proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

WINTER 18

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WINTER 2018

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POST-OP

FEATURES

on the cover

The organoid is a tiny version of a human organ, grown from a single cell. These avatars of the body are changing many fields of research, but none so much as the study of the human brain.
// Photograph by Andrew B. Meyers

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

proto®

Founded in 1811, Massachusetts General Hospital is a 1,000-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.

Two major discoveries featured in this issue are very, very small. The first is the organoid—a tiny version of a human organ that can be grown and studied in the laboratory, yielding keen insights about the human body. Organoids offer researchers across specialties a new way to see both how organs develop and how they respond to genetic changes and treatments.

The second frontier, nanotechnology, is even smaller—by many orders of magnitude, in fact. Researchers in this field aim to engineer microscopic materials that will lock onto specific structures in the body, such as a tumor, and either work as a diagnostic tool or deliver a payload of medication.

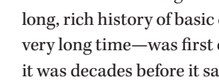
These two exciting developments are united by more than tininess. Both rely on a long, rich history of basic discovery. Nanotechnology—existing in science fiction for a very long time—was first explored as a potentially feasible technology in the 1980s, but it was decades before it saw its first real-world applications. Organoids became practical much more quickly, but their development depended on more than 50 years of incremental insights into growing and maintaining cell cultures outside the human body.

The investment in long-range, basic research leading to these kinds of innovations is crucial to the future of medicine. It is also increasingly under threat. The amount of research funded by the National Institutes of Health declined by nearly 25% between 2003 and 2015, and that decrease has caused significant harm, particularly to researchers starting out in their careers—which, in turn, is threatening the next generation of science (“A Future Defunded,” page 10).

At Massachusetts General Hospital, members of our research community authored about 7,000 journal articles in 2017, many focused on questions that are decades away from direct application. Laying this fundamental groundwork for the future, however, requires support, and federal funding for science is clearly falling short.

The MGH Research Institute is working to fight this tide. This initiative looks for new ways to fund the research happening in more than 30 of the hospital’s departments, centers and institutions. The institute has created groundbreaking alliances with industry and venture capitalists that help our researchers continue their investigations into the future—into epigenetics, cancer immunotherapy, neurosciences, the microbiome and many other promising fields.

The questions that scientists are raising today are potentially game-changing, and the time and support required to explore those questions must not be viewed as optional. Indeed, if we are to advance medicine and improve health and humanity, committing resources to research is imperative.



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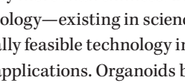

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FOCUS

This work of art began as the brain scan of Elizabeth Jameson, an artist with multiple sclerosis. She has received dozens of MRIs over the years and said in a recent TedX talk that “they were black, ugly, scary Halloween-like images.” Jameson transformed the image by sketching it on silk and then painting over it with dyes—one of several MRI works she has created in various media.

In cases of MS, the immune system attacks myelin, the protective coating around nerve fibers. This disrupts communication between the brain and body. While the cause is still largely unknown, new treatments have been making headway. In 2017 the Food and Drug Administration approved Ocrevus, the first treatment for the most destructive form of MS. Researchers are also exploring the use of stem cells to repair damaged myelin, a technique that was successfully demonstrated in rats last year. And clarity about the role of gut bacteria in the disease may also help. Last October, scientists in Germany showed that dietary fatty acids alter the composition of the microbiome in a way that changes the behavior of immune cells in MS patients.

ELIZABETH JAMESON

INTERVIEW

The Shape of Things

Design choices pervade the health care system, and pediatrician Joyce Lee wants to make them smarter.

BY KRISTEN FRENCH

Joyce Lee is a professor at the University of Michigan and a pediatrician at C.S. Mott Children's Hospital in Ann Arbor. Over the past several years, however, she has made a name for herself in a different specialty: design, which is the art of deciding not only how a product looks but also how a process functions.

