tests, the actual risk is very low. All deceased organ donors are screened, and that catches most if not quite all possible infections, leaving an approximately 0.2% chance that a donated organ might transmit a disease physicians didn't anticipate, Wolfe estimates. There has been no unintentional transmission of HIV through transplant since 2009, and only a handful of missed early infections of HCV.

ORGANS FROM HCV-INFECTED DONORS, WHICH HAD BEEN DISCARDED, CAN NOW BE USED FOR TRANSPLANTS.

How many viable organs in this classification go to waste? In a recent study, Durand found that more than 2,300 were discarded from 2000 through 2007 after being procured from increased-risk donors or those who tested positive for HCV. Another study found that 20% of kidneys from such donors in 2016 weren't transplanted. "This is just the tip of the iceberg," Durand says. "Many more of these organs are never even offered to those on the waiting lists."

Among patients who were offered a heart from an increased-risk donor—and chose not to take it—21% were still waiting for a transplant a year later, and 8% had died or were near death, according to research by Michael Mulvihill, a transplant surgery resident at Duke University School of Medicine. "By declining the organ, there was a real risk that they wouldn't live to receive another offer," says Mulvihill, who also found reduced survival rates among patients who turned down lungs from increased-risk donors.

Because there's not yet a cure for HIV, organs from donors with that virus are in a special category. Transplants from HIV-infected donors were illegal until the law changed in 2013, and it wasn't until 2016 that physicians at Johns Hopkins conducted the first transplants of kidneys and livers from HIV-positive donors to recipients who also had the virus. (South Africa, with the world's highest incidence of HIV, began HIV-to-HIV transplants in 2008.) Such transplants remain rare in this country, with only about 100 performed to date, in part because of strict certification rules that require centers to have experience transplanting HIV-negative organs into HIV-positive recipients—operations that didn't begin until the early 2000s and have remained relatively rare. "Fewer than 30 centers have been approved, and only 15 have done the transplants so far," Wolfe says.

Most transplant physicians believe those restrictions are excessive and hope they'll

PHOTOS BY SARA MORRIS

be relaxed soon. But there are also medical barriers, which include potential complications affecting people with HIV who receive organs, even when the donated livers or kidneys aren't infected with HIV. Those patients' immune systems seem to reject new organs at marginally higher-than-normal rates, possibly because antiretroviral HIV medications interact with the immunosuppressant drugs necessary after a transplant. Also, the immune system of patients living with HIV may be more reactive in general, and therefore prone to recognizing the donated organ as foreign. In an HIV-to-HIV transplant, there's also a very small chance of "superinfection," in which the organ recipient gets infected with a different strain of HIV that resists treatment.

IT IS INCUMBENT ON TRANSPLANT PHYSICIANS TO FIND WAYS TO USE EVERY AVAILABLE ORGAN.

Some questions about the safety of HIV-to-HIV transplants may be answered by the results of two five-year trials now getting started. One will enroll 160 HIV-positive patients who will receive a kidney from an infected or uninfected donor, and a similar study will look at liver transplants. The results may further pave the way to a lifesaving role for HIV-positive donors.

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If transplanted organs are to save lives, they must make their way to people who can make the best use of them. But the rules for deciding who that may be could also be outdated. In the past, people with alcohol-associated liver disease had to achieve complete sobriety before becoming transplant candidates, including completion of addiction treatment and a prolonged period of abstinence. People who suffered from obesity, which can damage the liver and other organs, were also denied transplants unless they lost weight. Those recovering from drug addictions and using maintenance therapies, such as methadone, typically weren't considered at all. But now those rules are tentatively being rethought.

"Until very recently, most transplant programs wouldn't even consider people if they hadn't been sober for at least six months," says Norah Terrault, professor of medicine and chief of gastroenterology and liver diseases at the University of Southern California. Many people with alcoholic hepatitis die within months of the onset of their disease, leaving them no opportunity to stop drinking, let alone wait in line for a new liver. But it turns out that giving those patients new livers may do more than give them a temporary reprieve. In 2011, an influential French study of 26 carefully selected patients with alcoholic hepatitis who received transplants without a requisite period of abstinence from alcohol found that only three of the 26, who had been chosen because of their supportive families and a strong commitment to stop drinking, resumed drinking within two years of their surgery. Moreover, 77% of those who got transplants were still alive two years later, a dramatically better survival rate than the 23% of a control group of patients who didn't receive early transplants.

A recent large U.S. study has shown similar findings. "Data to support the use of the mandated six months of sobriety are weak, but many transplant centers adhere to it," Terrault says. Taking a step away from that rule, a pilot study at MGH is providing liver transplants for a few patients with alcoholic hepatitis who fall short of the sobriety rule but meet other strict criteria. They can't have been previously hospitalized for the disease and must have good family support. "These are patients who haven't been fully educated on the ramifications of heavy drinking and haven't been given a chance to get sober," says James Markmann, chief of the division of transplantation at MGH. "Alcoholic hepatitis is a disease, and if the outcome is that 90% of patients abstain from drinking after transplant, why wouldn't we give them a new liver?"

Rules based on obesity might also need to be rethought. The condition often comes with a buildup of fat in the liver, which can cause scarring similar to that found in alcoholic cirrhosis. Nonalcoholic fatty liver disease often destroys that organ, leaving these patients in need of a new one, but their obesity typically means they can't get a transplant. "We found that obese patients who got a transplant often didn't do well," says the Mayo Clinic's Julie Heimbach. "Recovery is difficult, complications are more prevalent and the fatty liver disease could return, along with other problems related to obesity, such as heart disease or diabetes."

Standard care is to encourage weight loss before someone is added to a transplant list, but many people fail to shed the pounds. In 2009, in tandem with a liver transplant, Heimbach began to perform a sleeve gastrectomy—a type of bariatric surgery—so that patients would have a better chance of maintaining a healthy weight after receiving a new liver. These patients had been too sick for bariatric surgery before a transplant, but because the stomach is next to the liver, combining a liver transplant with a sleeve gastrectomy is "very straightforward" surgery, Heimbach says. Three years later, all of the patients who had the combined operations have maintained a healthy weight versus just 29% of patients who had shed sufficient pounds to meet the normal requirements for a transplant. Now patients from around the country who have been rejected as transplant candidates because of their obesity are lining up for the surgery. "One patient in his fifties had been in hospice. He had the combined surgery and is doing great now," Heimbach says.

Changing rules for those who have struggled with addiction may also have outsized benefits. Former intravenous drug users who keep their addiction at bay with opioid agonist therapy (OAT), taking prescribed methadone or buprenorphine, are often not considered suitable candidates for organ transplants. An estimated 30% of transplant centers require that people stop the maintenance therapy for at least six months before they can go on a transplant list. This is a harmful policy not based on evidence, says MGH addiction specialist and psychiatrist Ana Ivkovic. "Asking people to come off OAT to be listed for transplant is like asking a diabetic to stop taking insulin before transplant," Ivkovic says.

One study followed 36 patients on methadone maintenance therapy for five years after liver transplant. Only 11% went back to taking intravenous drugs, and transplant outcomes for the group matched overall national averages. The best predictors of successful transplants among former drug users are solid social support networks and treatment for substance abuse disorder as well as for concurrent psychiatric illnesses such as depression and anxiety, Ivkovic says. "We want to give everyone with opioid use disorder a solid chance," she says.

The timing for revisiting these rules could not be more important. Rates of chronic liver disease are on the rise, and in 2018, a record 36,527 U.S. transplants were performed, continuing a five-year upward trend. Someday, transplants may not need to be governed by laws of scarcity, says MGH's James Markmann. "There are some amazing new technologies coming that have the potential to dramatically change how we do transplantation, such as reducing the need for immunosuppression, genetic editing to make animal organs suitable for use in humans, and stem cell technologies that will eliminate the need for some transplants," he says. "I can see a time when there will be no shortage of organs for transplantation."

Until then, however, it's incumbent on transplant physicians to find ways to use every available organ, and to get them to the patients who are desperately waiting. Says Christine Durand of Johns Hopkins: "Donors and their families give organs to save lives. It's up to us to find the best ways to honor those gifts."

DOSSIER

"Personal Viewpoint on Opioid Agonist Therapy and Transplantation," by Ana Ivkovic and Sarah Wakeman, *American Journal of Transplantation*, September 2018. This editorial argues that transplant centers that require people with opioid use disorders to discontinue opioid agonist therapy are employing an outdated and harmful policy.

"The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States," by Christine M. Durand et al., *Annals of Internal Medicine*, April 2018. This study found that patients who received organs from overdose death donors did as well as patients who received organs from non-overdose death donors.

"Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients," by Ann E. Woolley et al., *The New England Journal of Medicine*, April 2019. This study shows that treatment immediately after a transplant can wipe out the infection from hepatitis C–positive lungs and hearts.

The Solid Tumor

BARRIER

New T cell therapies succeed with a narrow band of cancers. Can they be made to work for the rest of them, too?

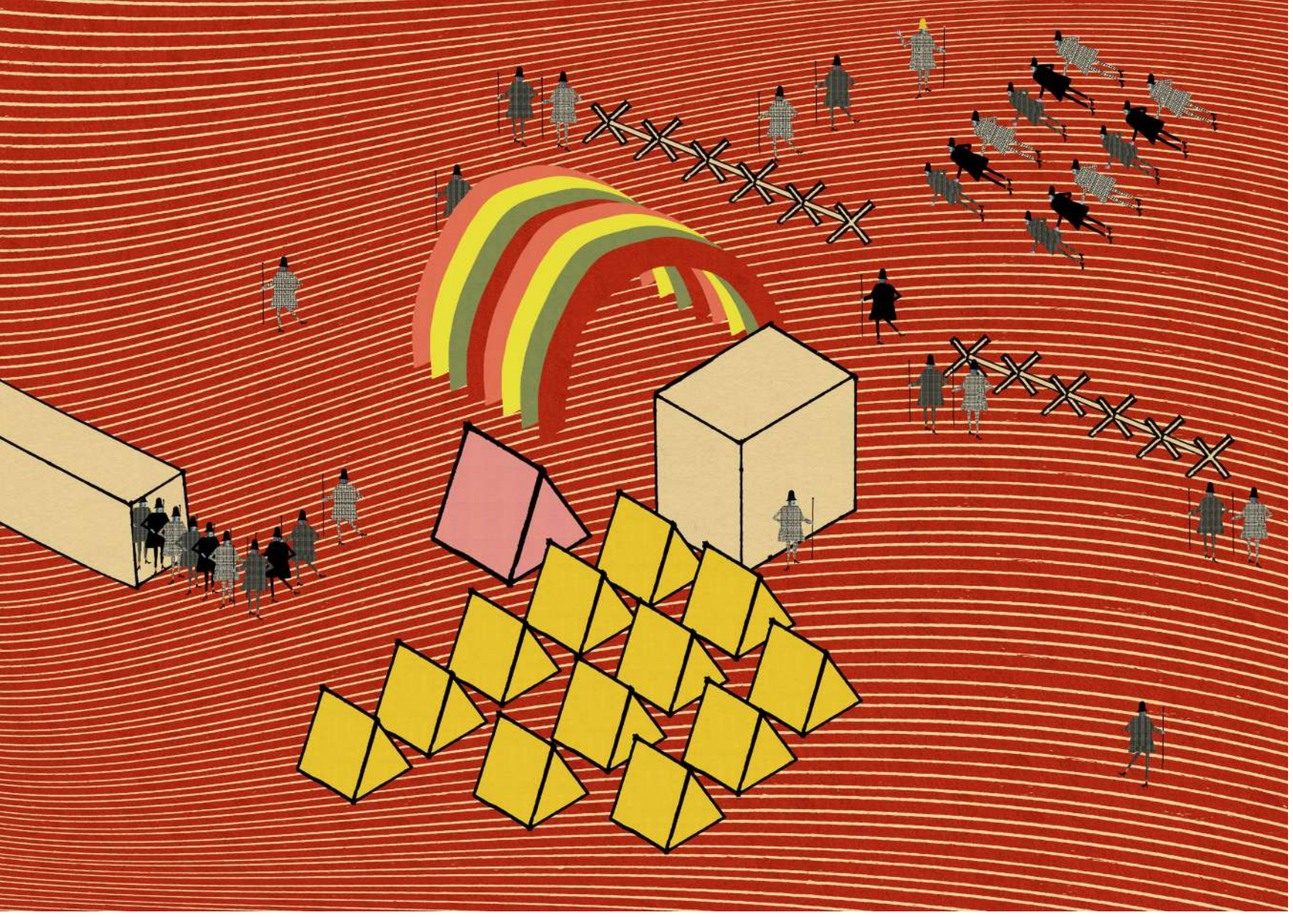
By Jane Palmer // Illustrations by Ryan Peltier

On a bright, Kansas summer morning, Emily Dumler was at a friend's house with her children when her stomach began to hurt. She went to the restroom and was shocked to see blood in her stool. Her doctor advised her to go straight to the emergency room, which became the first stop in a 43-day hospital stay, and resulted in the removal of her spleen and an eventual diagnosis of non-Hodgkin's lymphoma, a cancer that starts in white blood cells.

For the next two years, Dumler received a barrage of treatments. She went through rounds of chemotherapy and her bone marrow was seeded with stem cells in the hope they would generate a healthy new crop of blood. The cancer continued to progress, however, and in May 2015 Dumler was given fewer than six months to live.

Her physician told her about an experimental new treatment and helped her secure the last opening in a trial taking place at the MD Anderson Cancer Center in Houston. Clinicians there extracted T cells from Dumler's blood, genetically modified them to make them targeted cancer killers, then reinfused them into her body. The process is called chimeric antigen receptor T cell therapy, or CAR T cell therapy, and Dumler was the third lymphoma patient in the world to receive it.

Dumler returned home nine days after the treatment, and within weeks she felt better. Scans in August 2015 showed that her cancer had gone completely, and tests since then have



found no sign of its return. “Everything I do today, I didn’t think I would ever be able to do again,” Dumler says. “This treatment gave me back my life.”

For the past 45 years, researchers have been looking for ways to amplify the body’s immune response to cancer. Among these, CAR T has been a recent standout, achieving initial remission rates of as high as 90% in some cancers. In 2017, the U.S. Food and Drug Administration approved the first of two new CAR T therapies to treat blood cancers, and the American Society of Clinical Oncology named CAR T the 2018 Advance of the Year.

But while CAR T therapies have proved very good at their current FDA-approved use—curing blood cancers—their track record has been mixed for the much more common varieties of cancer that begin in epithelial cells and form solid tumors. Almost 90% of cancer deaths in the United States—including those from breast cancer, prostate cancer and colon cancer—fall into the second category. The fight against these solid tumors has always put immune cells at a disadvantage. Tumors often grow in parts of the body that are difficult for immune cells to reach, and create microenvironments that can impede any immune cells that do mount an attack.

CAR T’s proponents believe that each of these obstacles could be overcome by clever engineering. This enthusiasm has not only sparked hundreds of investigations, but also renewed interest in older methods of extracting and manipulating T cells to fight cancer. Steven Rosenberg, chief of surgery at the National Cancer Institute and a pioneer of cell-based cancer therapy, continues to pursue a related method in which T cells are also multiplied outside the body and reinjected, which has shown great promise against solid tumors. “We’re working around the clock to try to solve the challenges,” Rosenberg says. “The main stimulus for this research is that we know it can work.”

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The chimera was a mythical beast that contained parts from three different animals. Chimeric antigen receptor therapy, similarly, is a curious hybrid not found in nature. At its base is a human T cell, which normally scours the blood stream for threats to the body. When it finds them, it marshals a wider immune response, sometimes attacking directly, and it recognizes these threats by means of a claw-like extension called an antigen receptor. In CAR T cell therapy, clinicians take these T cells out of the body and reprogram their antigen receptors to look for specific proteins found on cancer cells—and instructs them to attack every time.

Since the approval of the first two CAR T therapies in 2017, studies of Tisagenlecleucel (Kymriah) in treating acute lymphoblastic leukemia have shown initial remission rates of 80% to 90%. Axicabtagene ciloleucel (Yescarta) kept 39% of treated patients in remission from refractory non-Hodgkin’s lymphoma for more than two years.

Now many research centers are working to refine CAR T, focusing on the indications that have been proven to work—treating cancers of the circulatory and lymphatic systems. A chief goal for the next generation of treatments is to mute side effects, which can be dangerous and sometimes fatal.

One thread of current research is looking at why some CAR T therapies are less harmful than others. Although both Yescarta and Kymriah target the same antigen—CD19—they use different methods to kick T cells into action. Yescarta delivers a fast and intense T cell response, while Kymriah takes a slower, steadier approach.

Jeremy Abramson, director of the Jon and JoAnn Hagler Center for Lymphoma at Massachusetts General Hospital, is the principal investigator of a trial testing liso-cel, another CAR T therapy for treating non-Hodgkin’s lymphoma. Liso-cel uses a mechanism of action similar to that of Kymriah, and “it looks like those two products do have a more favorable safety profile,” he says. Liso-cel differs from Kymriah, however, in the mix of CAR T cells that it uses. T cells come in two major subtypes, CD4+ and CD8+, and liso-cel administers these to patients in a 1:1 ratio. Studies in mice suggested that the fixed ratio improves effectiveness, though it remains to be seen whether this will prove true in humans, Abramson says.

Even the existing CAR T therapies would likely be more effective if they were used in earlier stages of lymphoma. Currently they are approved only to treat patients who have received two other forms of cancer therapy without success. “These patients are usually fairly beat up, and they often have a lot of lymphoma in their bodies,” Abramson says. Starting treatment earlier might also enable researchers to collect healthier T cells that haven’t been weakened by chemotherapy.

FOR THE PAST 45 YEARS, RESEARCHERS HAVE BEEN LOOKING FOR WAYS TO AMPLIFY THE BODY’S IMMUNE RESPONSE TO CANCER.

Three clinical trials exploring this approach are underway.

On the whole, the future appears bright for using CAR T cell therapy in the treatment of blood and lymphatic cancers. “We’re offering a potentially curable therapy to previously incurable patients,” Abramson says. But many have their eyes on a different prize—a form of the therapy that would work against the much larger class of solid tumors.

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T cells can easily find their way to cancers of the blood or lymph nodes because these are where T cells naturally circulate. But solid tumors can occur anywhere in the body, including in regions such as the brain, where immune cells rarely go—and where an overactive immune system can cause multiple sclerosis or other kinds of collateral damage.

Some researchers believe that the best way to sidestep that problem is to deliver CAR T cells directly to the tumor. Christine Brown, associate director of the T Cell Therapeutics Research Laboratory at City of Hope in Duarte, California, has pioneered a way to get the cells near the tumors of glioblastoma, the most common form of brain cancer. She injects the cells into the tumor and into two cavities called the lateral ventricles, where cerebrospinal fluid is made. Together, these delivery methods have shown promising results in preclinical trials.

In 2015 Brown and her team engineered CAR T cells to target the antigen IL13Rα2, a substance produced by glioblastoma, and used this method to infuse several doses of CAR T cells into a man with aggressive cancer. The patient’s brain tumors completely disappeared. Tumors that contained less of the same antigen later sprung up, however, and he died 20 months later.

Delivering CAR T cells close to a solid tumor is only part of the solution. The microenvironment around tumors lacks oxygen and nutrients, which smothers and starves immune cells. It also contains chemical signals that fool the immune system into thinking it isn’t needed. “The solid tumor puts up lots of biologic and physical fences,” says Marcela Maus, director of cellular immunotherapy at Massachusetts General Hospital Cancer Center, whose group is also investigating CAR T therapy for glioblastoma.

Some labs are experimenting with also using checkpoint inhibitors, established immunotherapy drugs that can shut down the false signals that a tumor broadcasts. Still others have engineered countersignals into the CAR T cells themselves. These can both scramble the tumor’s protective signal and call for additional immune support.