Design in all aspects of medicine can feel like an afterthought, says Lee. Effective design takes its cue from users' experiences and is shaped to suit their habits and preferences. Medical culture, on the other hand, almost universally solves its problems from the top down, she says, from doctor or administrator to patient.

She leads a collective, healthdesignby.us, which educates health care professionals about the importance of design in their work. It also hosts events where lay inventors can meet to share ideas, and conducts research on patient-driven design. Lee is frequently invited to lecture about these ideas at conferences, academic centers and federal agencies, including the Food and Drug Administration.

NICK HAGEN FOR *PROTO*

DEEMAK DAKSINA FOR THE NOUN PROJECT

Q: When did you realize that design was overlooked in medicine?
A: I was on sabbatical in the Bay Area with my two small children. They both have life-threatening food allergies, so I needed to teach the person taking care of them how to use an EpiPen. The design of the EpiPen and instructions for using it are wildly counterintuitive. The cap end, for instance, is not where the needle comes out, which is misleading and which studies have shown may lead to unintentional sticks. My son and I decided to make our own amateur instructional video, which went viral. That experience gave me the push to start thinking and writing about this.

Q: How else can design cause problems?
A: In health care a lot of design just happens—and fails to consider the end user. A classic example occurred this year when an insurer sent letters to more than 12,000 of their customers who take HIV-related medications. They used a windowed envelope that visibly displayed the beginning sentence of the letter, revealing the individual's HIV status to anyone who saw the front of the envelope. This represents a series of sloppy design choices—letter formatting and envelope selection—that might seem minor but may have had catastrophic consequences for the patients.

Q: How receptive is the health care industry to making changes?
A: Design is still a pretty foreign concept here. When you look at industries in consumer technology, such as Apple or Google or Airbnb, user experience is one of the first things they think about. But when you think about how health care systems are developed, there are rarely any patients at the table.

Q: Are there exceptions?
A: I'm excited about patient-driven design and the maker movement, which are both relatively new paradigms. The maker movement has this do-it-yourself ethos that places low-cost electronic computing tools and 3D printers into the hands of patients and caregivers so they can develop their own personalized solutions.

One really amazing example is an online group called e-NABLE, which works to design and print 3D prosthetics for kids with upper-limb deformities. It's made up of teachers, students, scientists, tinkerers and artists from all over the world. It was started by a guy who designed a mechanical hand in 2011 as part of a costume, which he filmed and put on YouTube. Someone in South Africa saw the video and said, "Oh my gosh, I lost my fingers. Can you make a prototype for me?"

Q: What are you working on now?
A: I'm looking at the design of our electronic health record interfaces, to minimize the frustrating number of clicks required to perform any simple task, such as putting in a treatment order. I'm trying to figure out new opportunities and incentives for our patients to input their health data through web and mobile apps, which can help their doctors keep a better eye on their health between visits.

There's a big learning curve for this kind of work, but design is one of several new competencies in medicine. In 2017, as physicians, we need to know about more than physiology. We need to think about the structures and hidden messages of the health care system we inhabit, too.

BY THE NUMBERS

Plant Meds

250

Types of plants, including poppy, henbane and mandrake, used in the drug recipes found on one set of Sumerian clay slabs. These 5,000-year-old records are the first to describe plants used in drug preparation.

50,000

Estimated number of cyclotides—circular proteins found in plants, many of which are useful in medicine. The first was isolated in 1973 after Norwegian researcher Lorents Gran observed women in the Congo ingesting *Oldenlandia affinis* leaves to accelerate childbirth. The plant's active ingredient, kalata B1, can induce uterine contractions.

35,000

Number of plants collected and screened by the National Cancer Institute between 1960 and 1981 in hopes of finding new anticancer agents. A chemical isolated from the Pacific yew tree became one of the most highly prescribed cancer chemotherapy drugs, known today as paclitaxel.

400

Number of botanical drugs—which contain actual vegetable matter as ingredients rather than chemicals derived from plants—submitted to the Food and Drug Administration between 2004 and 2015. Only two have been approved.

54

Billions of dollars in U.S. health care costs that could be saved by developing and adopting biosimilar drugs—less costly imitations of drugs isolated from plants and other living organisms—during the next decade. So far, only seven have been FDA approved.

UPDATE

The Not-an-Opioid Epidemic

More physicians are prescribing a class of drugs called gabapentinoids to manage pain. Should we be worried?

BY TIMOTHY GOWER

The opioid epidemic has left physicians desperate for alternatives that will effectively treat chronic pain without the risk of addiction. While new classes of safer analgesics may be on their way ("Build a Better Painkiller," Winter 2017), clinicians need other options now, and many appear to be turning to gabapentinoids, including Neurontin (gabapentin) and Lyrica (pregabalin).

The number of prescriptions for gabapentin jumped 64% between 2012 and 2016, making it by some accounts the 10th most commonly prescribed medication in the United States at that time. Last June doctors in Ohio wrote more prescriptions for gabapentin than for any other drug.

The recent popularity of gabapentinoids has raised two major concerns. First, evidence suggests that these drugs just aren't very good at treating many common forms of pain, thus putting patients at risk of unnecessary costs and side effects. Second, emerging data suggests that some patients who receive gabapentinoid prescriptions misuse or sell the pills, which are becoming an increasingly popular street drug.

Neurontin was approved by the Food and Drug Administration as an antiseizure medication in 1993, and later it gained approval for treating postherpetic neuralgia, which results from nerve damage caused by shingles. The chemically similar Lyrica, which arrived in 2004, was approved for the same uses, and to treat fibromyalgia as well as pain associated with nerve damage from diabetes.

The precise mechanism of gabapentinoids is unknown, though they can dampen pain signals sent to the brain by damaged nerves, says Harsha Shanthanna, an anesthesiologist at St. Joseph's Healthcare at McMaster University in Hamilton, Ontario. Yet damaged nerves don't play a role in most common kinds of pain, he adds. In a 2017 review of eight randomized trials published in *PLOS Medicine*, Shanthanna and several colleagues found little evidence that gabapentinoids relieve chronic low-back pain. Moreover, while gabapentinoids may reduce acute pain immediately following an operation, a separate review last year also found them ineffective for managing long-term pain after surgery.

Yet physicians continue to prescribe the drugs off label for treating other forms of pain, including chronic pain. Gabapentinoids not only fail to help in many cases, says Shanthanna, but they also put patients at risk for adverse side effects that include dizziness, fatigue, visual disturbances, and what some users describe as a zombie-like mental state.

Meanwhile, gabapentinoids' popularity as a recreational drug is on the rise. The drugs can induce mild euphoria, and heavy users report feeling more relaxed, sociable or uninhibited. Moreover, some surveys have found that gabapentinoid abuse is more prevalent among those who also misuse opioids.

"Gabbies" cost just a dollar or two per 800-milligram pill on the street, says Thomas Sherba, principal investigator for the Ohio Substance Abuse Monitoring Network, which tracks drug addiction trends in that state. The pills may be swallowed whole, crushed and snorted, combined with heroin or an opioid to intensify that drug's high, or ingested in other ways. There have been reports of patients obtaining the medications by doctor shopping and faking symptoms. Those in treatment for opioid misuse who are on opioid-replacement therapies such as Suboxone or Vivitrol often receive gabapentin to ease withdrawal symptoms (which can include pain). Some users have reported, however, that combining opioid replacement with extra-large doses of gabapentin produces a heroin-like high, says Sherba.

The Drug Enforcement Administration classifies one of the two gabapentinoids—pregabalin—as a Schedule V drug, which means that the medication has a low risk for abuse, but there are few limits on how it can be prescribed. While the DEA currently has no plans to do the same for gabapentin, the state of Kentucky recently classified it as a controlled substance.