Perhaps the most daunting task with solid tumors, however, is pointing T cells toward the right antigen—the molecule on the cancer cells that they must latch on to. For a CAR T treatment, an ideal antigen is one that’s expressed by most of the cancer cells

but by very few healthy cells. In cancers of the blood, researchers have found such an antigen—CD19—but finding an equivalent target in solid tumors has been more difficult. One batch of CAR T cells was designed to target HER2, an antigen characteristic of some aggressive breast cancers. The treatment, however, seemed to attack cells in the lung that naturally expressed HER2, with fatal results.

Maus's team is developing a CAR T therapy that targets two or more antigens. This allows them to narrow in on more specific cells in the same way that an internet browser can get more specific when it uses more than one search term. And like a browser search, Maus says, her CAR T cell can use basic logic. With an "AND" function, it requires both antigens on the same cell to fire. It can also be programmed with an "OR" function, which means that the CAR T cell works if either of the receptors is engaged—an ability that allows the researchers to use one treatment to target, for instance, two different types of cells in the same tumor.

Another researcher—Robbie Majzner, a pediatric oncologist at Stanford University School of Medicine—led a group that screened 388 tumor samples from various forms of pediatric cancer. The researchers found that one antigen—B7-H3—was present on 84% of cases, and present at high levels in 70% of cases. Yet one prototype after another of B7-H3 CAR T failed in vitro. Finally, after more than 15 formulations, they produced a version that worked. It took hold in mice with the bone cancers osteosarcoma and Ewing sarcoma. "In the first few days, the tumors continued to grow," Majzner says. "But then the T cells began chipping away at them until they were gone."

More than 270 CAR T cell trials had been registered at the U.S. National Library of Medicine by the end of 2018, with about one-third of that number investigating CAR T cells for the treatment of solid tumors. Maus is realistic about the obstacles. "It is going to take some time," she says, "but we're working hard, and there is good reason to hope."

NCI's Steven Rosenberg, meanwhile, has continued to pursue another promising branch of his early T cell research. In the 1980s, he began to extract T cells directly from tumor sites and used those cells—tumor-infiltrating lymphocytes, or TILs—that had broken through the tumor's defenses as a "starter batch" for further therapies. By 1988, he had refined this TIL treatment to achieve sustained remissions in about 30% of his patients with metastatic melanoma. But further studies showed that although TILs could be grown in the lab from virtually any kind of tumor, only TILs from melanomas had significant antitumor activity. And even for melanoma, a different kind of immune therapy—checkpoint inhibition—proved to be much more effective than TIL treatment.

Yet Rosenberg continued to investigate why TIL treatment sometimes worked in melanoma. That cancer turned out to have unusually high mutation rates—and mutated DNA not only gives rise to cancer, but also to proteins called neoantigens, which are not found naturally in the body. Rosenberg suspected his TIL cells could have been very good at targeting these neoantigens—and that while melanoma may give rise to more of these targeted T cells, he might be able to find and amplify neoantigen-focused T cells in all cancers.

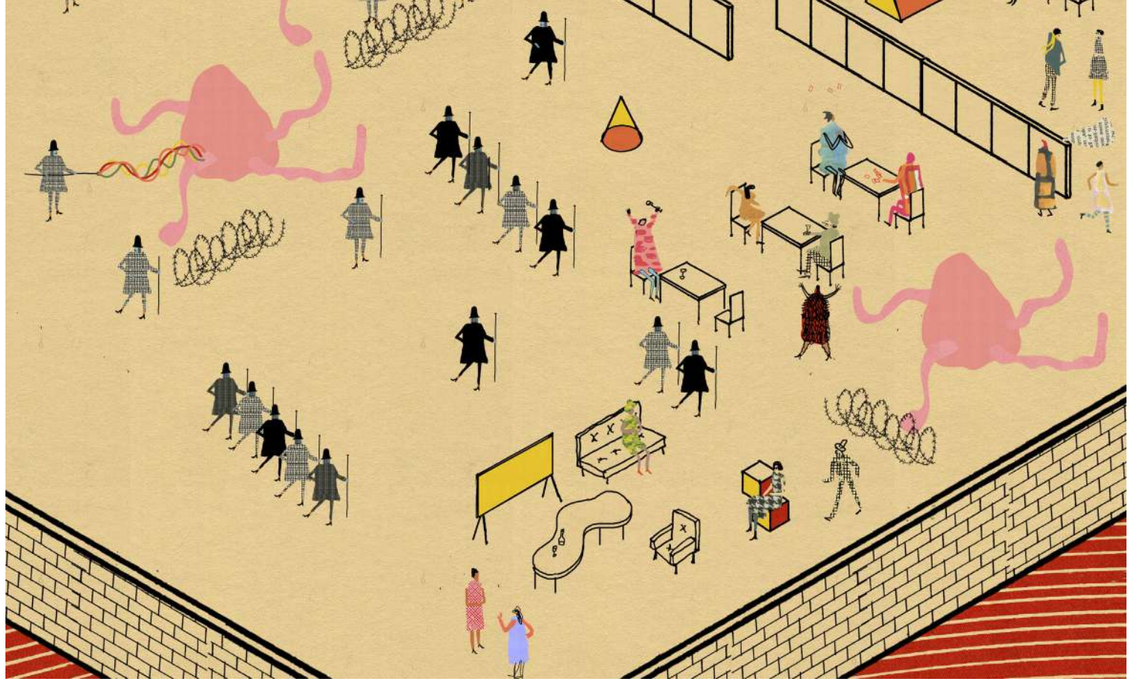
"WE'RE WORKING AROUND THE CLOCK. THE MAIN STIMULUS FOR THIS RESEARCH IS THAT WE KNOW IT CAN WORK."

Advances in genetic screening and other technologies made it possible to test this hypothesis. Since 2010, his team has looked at tumors and T cells from more than 100 patients with a variety of solid cancer types. Of these patients, 70% to 80% mounted T cell responses to the neoantigens specific to their cancer. Rosenberg says he believes that this could represent a "final common pathway" that explains the effectiveness of so-called natural immunotherapies—treatments such as IL-2, checkpoint inhibitors and TILs that rely on increasing the number of the body's own immune cells, without modifying or changing them in the lab. These T cells train themselves to home in on the neoantigens created by mutated genes. "The very products of the gene mutations that caused the cancer are likely the best targets," Rosenberg says.

His strategy for harnessing the approach is promising, if labor intensive. His team removes cancer tissue that contains T cells and performs whole-exome and RNA sequencing of the tumor. Researchers then perform the same process on normal tissue to identify which mutations are specific to the cancer. After that, they find the T cells that have homed in on those cancer-specific mutations and put them in a medium to multiply the cells in the lab, and finally reinfuse them into the patient.

In 2014 Rosenberg published the first successful TIL treatment of a patient with a common epithelial cancer—bile duct cancer. In 2016 a patient with metastatic colon cancer showed regression of the disease under TIL therapy. That same year, his team treated a woman with breast cancer who had been unresponsive to all other treatments. The screens found 62 different mutations in the patient's tumor cells and identified strains of TILs that recognized four of these mutations. The researchers then expanded these four strains in the lab and reinfused them. The patient's cancer regressed and has been in remission for more than three years. Results were published in *Nature Medicine* in 2018.

This approach, in theory, could work for any cancer because all tumors have mutations that don't exist in healthy cells, Rosenberg says. And it may be further improved by modifying TIL cells to help them compete more effectively in the tumor microenvironment—for example, by equipping them with ways to compete with deceptive immune signaling coming from the tumor.



TIL is a highly personalized therapy. In the 100 cancers that Rosenberg studied, virtually every patient's T cells recognized a different neoantigen. "We need to create a unique treatment for each patient because all of their antigens are different," Rosenberg says.

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One challenge for both TIL and CAR T cell therapies is their very high price tags. It can cost more than $1 million to treat a patient with Kymriah or Yescarta, once hospital stays and follow-up care are factored in. Because the treatments are labor-intensive and personalized, they will never be inexpensive, but new research into reducing side effects—which may include fever, low blood pressure and cognitive disruptions—could help cut hospital costs.

Automation in the lab is also helping reduce the time needed to engineer and expand T cells, from four months a decade ago to just a few weeks today. In a recent mouse study, Carl June, a pioneer of CAR T cell therapy and director of the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania, demonstrated that the typical nine to 14 days needed for expanding the cells could be reduced to three days—and the CAR T cells infused after three days appeared to be more potent than those that mature longer.

Ultimately, there could be an off-the-shelf CAR T therapy that doesn't require modifying the cells from individual patients but instead uses T cells from healthy people, and somehow fine-tunes them for a particular patient, perhaps through genetic manipulation. A current study at MGH is testing such cells. "They need a bit more tweaking to make them mass produced and widely available," Maus says, "but we are making progress."

Rosenberg has no doubt that there will be ways to simplify his TIL therapy as well and bring its costs down. But with cancer, he says, the hope of a simple, one-size-fits-all manufactured therapy may never have been an option. "Cancer is not one disease," he says, "so it's very unlikely that a single drug is ever going to solve this problem."

DOSSIER

"Making CAR T Cells a Solid Option for Solid Tumors," by Andrea Schmidts and Marcela V. Maus, *Frontiers in Immunology*, November 2018. This review focuses on novel techniques to improve the effectiveness of CAR T cell therapy in a hostile tumor environment.

"Emerging Cellular Therapies for Cancer," by Sonia Guedan et al., *Annual Review of Immunology*, April 2019. Researchers outline the various T cell therapies for cancer and detail the challenges of and recent advances in CAR T therapy.

"'Final Common Pathway' of Human Cancer Immunotherapy: Targeting Random Somatic Mutations," by Eric Tran et al., *Nature Immunology*, February 2017. This study highlights evidence indicating that many effective cancer immunotherapies act via a common pathway in fighting tumors.

LIVING MEMORY

How does the brain remember? As memory disorders become more common, the research race is on to determine how the process works, what can go wrong and how worn memories can be made whole again.

By Adam Bluestein // Photos by Dan Winters

It is possible to watch a memory forming in the brain. Researcher Sheena Josselyn at the Hospital for Sick Children in Toronto, for instance, looks through an ultralight "mini endoscope" attached to a lens in the brain of a mouse. The animal's brain cells have been tagged with substances that make them light up when they become active, and she waits to see exactly which neurons "switch on" in response to an event she thinks the animal will remember—most often, a mild electric shock.