Deflating gabapentinoids' hype as an opioid alternative will leave many physicians back where they started—with an immediate need for drugs that treat pain without the addiction risks of opioids. Shanthanna notes that some antidepressants show promise for treating pain, and he is optimistic about research into nonpharmacological approaches, such as exercise or cognitive behavioral therapy. "We need to do more for our patients and not just prescribe something indiscriminately that we think will work," he says.

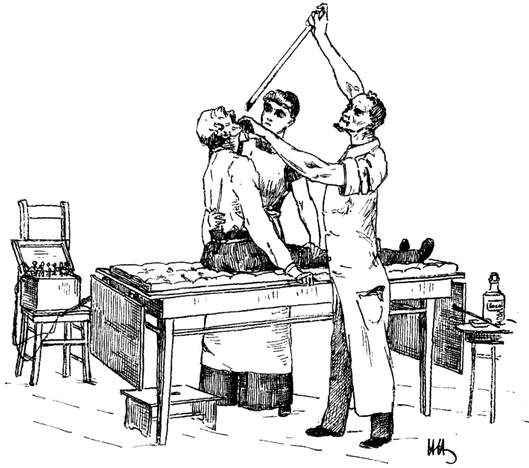
DAN SAELINGER FOR *PROTO*

MILESTONE

Into the Depths

The first endoscope went on display with the help of a talented sideshow performer.

BY PETER SMITH



One measure of medicine's progress is how far inside a living human body the physician can peer. Before X-rays and other imaging technologies, that job fell to ingenious devices and the naked eye. One of the most significant advances happened when a series of 19th-century innovations encountered the services of a professional sword swallower.

The idea of an endoscope—a tube that could be engineered to look deep inside the body—may have started with the "Lichtleiter," or light conductor, conceptualized by Phillip Bozzini in 1806. This improved on the more primitive speculum by adding a mirror, a wax candle and a series of "viewing tubes" that could peer into orifices. A major advance on this idea came in 1853, when Parisian urologist Antonin Desormeaux used a tube, a kerosene lamp and a concave mirror to reflect light into the urethra, allowing for the first examination of the bladder.

Adolph Kussmaul, a physician from the University of Heidelberg in Germany, wanted to apply Desormeaux's technique to observing the gastrointestinal tract. The son of a country doctor, Kussmaul had already, in 1845, come up with a device that inverted the lens design of a simple telescope and was supposed to show the interior of the eye. The ophthalmoscope had only one defect, he asserted—namely, that nothing could be seen with it.

Kussmaul added a straight tube, about nine inches long, to Desormeaux's design and attempted to snake it down the throat of a man to locate a tumor. Unfortunately the limitations of the man's esophagus prevented Kussmaul from getting the device deep enough. That's when he turned to a man with an unusual talent: sword swallowing.

In a 1901 account by Gustav Killian, a student of Kussmaul, the doctor discovered an entertainer—allegedly known as "The Iron Henry"—who was able to relax his throat to an impressive degree. This allowed Kussmaul to insert an 18.5-inch tube with ease, thereby performing the first endoscopy of the upper gastrointestinal tract in 1868, 150 years ago.

Kussmaul then performed his innovative examination before audiences at several medical societies. One drawing that may have been based on this depicts the doctor sinking the scope down a patient's throat, then laying him down on a raised table, head thrown back. The physician is shown squatting next to the table and peering through one end of the instrument.

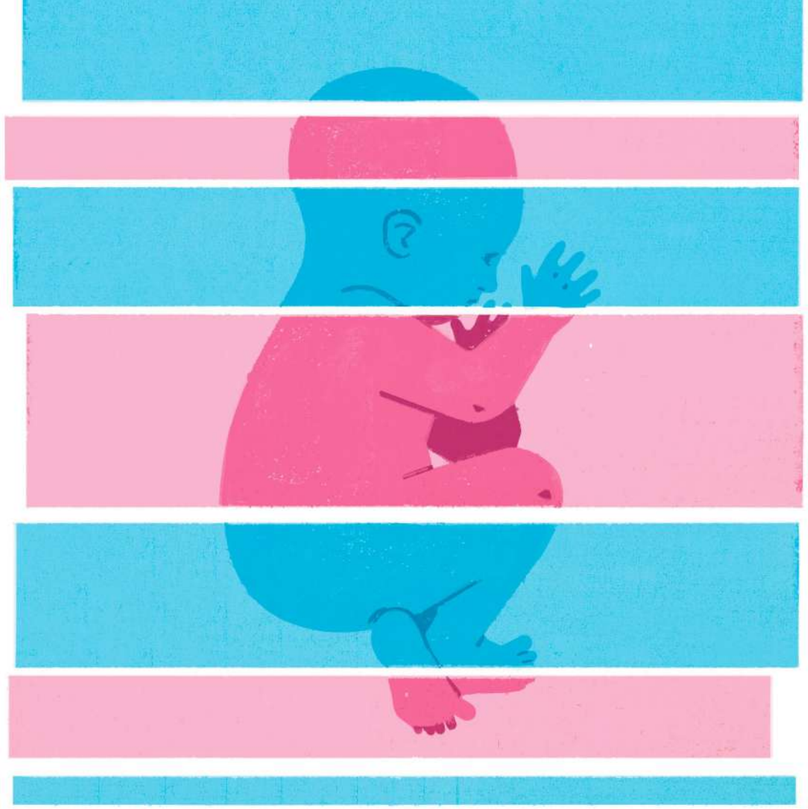
Those unaccustomed to swallowing swords had a difficult time tolerating the device, and it afforded limited visibility at best. Despite these drawbacks, Kussmaul is recognized for scoring a major advance in the field.

POLICY WATCH

Boy or Girl?

When a baby is born and its sex is ambiguous, what should happen next?

BY LINDA KESLAR



CHRIS GASH

The first thing most new mothers hear, even before the cry of their newborn child, is a physician saying "It's a boy" or "It's a girl." But in about one out of 2,000 deliveries, that determination can be hard to make.

Some babies are born with sex organs or genetic features that are not typical for their biological sex. They are dubbed "intersex," a term that covers more than 30 conditions clinically known as disorders of sex development (DSD) or, sometimes, differences of sex development. Physicians have generally performed genital "normalizing" procedures on intersex children during their first year, bringing their bodies—at least cosmetically—in line with one sex or the other.

But these surgeries have physical and psychological costs. Many intersex people embark on a life of hormone replacement therapy, and they may have physical scars that can impair genital intercourse or ensure that they will never be able to have biological children. Studies of adults who had such surgery as infants show mixed satisfaction with the results, and some recount harrowing experiences, particularly when they did not grow up to identify as the sex that their surgery assigned them.

It may be time to rethink the treatment of intersex children, says Joshua Safer, medical director of the Center for Transgender Medicine and Surgery at Boston Medical Center. "These surgeries were the norm when we thought that gender identity could be manipulated," he says, "but there's a growing recognition that gender is substantially a biological phenomenon. It's essentially hardwired." Patients, given time to grow up a little, will be in a better position than their doctors to know which sex they are.

Some advocates have called for curtailing these surgeries, if not prohibiting them outright. A 2013 report by the United Nations' Commission on Human Rights called for an end to "genital normalizing" of intersex children. A year later, several U.N. agencies, including the World Health Organization and UNICEF, condemned unnecessary surgery on intersex children without their consent, with Malta in 2015 becoming the first country to outlaw the procedures.

Momentum is also growing in the United States, where the State Department, major LGBTQ rights organizations and three former U.S. surgeons general also supported calls for a ban over recent years. This past July, Human Rights Watch and InterACT, a group advocating for intersex youth, coordinated a major push that asked federal legislators, regulators and medical societies to delay these procedures, if medically possible, until patients can participate in the decision.