Josselyn is fascinated by fundamental questions about memory, including how individual neurons "decide" to become part of a particular memory, called an engram. In a landmark experiment, published in 2009 in *Science*, she noted the role of neurons' "excitability." At any given time, certain neurons show an increased readiness to pass along electrical signals and connect with other neurons. Using a genetic tweak in mice to increase levels of a protein called CREB, she was able to increase the excitability of particular neurons, and found that this

influenced where in the brain a memory was encoded. She showed that the CREB-boosted cells were nearly four times as likely as neighboring neurons to become part of the engrams that her team prompted.

The memory in that experiment was an association between a shock and a musical tone. To prove that the neurons actually encoded this, she turned off the brain cells that had lit up during memory formation, selectively killing them with a toxin. When exposed to the sound again, the mouse appeared to forget what it had learned, no longer freezing in anticipation of a shock.

Josselyn has conducted a host of similar experiments, both refining her team's ability to map engrams and devising new techniques to switch them off and on again. Learning how to manipulate specific engrams in this way could yield revolutionary applications not only for memory disorders but also depression—for example, by restoring positive memories—and addiction, by eliminating pleasurable memories of using alcohol or drugs. And Josselyn says she thinks a similar approach could, if scientists can figure out how to map the complex engrams of human trauma, provide relief from a condition such as post-traumatic stress disorder.

"MEMORY IS A FUNDAMENTAL BUILDING BLOCK OF WHAT CONSTITUTES HUMANITY."

Josselyn's work is part of a new wave of research in neuroscience, aided by a convergence of increasingly powerful technologies, that seeks to reveal how memories are made, lost and might be restored. It could hardly be more timely, as the world's population rapidly ages and Alzheimer's disease and other forms of dementia threaten to erode the memories of millions of people. The National Institutes of Health is expected to spend more than $2 billion on Alzheimer's research in 2019. But most of that work remains focused on the plaques and neurofibrillary tangles that are known to cause destruction in the brain as the disease progresses. Finding how to preserve and retrieve memories that may be hidden but not yet destroyed could prove to be an important complement to the work on plaques and tangles—and an essential step in helping people avoid or mitigate the loss of an essential part of who they are. "Memory is a fundamental building block of what constitutes humanity," says Alcino Silva, professor of psychology at UCLA's Brain Research Institute. "Without memory, how much of you is left?"

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There are many types of memory. Implicit memories, such as the motor memory of how to ride a bike, are acquired and used without conscious thought. They reside in the cerebellum and the basal ganglia, deep in the brain's core. Short-term working memory, a sort of mental scratch pad that retains a small number of items for less than a minute, uses the prefrontal cortex. But most research that looks at memory—and the fear of losing it—studies declarative memory. This includes both memory of events (episodic, or autobiographical memory) and more general facts (semantic memory). It relies on three principal areas of the brain: the hippocampus, the neocortex and the amygdala.

The hippocampus, tucked deep inside the brain's temporal lobes, is where such memories are formed and indexed. Through an ongoing process called memory consolidation—which happens over the course of weeks in humans, as they sleep and dream—memories initially encoded in the hippocampus are transferred for long-term storage to the wrinkly neural tissue of the neocortex, on the brain's surface. The amygdala, an almond-shaped structure in the brain's temporal lobe, attaches emotional content to memories, making them more durable. The amygdala plays a key role in forming new fear-related memories, which tend to form quickly—making mouse experiments that use electric shocks or loud noises a popular way to investigate the mechanisms of memory formation and retrieval.

Wherever they reside in the brain, all memories, at the most fundamental level, rely on what happens in synapses, the junctions between neurons. The theoretical idea that "neurons that fire together, wire together"—that memories are formed through the strengthening of connections that happen in these synaptic junctions—was first proposed by Donald Hebb, a Canadian psychologist in 1949. What came to be known as Hebb's rule has been the fundamental insight driving the neuroscience of memory ever since, confirmed experimentally across many organisms.

An engram is born, in other words, when electrochemical signals pass through a synapse and this strengthens the connection between the adjacent neurons. With repeated stimulation during learning and recalling these memories later, the synaptic connections form an even stronger bond, in a process called long-term potentiation. Silva calls Hebb's rule one of the most significant discoveries in neuroscience. "In heredity, the fundamental discovery is DNA," he says. "In memory, it is knowing that changes in synapses encode memories."

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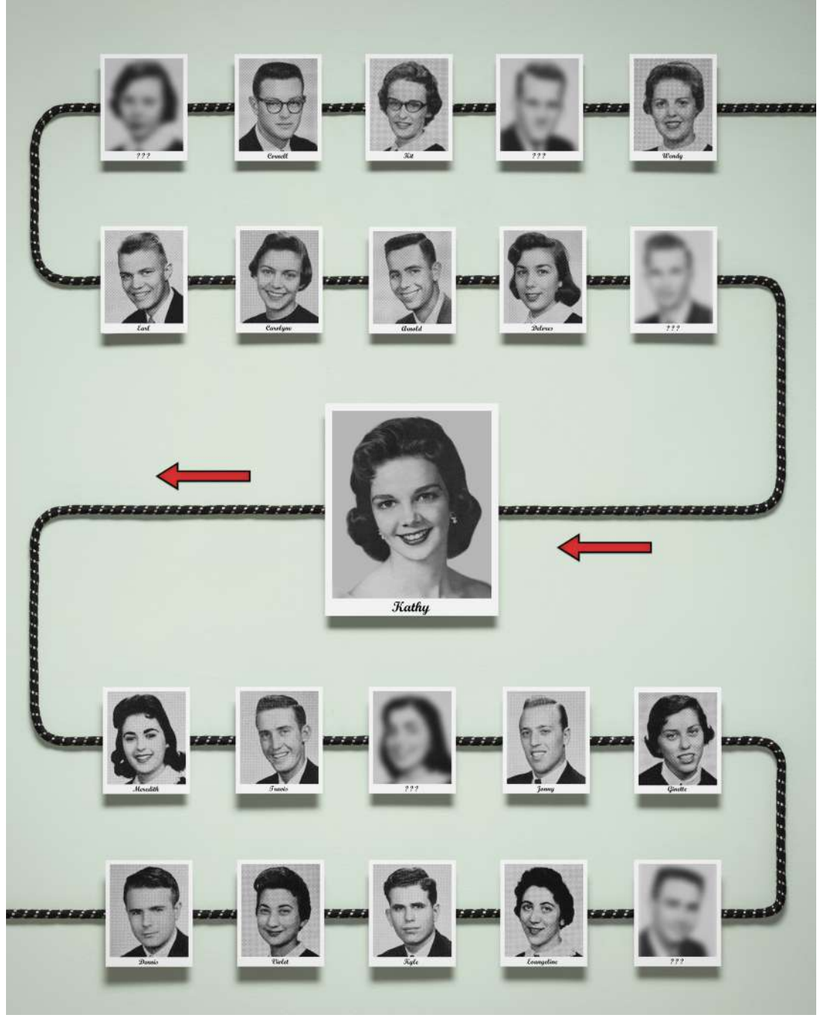
But memories don't exist in isolation. Rather, individual engrams overlap and link to each other, forming neurological webs that allow events to be anchored in time and place, and experiences to be cross-referenced with other occurrences. Silva has shown that some of the same processes involved in creating single memories are also essential in forming linked memories.



Silva hypothesized that after encoding a first memory, neurons stay in an excited state for a brief window of time, making it more likely they will participate in forming a second. Two memories created at about the same time thus would tend to use overlapping populations of neurons, increasing the chance that recall of one memory triggers recall of the other. Silva calls this the allocate-to-link hypothesis.

In a series of experiments reported in *Nature* in May 2016, researchers in Silva's lab, led by Denise Cai, now an assistant professor of neuroscience at Mount Sinai in New York, tested the allocate-to-link hypothesis in mice. First, they showed that memories linked closely in time were more likely to be recalled together. The scientists did this by placing individual mice in two different cages—first, one in which nothing happened, and then about five hours later, to a second cage in which they got a mild foot shock. After training, all of the mice froze, as expected, in the "shock" cage. But surprisingly, they also froze in the neutral cage. The memories of the two cages—and their association with a shock—appeared to be linked. Repeating the experiment, but leaving more time—longer than a day—between exposure to the two cages, the researchers found no overlap between memories. Rather, the mice behaved "normally," freezing only in the shock cage.

Next, the researchers looked at what was happening inside the mice's brains. Employing brain-imaging techniques similar to those used by Sheena Josselyn, they saw that when mice were exposed to the different cages within a few hours, they did, in fact, form memories in overlapping clusters of neurons. When the time between cages was increased, the engrams didn't overlap. Silva's group concluded that neurons, after encoding an initial memory, stayed more excitable, or plastic, for up to five hours, creating a window in which they were more likely to be folded into a second memory.