The groups issued a 186-page research report containing interviews with dozens of specialists and intersex adults. "The results of the surgeries are often catastrophic, the supposed benefits are largely unproven, and there are generally no urgent health considerations at stake," says Kyle Knight, the report's author. The document also decried a lack of standards for care of intersex patients and wide variation in treatment protocols.

"There is room for improvement," says David Sandberg, a pediatric psychologist and professor at the University of Michigan Medical School. Sandberg is a principal investigator for the DSD-Translational Research Network, a project funded by the National Institutes of Health to expand research into disorders of sex development and to establish best practices for diagnosis and treatment. But Sandberg is critical of the HRW-InterACT report's methodology and some of its conclusions. The researchers received input from 21 out of the 218 contacted health care practitioners, a number he considers insufficient. And the spectrum of conditions is too broad for blanket statements about care, he says.

Other specialists agree. "The report is spearheaded by activist groups, which makes it problematic," says Karen Lin Su, a pediatric endocrinologist at Weill Cornell Medicine in New York City. Su is particularly concerned about limiting the options available to physicians and patients. "Treatment should be approached on a case-by-case basis," Su says. "Some of these conditions can be life-threatening without surgery, and decisions about what to do should be made by the medical team and the family, not the political arena."

Boston Medical Center's Safer hopes that medical societies can move quickly to improve guidelines about when and how these surgeries should happen. "We need them to step up and give us detailed standards of care," he says.

Some advocates have called for curtailing these surgeries, if not prohibiting them.

The American Medical Association, the largest organization of U.S. physicians, doesn't currently have a policy addressing treatment for intersex babies. But the group is considering a recommendation to defer intersex surgery on infants, except for life-threatening conditions, until the child is able to participate in the decision-making. The 66,000-member American Academy of Pediatrics has said it is conducting an ongoing evaluation of treatments, and it has urged physicians to be transparent with patients' families about the potential risks and benefits.

In the meantime, a lawsuit—the first of its kind—was filed in South Carolina against a hospital system and the state's Department of Social Services by an intersex patient. He had been in their care as a baby and underwent surgery that assigned his gender as female, while he was too young to give informed consent. The patient now identifies as male. The case was settled out of court last summer.

SECOND OPINION

Better Care for Elders

"Special Treatment" (Fall 2017) is a compelling article about the benefits of specialized care for older adults. The piece highlights the Acute Care for Elders (ACE) unit, an evidence-based model that reduces functional decline, which can lead to prolonged stays, nursing home placements and even death. As the story correctly points out, the ACE model has yet to reach its full potential, but should it be widely implemented, it could dramatically change the quality of care older patients receive.

Clinicians understand that functional decline is often an avoidable complication of hospitalization. But a clear vision and strong leadership at all organizational levels can fundamentally redesign inpatient services to maintain older adults' physical abilities.

For more than 25 years, the ACE unit model has been a key component of the Nurses Improving Care for Healthsystem Elders (NICHE), an education and consultation program in more than 700 hospitals and long-term care facilities around the world. We work each day to ensure that acute and long-term care facilities prevent complications and provide quality, person-centered treatment. The time is now to adopt innovative models of care so that older people can receive the dignity and compassion they deserve, when they need it most.

Mattia Gilmartin // Executive Director, Nurses Improving Care for Healthsystem Elders, New York University Rory Meyers College of Nursing, New York, N.Y.

Fueling the Miracle Machine

It is an incredibly exciting time to be a human geneticist and data scientist. As "Is Genetic Privacy a Myth?" (Fall 2017) suggests, we may have approximately two billion human genomes sequenced by 2025, and the most important question facing us today is who controls this massive trove of data.

MISSED THE LAST ISSUE?
All stories from *Proto*, Fall 2017, are available at protomag.com.

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

New advances in data science, such as applying blockchain technology to safeguard digital information, promise new means of addressing this question. But the solution is not just about technology or just about policy. It will come from the deeper conversation we need to have about the global supply chain of biomedical data that is essential for fueling the "Miracle Machine," also known as our wondrous biomedical research engine.

The integration of electronic health records and genomics data will be key to precision health and increasing patient access to affordable care. By using data to identify individuals at risk and improve drug discovery and delivery, we take this crucial step forward.

But patients and consumers need to be put first, and should be included in these conversations. We need to ensure that their trust in our use of their most valued asset is not broken.

Carlos D. Bustamante // Department Chair and Professor of Biomedical Data Science, Stanford University, Stanford, Calif.

Young researchers are responsible for the future of medical discovery. What happens when their careers become economically unsustainable?

A F_ture Defunde d

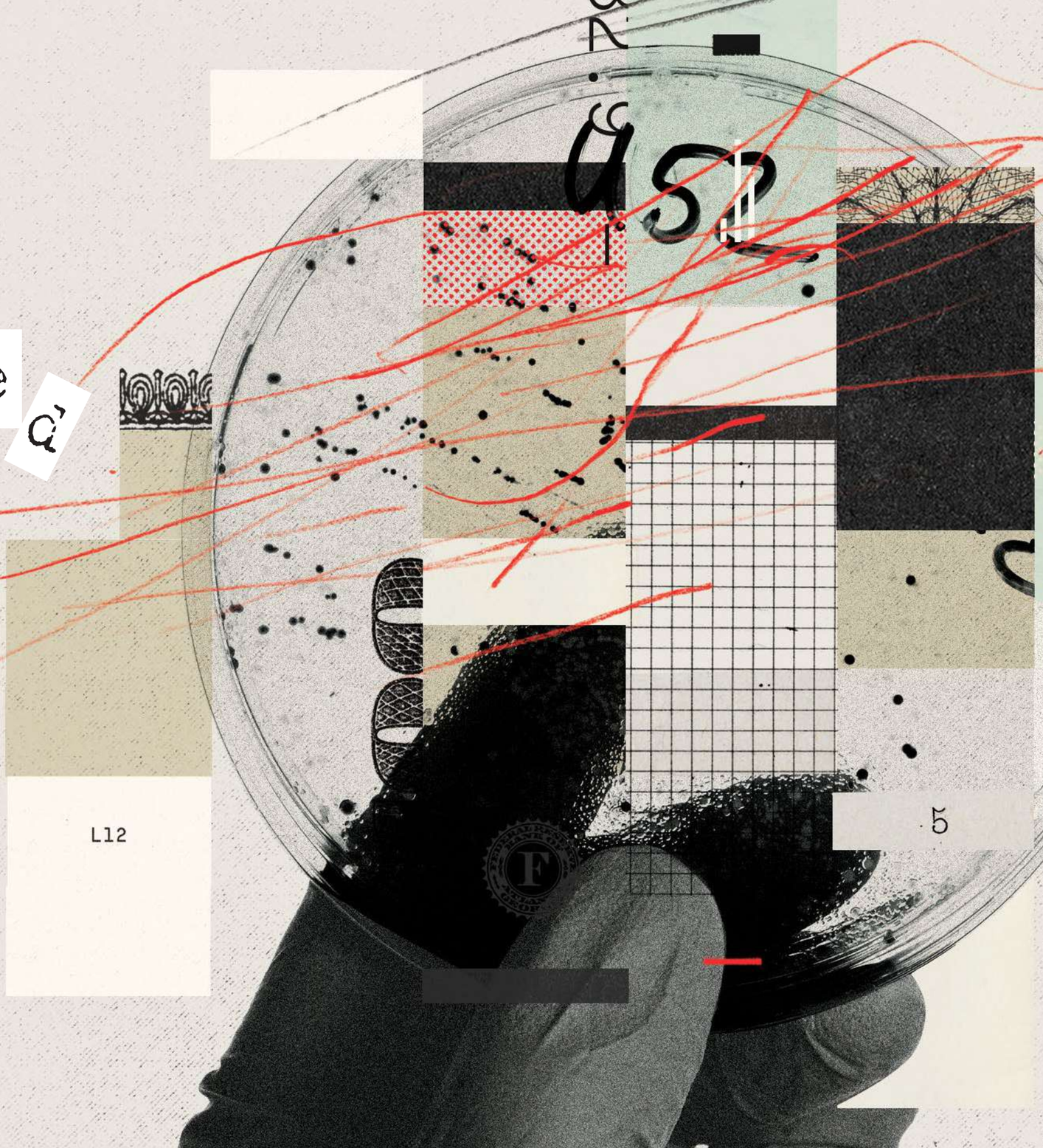
By Marcia Lerner and Charles Slack //

Peter Hotez became a biomedical researcher in a golden age, when the value of that work was seldom questioned. By his early 30s, he had a good job, as an assistant professor at Yale School of Medicine, and he received his first National Institutes of Health grant as a principal investigator in 1991, when he was 33. The subject of his research—the pathogenesis of hookworm infection—may have been arcane in the United States, but that wasn't a concern. After World War II there was a tacit agreement among the scientific community, the government and the American people that biomedical research, however obscure, was worthy of generous support.

For Hotez, now 59 and dean of the National School of Tropical Medicine at Baylor College of Medicine, that NIH funding ultimately led to a vaccine that entered clinical trials in the 2010s—more than 20 years after his grant proposal. Indeed, a steadily increasing flow of federal money beginning in the late 1940s helped countless other young scientists hone their skills and advance scientific knowledge while working with mentors in their fields. Between 1950 and 1959, the value of those grants more than quintupled, from less than $53 million to nearly $292 million. After that, the NIH budget roughly doubled every decade through the late 1990s.

That support, and the hospitals and research centers where the money was put to work, became a global magnet for students and young researchers. "The United States has always been the training ground for the best and brightest biomedical scientists," says Harry W. Orf, senior vice president for research at Massachusetts General Hospital. "People from all over the world have come here."