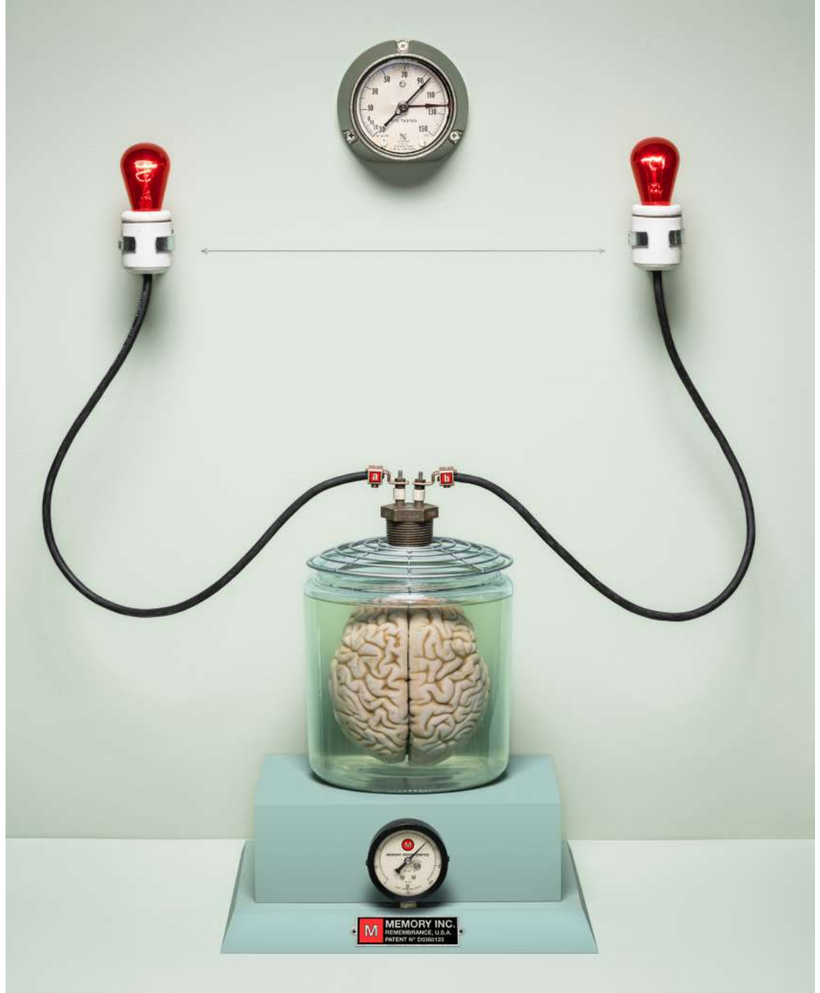
These findings about neuron excitability might also explain other kinds of links among memories, such as those that connect objects to words, or experiences to places. They also have implications for what may happen during aging. Repeating their experiments in older mice, for example, Silva's group found that while they could remember single memories as well as younger mice did, they weren't able to link memories of closely related events. The researchers suspected that this was because of a decline in neuron excitability. So they used specially targeted drugs to boost the excitability of specific neurons in older mice, which indeed restored their ability to form overlapping engrams and to link memories behaviorally. Therapies based on these findings are already under development, and could help treat not only age-related cognitive decline but also disorders such as schizophrenia, depression and bipolar disorder, in which problems with neuronal excitability are known to play a role.

The anatomy of the neuron itself may offer clues to why memory fails over time. Neuroscientists are increasingly focused on dendrites, branch-like extensions of nerve cells in the brain that probe the spaces between cells, picking up signals and communicating them to the cell body. Jutting out from these dendrites are thousands of tiny, bud-like appendages called dendritic spines, which serve as the actual points of synaptic contact with other neurons. The number and density of these spines is dynamic, fluctuating with time, and they appear to be particularly crucial in learning and memory formation.

For example, in juvenile zebra finches, commonly used in the lab to study vocal behaviors, a higher level of spine turnover—with new spines forming to replace the old—seems to be related to an increased ability to learn songs. As rodents age, however, dendritic spine formation in their brains appears to ebb, a condition that has also been observed in mice genetically engineered to have symptoms of Alzheimer's and in some forms of autism in humans.

In a 2018 study that tracked dendritic spine dynamics in mice, Silva's lab demonstrated for the first time in adult mammals that enhanced spine turnover and clustering indeed have a correlation with improved learning and memory. Mice engineered with a genetic mutation that reduces the production of the protein CCR5, which inhibits dendritic spine formation, did better on memory tests, and had more spine turnover before training, compared with nonmutated control mice. Silva says he believes that increased turnover of dendritic spines helps neurons increase synaptic connections during learning. He also thinks that, after learning, clustered spines may help to stabilize these new synapses.

Dendritic spines might also bolster resilience against Alzheimer's disease. In the October 2017 *Annals of Neurology*, scientists from the University of Alabama at Birmingham and Emory University School of Medicine compared dendritic structures in the autopsied brains of people divided into three groups: those with no signs of disease; those with some physiological indications of the disease but no symptoms of dementia; and those with full-blown Alzheimer's. Brains in the control group and from people without clinical dementia had similar levels of spine density, but the brains of people with Alzheimer's had a significantly reduced number. Variations in spine density could help explain why as many as half of older people with the pathology of Alzheimer's—for example, the presence of amyloid beta, a protein fragment that forms amyloid plaques in the brain—never develop dementia.



Other research, from Susumu Tonegawa's lab at the Picower Institute for Learning and Memory at MIT, suggests that enhancing the formation of dendritic spines could help recover certain kinds of "lost" memories. In studies of mouse models of Alzheimer's disease, in 2016, and retrograde amnesia, in 2017, Tonegawa's team found that a reduction in the number of dendritic spines contributed to the phenomenon of "silent" engrams, in which memories become inaccessible through normal cues, but can be reactivated artificially by stimulating neurons using optogenetics—targeting specially engineered cells with a light that makes them active—or treating them with a protein called PAK1 that increases spine density. In the late stages of Alzheimer's disease, the death of neurons wipes away memories completely, but Tonegawa's research has shown that some earlier memory failures could be a problem of retrieval related to reduced numbers of dendritic spines. That may offer hope that in those cases, memory loss could be reversed.

Right now, there's no feasible way to shoot bursts of light into the brains of living humans, but PAK1 or other experimental drugs might lend themselves to human therapies. In 2016, for example, a group headed by Jerry Yang at the University of California, San Diego reported it had developed a set of molecules, called benzothiazole amphiphiles, that boosted the growth of new dendritic spines in mice. But Tonegawa's research suggests that any such interventions would need to be highly targeted. Successfully retrieving silent memories in mice required increasing dendritic spines only in the affected memory cells, rather than in broader populations of neurons.

THE ANATOMY OF THE NEURON ITSELF MAY OFFER CLUES TO WHY MEMORY FAILS OVER TIME.

This highlights the importance of the work done by Sheena Josselyn and her colleagues, because if researchers can learn how to map engrams with greater accuracy, it will allow those engrams to become better therapeutic targets.

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While aging impairs many facets of memory, some of the most significant changes involve the inability to keep memories separate and distinct. "The best example of this is if you park your car in a different location in a parking lot every day. There will be many days when you can't find your car because of interference from other similar memories," says Amar Sahay, a neuroscientist at the Center for Regenerative Medicine at Massachusetts General Hospital and principal faculty member at the Harvard Stem Cell Institute. Older people often have trouble distinguishing between old and new memories, or may experience "false recognition"—such as when an older relative with dementia mistakes a new visitor for her long-dead husband.

A growing body of research is connecting these cognitive changes to age-related alterations in a tiny region of the hippocampus called the dentate gyrus. The dentate gyrus is where the heavy lifting of memory takes place. It's where all sensory information entering the brain is initially encoded as representations of "what, when and where" in engrams, before being conveyed to the prefrontal cortex for long-term storage. As the years wear on, the dentate gyrus can gradually become "overloaded" and start to display noisy and unreliable recall, as individual synapses attempt to satisfy the requirements of too many memories.

Counteracting this tendency is the ability of the dentate gyrus to refresh itself by generating new neurons throughout a lifetime, a process called neurogenesis. Apart from the amygdala and the olfactory bulb, which is responsible for the sense of smell, the dentate gyrus is the only part of a mammal brain that continues to grow new cells into adulthood. By providing a steady supply of new cells, neurogenesis ensures that there will be a place for new memories to form, so that new experiences can continue to register clearly and distinctly and be recalled without confusion.

Yet while neurogenesis is an ongoing process, numerous studies in animals and humans have shown that the production of fresh cells ebbs with age. Researchers at the Autonomous University of Madrid measured roughly 42,000 new neurons per cubic millimeter in the hippocampus of a 43-year-old, while a 60-year-old had only between 30,000 and 40,000 per cubic millimeter. But Sahay's research suggests that such declines may be, in part, reversible. In a study published in *Neuron* in 2016, scientists in Sahay's lab, led by Kathleen McAvoy, effectively doubled the population of "fresh" neurons in mice and found that this led to improved memory precision in both middle-aged and older mice. The mice were better able to differentiate between their memories of getting a shock in similar-looking environments and did well in other tests of spatial and context discrimination. "When you improve neurogenesis, the animals are better at discriminating between similar experiences," Sahay says.

Increasing neurogenesis might also play a role in combating the development of Alzheimer's, which appears to be accompanied by a sharp decrease in the formation of new cells. In the Madrid brain study, older people with dementia had much lower rates of neurogenesis, with the brain of a 78-year-old who died with Alzheimer's having only about 10,000 new neurons per cubic millimeter, compared with 23,000 in a healthy brain of the same age.

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Sahay says that in disorders such as Alzheimer's disease, the connectivity between neurons in the hippocampus are disrupted, leading to inefficient consolidation and storage of memories in the prefrontal cortex, and a nearly universal problem of the aging brain—that memories tend to become less precise over time, losing important details.

This generalization of memories is more pronounced in people with age-related cognitive impairments, and it's connected to what happens in the brains of people with PTSD, in which specific fearful experiences cast a pall over wide swaths of memory.

According to Sahay, growing evidence suggests that these kinds of fuzzy memories stem from an imbalance of excitatory and inhibitory signals passing from the dentate gyrus to the CA3—a section of the nearby Cornu Ammonis region, also in the hippocampus. It serves as a way station where engrams are stabilized and promotes long-term storage of memories in the prefrontal cortex. With aging, the inhibitory signals to the CA3 decrease, thus letting the excitatory signals prevail and resulting in hyperactivity of that part of the brain. That's a characteristic of mice models of Alzheimer's and is also seen in humans with mild cognitive impairment.

cells perform like younger ones by rewiring their connectivity with inhibitory interneurons. The researchers' method relied on a complex system of checks and counterchecks. Their principal target was abLIM3, a protein that works against the inhibitory, CA3-calming signals coming from the dentate gyrus. By using an engineered virus to decrease levels of abLIM3, they restored connections with inhibitory neurons, reducing hyperactivity in the CA3 and helping improve memory precision in middle-aged and older mice.

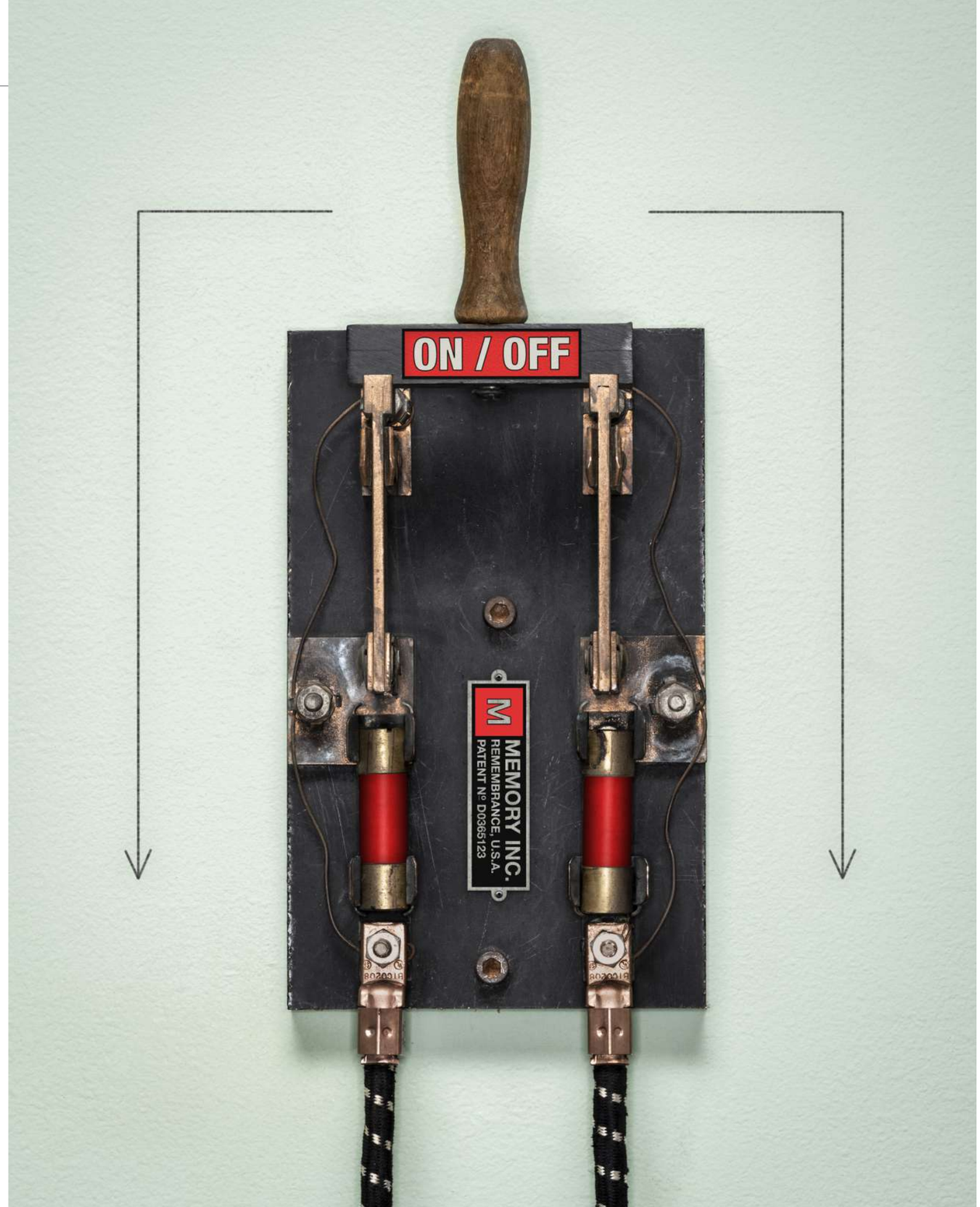
That work could relate to an emerging model of long-term memory called multiple trace theory, which suggests that recalling memories depends on ongoing connections between partial engrams that remain in the hippocampus and fuller versions that are stored in the cortex. Sahay says he believes that reducing hyperactivity in the CA3 helps to maintain those engrams in the hippocampus,

"IT'S A MILLION PART PUZZLE. BUT WE HAVE FIGURED OUT AN IMPORTANT CORNER OF IT."

In healthy brains, hyperactivity in the CA3 region is constrained in part with the help of special cells called inhibitory interneurons—neurons that sit between excitatory neurons and can boost, or weaken, the signals passing between them. In ongoing studies of neurogenesis, Sahay has observed that new, adult-born neurons are better at "recruiting" inhibitory interneurons than older cells, suggesting that any therapy that boosts neurogenesis might, in turn, also help dampen hyperactivity and improve long-term memory precision.

In research published in *Nature Medicine* in 2018, a team in Sahay's lab, led by Nannan Guo, showed that it is possible to complement natural neurogenesis by making older which serve as a kind of index that helps make memories less vulnerable to erosion over time.

Sahay imagines that a variety of approaches aimed at stimulating neurogenesis—or that can mimic the effects of neurogenesis on brain circuitry—will ultimately play key roles in combating Alzheimer's disease as well as milder forms of memory impairment. He and others see potential in metformin, a drug already approved by the U.S. Food and Drug Administration, which has been shown to increase neurogenesis in mice. Some antidepressants also boost the formation of new neurons. And aerobic exercise has a well-documented role in boosting neurogenesis. "Running is the best natural intervention," Sahay says.



These approaches would complement existing efforts in Alzheimer's research that focus on amyloid plaques and neurofibrillary tangles, offering opportunities for earlier interventions. Hyperactivity in the CA3 region, left unchecked, may contribute to the accumulation of beta-amyloid and tau proteins and the subsequent death of neurons. "The way to think about the problem," Sahay says, "is disrupting the feedback loop." In 2018, Sahay's lab received an Alzheimer's Association research grant to explore whether reducing abLIM3 might also help limit beta-amyloid accumulation and improve memory in people with Alzheimer's.

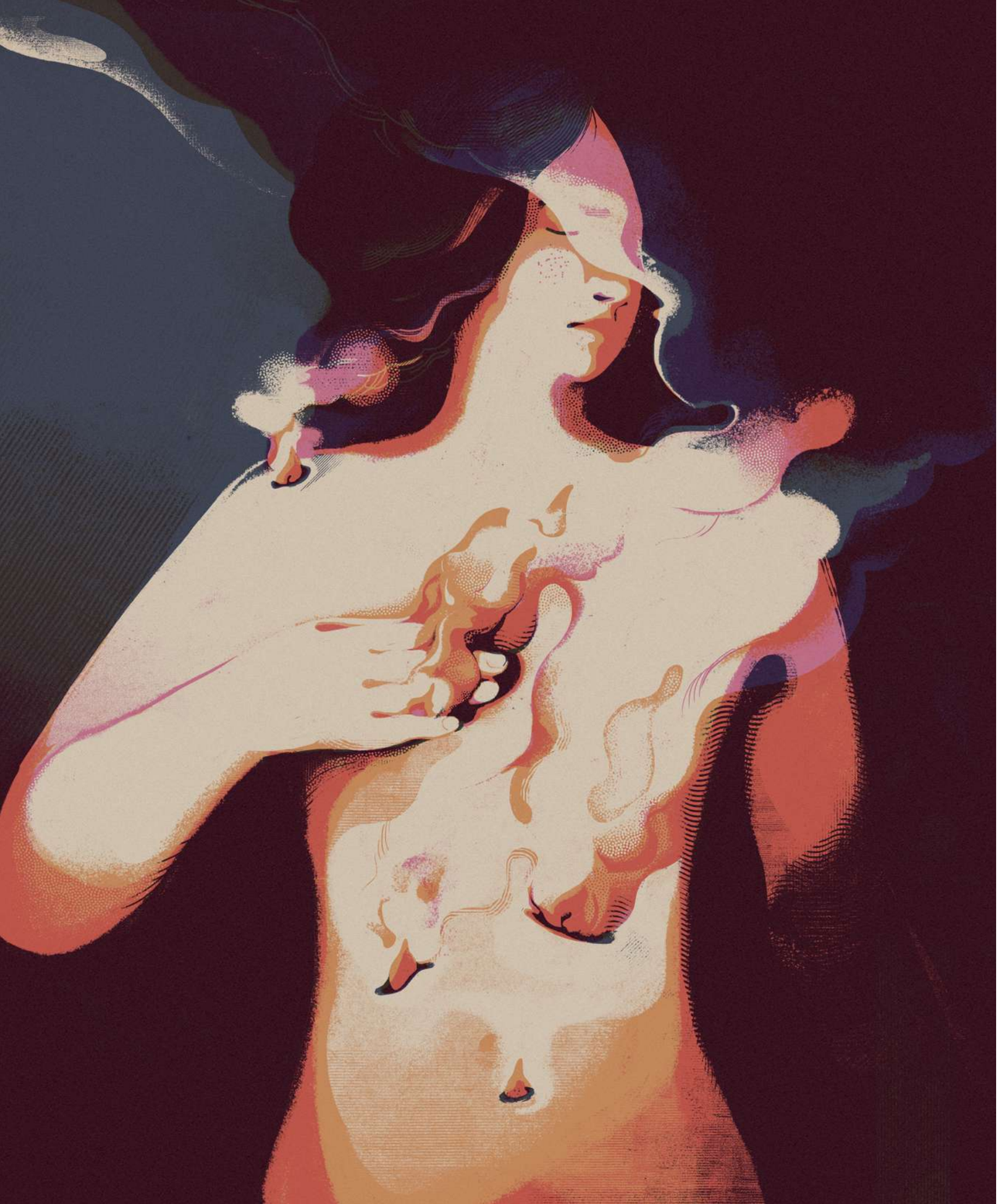
Advances in the basic understanding of what memory is and how it functions "will have more impact on the species than anything else in science in the past 30 to 40 years," suggests UCLA's Alcino Silva. "It's a million-part puzzle. But we have figured out an important corner of that puzzle."

DOSSIER

"Neuronal Competition: Microcircuit Mechanisms Define the Sparsity of the Engram," by Priyanka Rao-Ruiz et al., *Current Opinion in Neurobiology*, February 2019. This scientific review examines recent studies on the mechanisms that shape engram architecture and how these processes might regulate memory function.

"Silent Memory Engrams as the Basis for Retrograde Amnesia," by Dheeraj S. Roy et al., *Proceedings of the National Academy of Sciences*, October 2017. This paper provides original research being done on silent engrams and methods to reactivate them.

Cognitive Aging Summit III, by the National Institute On Aging, YouTube, June 2017. This 12-minute video, featuring Amar Sahay of Massachusetts General Hospital, explains strategies for targeting adult hippocampal neurogenesis to preserve memory in the aging brain.



energy crisis

Those who suffer from chronic fatigue syndrome often face years of doubt from their medical providers. But now the physical hallmarks of the disease are coming into focus.

By Lauren Arcuri // Illustrations by Juan Bernabeu

Katie Hart has been sick most of her life, but it took more than three decades for her to find out what was behind her debilitating fatigue, persistent headaches, muscle pain and dizziness. During her adolescence, medical tests didn't point to any clear answers, and her symptoms were dismissed as hypochondria. It wasn't until 15 years later, in 1988, that she was diagnosed, first with fibromyalgia and then with chronic fatigue syndrome. "But even those names were met with more resistance than validation," Hart says. She was later misdiagnosed with depression and treated as a psychiatric patient. But the medications she was prescribed only made her feel worse. It wasn't until Hart was in her mid-thirties and living in the United Kingdom that she received a diagnosis of myalgic encephalomyelitis, a disease that the Centers for Disease Control and Prevention and most medical institutions now recognize as myalgic encephalomyelitis/chronic fatigue syndrome, or ME/CFS.

Hart's experience is typical for this condition, which has remained enigmatic since it first drew widespread attention in the 1980s. Because the symptoms of ME/CFS can sometimes be vague and overlap with those of other common diseases, getting to a diagnosis is a painstaking process that largely involves excluding other conditions. There have been no offical blood tests or other diagnostic tools, which means that physicians sometimes turn to psychological explanations.

Often enough, as in Hart's case, they point to depression or overwork as the likely culprits.

Even today, ME/CFS resists easy categorization. Hart's symptoms came on gradually, but in many cases a single trigger sets the disease in motion. It might be an infection such as influenza or mononucleosis, the physical trauma of a car accident or surgery or psychological trauma, such as the death of a loved one. A cascade of symptoms follows and lasts for months or years. Unrelenting fatigue is always one of them, but a long list of others includes enlarged lymph nodes in the neck or armpits, impaired short-term memory, poor concentration, unrefreshing sleep and joint pain. It often causes "orthostatic intolerance," in which sitting or standing interferes with blood pressure and blood flow to the brain. And patients suffer from a severe crash in energy levels lasting days or weeks after physical activity—which may, in some cases, involve nothing more than leaving the house to do an errand or walking to the bathroom.

Having the disease also means coping with its persistent stigma. Many people, including physicians, have simply not believed that ME/CFS is a real physiological condition, even with an estimated 1 million to 2.5 million people in the United States thought to be suffering from it. This may stem from the uncertainty that still swirls around its diagnosis. Physicians now have multiple sets of criteria for identifying ME/CFS—some that may be overly broad, others overly restrictive and almost all hotly debated among medical and lay groups. Researchers now also believe that hidden beneath what has ultimately been described as a "clinical syndrome"—in which symptoms tend to occur together—several subtypes may exist, with varying ranges and severity of symptoms and diverse underlying causes, each of which may call for a different approach to treatment.

In recent years, however, research on ME/CFS has turned a corner. Greater awareness has led to a few tantalizing clues about how people with ME/CFS differ from their healthy counterparts. Some of these were covered in a landmark gathering of ME/CFS researchers at the National Institutes of Health in April. Abnormalities in the immune system, impaired cellular metabolism and other problems affecting blood pressure and heart rate regulation seem to be hallmarks of the disease. More powerful tools are helping scientists search for molecular pathways that may set those problems in motion, and collaboration among researchers in pulmonology, neuroimmunology and other disciplines is leading to new insights. One major goal is to find biomarkers that could produce definitive laboratory tests for diagnosis and help tease apart underlying mechanisms that may split what is currently a clinical syndrome into several clearly-defined disorders. And a few of these may have the promise to move toward effective treatments—a promise that, in some cases, is already heading into clinical trials.

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Until recently, very little was known about what might cause post-exertional malaise (PEM), a defining symptom of ME/CFS. Symptoms of ME/CFS often worsen after minimal exertion, and even getting up for a glass of water may leave someone exhausted for days or longer. New tests have shown that PEM may result from cardiopulmonary and nervous system abnormalities. David Systrom, director of the Invasive Cardiopulmonary Exercise Laboratory at Brigham and Women's Hospital in Boston, has been chasing these down with the help of his invasive cardiopulmonary exercise test, or iCPET.

Normally, blood depleted of oxygen returns to the right side of the heart, filling the atrium and then the ventricle. The right ventricle pumps blood to the lungs, and that blood, filled with oxygen, returns to the left side of the heart. From there it is sent out to the muscles, where the blood unloads its oxygen to feed mitochondria, which in turn provide cells with energy. Breathing hard during exercise steps up this process, delivering additional oxygen to the blood. The heart also works harder to get more blood to the muscles as exertion increases, and the veins return more blood to the right side of the heart.

The iCPET looks at all of these cardiopulmonary processes in a patient and collects data about how they might deviate from the norm. As the patient cycles to exhaustion on a stationary bike, a mouth piece collects the breath-by-breath exchange of gases and measures oxygen uptake; a 12-lead electrocardiogram measures heart function; and two catheters, one inserted at the neck and the other at the wrist, measure pressure and pull blood samples to detect changes in blood oxygen content in the veins and arteries.

Systrom and his colleagues developed the iCPET to help spot heart failure and pulmonary hypertension in their initial stages, when the subtle signs are hard to detect in a person at rest. But soon Systrom and his team began using iCPET to test people with ME/CFS, and those patients now account for almost half of iCPET testing at Brigham and Women's. Almost all of them show specific patterns of cardiovascular dysfunction distinct from other heart and lung conditions.

For some reason, in these test subjects, the large veins in the lower body fail to constrict effectively during exercise. This results in less blood being pushed up to the right atrium. Systrom calls this phenomenon "preload failure," a condition that is particularly pronounced when exercising in an upright position, suggesting it may also be related to the common ME/CFS symptom of orthostatic intolerance, in which problems become worse when sitting or standing.

In many of those same patients, Systrom has also found abnormalities in a measurement of how well muscles extract oxygen from the blood—an indication that their mitochondria-rich muscle fibers aren't getting sufficient oxygen. That adds to the problems of preload failure and clearly distinguishes ME/CFS patients from others whose muscles have lost conditioning because of inactivity.

For patients such as Katie Hart, whose iCPET results showed preload failure, this kind of objective finding can be reassuring. "When we show them their abnormal physiology in the exercise lab—when we can give them reasonably hard data that this is a real illness—they are so relieved," Systrom says.

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Spurred by these discoveries, Systrom teamed up with Anne Louise Oaklander, a neurologist who directs the nerve unit at Massachusetts General Hospital. Oaklander specializes in small fiber neuropathy (SFN), in which small nerve fibers are damaged and misfire. SFN is characterized by chronic pain but also chronic fatigue and other symptoms often shared by patients with ME/CFS. Oaklander and Systrom began to look into whether the ME/CFS patients he was testing with iCPET might also have SFN. In about 40% of those who showed preload failure in the iCPET, they found a positive match.

The tiny nerve fibers involved in SFN are found everywhere and may affect the proper functioning of the autonomic nervous system, which regulates blood pressure, breathing, digestion and other automatic body processes. Systrom and Oaklander suspect that the physiological problems Systrom documents with his test—preload failure and poor oxygen extraction in muscles—may, in some patients, be caused by an autonomic nervous system that is out of whack because of SFN. "We're marrying the physiology to the neuroanatomy," Systrom says.

many people have simply not believed that ME/CFS is a real physiological condition, even with an estimated 1 million to 2.5 million people suffering from it.

A New Blood Test?

Biochemist Ronald Davis spends much of his life caring for a son with a severe case of ME/CFS. When he is in his lab at Stanford, however, he and his fellow researchers are hot on the trail of a new test for the disease.

Their approach uses a "nanoneedle bioarray" that can detect changes in the flow of electrical current in cells. This is one way to measure a cell's response to stress. For a recent study in *The Proceedings of the National Academy of Sciences*, the researchers introduced stress—in the form of salt—to immune cells and plasma taken from patients' blood.

The samples from 20 patients with ME/CFS showed a sharp spike in electrical current, an indication of an exaggerated stress response. In contrast, none of the cells from 20 healthy controls showed such a response, staying relatively even-keeled.

Davis and his colleagues can't yet explain the reason for the discrepancy in how the cells responded. They are now trying to confirm their initial findings in a larger population. As part of that, the team will explore whether cells from people with autoimmune diseases such as multiple sclerosis or with an acute infection might respond in a similar way.

The scientists also plan to use the device to test potential new treatments for ME/CFS. They have already found one drug that appears to block the spike in electrical current in affected cells.

While the researchers don't yet know for sure what causes SFN, they suspect that inflammation, perhaps brought on by infection or another trigger, might set off an autoimmune process that then attacks the small nerve fibers. "We know there is a large overlap with autoimmunity and inflammation," Systrom says. And patients with some autoimmune conditions—particularly Sjögren's syndrome, which attacks tear and salivary glands—also have a high prevalence of SFN. Now Systrom and Oaklander are analyzing biomarkers to explore possible connections.

Even before the physiology of these conditions is fully mapped out, Systrom is looking at possible treatments. A drug called pyridostigmine, approved by the U.S. Food and Drug Administration to treat myasthenia gravis, an autoimmune disorder, prevents the breakdown of the neurotransmitter acetylcholine. Increasing the effectiveness of acetylcholine appears to improve the functioning of nerves that interact with slow-twitch muscle fibers—the same fibers that, in Systrom's exercising patients, aren't getting enough oxygen. Pyridostigmine also promotes constriction of veins, helping pump more blood back to the heart during peak exercise. Benefits may also come from the drug's anti-inflammatory and immune system effects, although Systrom doesn't yet understand exactly how that might happen. Systrom has treated about 300 ME/CFS patients with good results and has recently launched a phase 3 trial.

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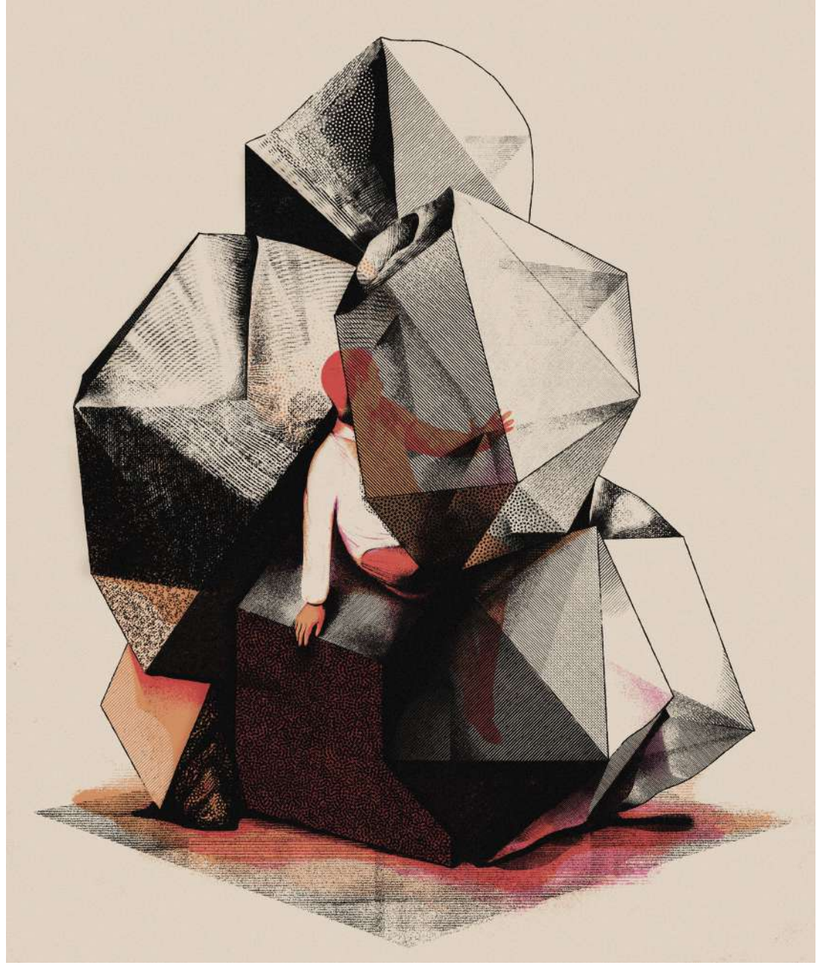
Better imaging could help scientists understand more about the role of inflammation in ME/CFS. Michael VanElzakker, a neuroscientist at the Martinos Center for Biomedical Imaging at MGH, is using functional magnetic resonance imaging (fMRI) to study the brains of these patients both at rest and after they've undergone Systrom's exercise test. VanElzakker's work is centered on the function of the vagus nerve, a key nerve in the autonomic nervous system that has acetylcholine as its primary neurotransmitter. He hopes his research will help researchers see what happens when patients experience post-exertional malaise and how that may be related to problems with the autonomic nervous system. Another study with positron emission tomography, which uses radioactive substances that bind to certain proteins, will help them see whether and where neuroinflammation may exist in the brain.

In other work, Jose Montoya, an infectious disease specialist at Stanford Medical School, used MRIs of patients with ME/CFS to discover an abnormal thickening of the right arcuate fasciculus, which connects the brain's frontal lobe with its temporal lobe. Although the function of the arcuate fasciculus isn't fully understood, the researchers were intrigued to find that the patients in which it was thickest also had the most severe symptoms.

Images also show another possible result of inflammation—abnormally low levels of white matter, the long, myelin-coated, cable-like tracts of nerves that carry signals between the widely dispersed "gray matter" in the brain. And in this case too, there seemed to be a correlation between the extent of the abnormality and the severity of symptoms, a way of sorting data that Montoya is convinced will lead to significant clues about the processes at work in ME/CFS.

Jarred Younger, a clinical researcher and director of the Neuroinflammation, Pain and Fatigue Laboratory at the University of Alabama in Tuscaloosa used MRIs to map brain temperatures and found that patients with ME/CFS had warmer brains than healthy people. The brain areas most affected were known to cause feelings of malaise, fatigue and depressed mood. But those higher temperatures were found in only about a third of patients, who may represent a subgroup with unusually high levels of neuroinflammation. Younger believes that these patients may have highly active microglia, immune cells in the brain, which release small proteins called cytokines that produce inflammation and may cause some symptoms of ME/CFS.



Yet even the hypothesis that neuroinflammation is a core part of ME/CFS doesn't point to a specific cause for the disease. Montoya says he believes that in many cases of ME/CFS, a viral infection such as Epstein-Barr or human herpesvirus 6 has altered the immune system, which overreacts, gets stuck in overdrive and can't reset itself to proper functioning. Some of Montoya's ME/CFS patients who have tested positive for chronic viral infections have improved or recovered by taking antiviral medications.

Younger suspects that there are multiple subgroups of people with ME/CFS—some who have an infection with a chronic pathogen such as Epstein-Barr, and some who don't have a chronic infection but do have an abnormal immune response in the brain. In that second set of patients, microglia are likely to have become traumatized in some way, he suggests. "The microglia are on a hair trigger and it takes very little to set them off," Younger says. "In these patients, things that most people encounter every day without a problem cause a cytokine release." Younger is now testing treatments that could return the microglia to a resting state.

Montoya and other researchers are also looking for ME/CFS biomarkers in the immune system, and they're especially interested in cytokines. In one study, Montoya measured 51 cytokines in several hundred patients with ME/CFS as well as in healthy subjects. His team found 17 cytokines that were significantly associated with ME/CFS severity, and 13 of those are known to cause inflammation. The higher patients' cytokine levels were, the more intense their symptoms. "It's exciting to see a clear correlation between symptoms and a biological signal," Montoya says.

The fact that the disease affects so many body systems—the nervous system, the muscular system, the cardiovascular system and the immune system—may add to its complexity, and help explain why causes and mechanisms have taken so long to unravel. As specialists from each of these fields pin down some of the details, however, a clearer picture of ME/CFS is emerging. The next step requires these pieces to come together, as researchers collaborate and share research to finally get to the bottom of a disabling and long-neglected disease.

DOSSIER

"Evidence of Widespread Metabolite Abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Assessment with Whole-Brain Magnetic Resonance Spectroscopy," by C. Mueller et al., *Brain Imaging and Behavior*, January 2019. This study shows evidence that ME/CFS involves neuroinflammation.

"Cytokine Signature Associated with Disease Severity in Chronic Fatigue Syndrome Patients," by Jose G. Montoya et al., *Proceedings of the National Academy of Sciences*, August 2017. Some cytokines cause flu-like symptoms and inflammation. This study discovered 17 that correlated with the severity of ME/CFS symptoms.

"Exercise Intolerance in Preload Failure Treated with Pyridostigmine," by M. Faria Urbina et al., abstract presented at the American Thoracic Society International Conference, May 2018. This study shows that preload failure, the inability of large veins to push blood to the heart, is present in ME/CFS patients and can be treated with pyridostigmine.

FIRST PERSON

How to Get Home

BY MICHELLE GOODMAN

The EMTs strapped my husband into the gurney. He didn't look like a man dying of cancer. Tired and heartbroken, yes. But still ruddy and robust. He sat upright, long legs outstretched, beefy hands resting in his lap. I grabbed one of them and squeezed. "I'll see you at home," I said.

I didn't think I would get to say those words again. The oxygen tube in his nose was a reminder of the absurdly complicated task we had set ourselves—managing his final few weeks in our home, rather than at the state-of-the-art oncology ward we had come to know by heart.

The ambulance doors slammed shut and the vehicle sped off with Greg, sirens blaring. I set out to the hospital pharmacy to load up a shopping cart's worth of supplies and medications, including the Ativan, codeine, morphine and oxycodone that would help Greg manage the end-of-life pain and anxiety.

Two years ago Greg's cancer was just an ache, something his doctor suspected was a case of kidney stones. That ache turned out to be a renal tumor, which spread to his lungs a year later. A constant assault of targeted and immune therapies had done nothing to stop the cancer. Soon it was also a tumor on his spine, then tumors on his lungs that required an oxygen tank for rapidly escalating breathing trouble.

Two days ago Greg's oncologist had broken the news that death was our next stop. He estimated that we had two weeks and gave us the choice of staying in the hospital or moving to a hospice facility. Home was our dream situation, but it wasn't an option. Greg required a high flow of oxygen to breathe—12 to 14 liters per minute—which couldn't be managed by a home oxygen concentrator.

We resigned ourselves to Greg dying at a nearby hospice facility. By 9 a.m. four members of the hospital pulmonology team came by for rounds. As they explained how the next two weeks would go—weakness, drowsiness, withdrawal, coma—I was surprised to see that their eyes were welling up, too.

"So, Greg. We understand you'd like very much to go home," one of them said.

Greg and I looked at each other in disbelief. The team had a plan, which was apparently a common home-hospice hack for getting around the limited oxygen flow of the concentrators. They would send us home with two concentrators and link them, allowing for a continuous flow of up to 20 liters per minute. Long story short, we could go home again. In the bleary hospital morning, it felt like winning the death lottery.

Greg's bedside quickly turned into a hospice war room. As the day wore on, a social worker walked us through the physical stages of death, including what to expect in the final days and hours. The medical equipment company called to ask where they should put the hospital bed. A nurse stopped by to give us a crash course in managing high-flow oxygen equipment.

Every so often a doctor would return with an announcement: They'd gotten approval from our insurance company. The three-page list of medicines Greg needed would be ready by the next morning. They'd secured the ambulance to get Greg home. Finally, we were good to go.

I arrived home to find our TV room humming with the familiar, frenetic energy of men talking late-season college football. Propped up in the hospital bed was Greg, surrounded by his history books and movie collection, with our black Labrador, Josie, at his feet.

I squeezed in the bed alongside him. He grinned and kissed my cheek.

"Hi, honey," he said. "I'm home."

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