Illustrations by Mike McQuade



The payoff has been unequivocal. Thanks in no small part to investments in researching cancer cells, gene sequencing, immunology and dozens of other fields, an American child born today can expect to live 30 years longer than one born in 1900. "Now we can take advantage of diagnostics, devices, drugs and behavioral interventions that were unimaginable when I was in training 30 years ago," says Christopher Austin, a neurologist and the director of NIH's National Center for Advancing Translational Sciences (NCATS).

Early in the new century, however, the broad consensus that medical research was worth every penny began to unravel. A combination of budget cuts and modest but steady inflation led to an almost 25% reduction in the amount of research that was funded by NIH grants between 2003 and 2015. At the same time, competition for academic jobs like the one Hotez found at the outset of his research career became increasingly fierce. For the more than 40,000 new Ph.D.s in science and engineering earned each year in the United States, there are just 3,000 full-time jobs available at U.S. universities. According to a 2015 National Science Foundation survey, six in 10 newly minted Ph.D.s in the life sciences had yet to receive commitments for postdoctoral positions or other employment in their fields.

Pursuing a research career has always been challenging. But those who started a generation ago had a path to develop their skills and eventually, perhaps, direct their own labs, Hotez says. Indeed, ample funding didn't just spawn research; it also created a career pipeline by which promising postdoctoral fellows could gain essential experience before embarking on their own projects.

Now, as that pipeline clogs, a new exodus is taking shape. Gary McDowell was a postdoctoral researcher at Tufts University in Medford, Mass. when he left research for good in 2016. At age 31, he, like many of his peers, realized that years of experience and multiple degrees were leading only to an ever more difficult fight for grant money, lab space and recognition. What hope do young researchers have, he thought, when even luminaries are struggling to keep their labs afloat? The joint winner of the Nobel Prize in Physiology or Medicine in 2017, Jeffrey Hall, began his prize-winning work on biological clocks in the 1970s—but he gave up scientific research in 2008, telling *Current Biology* at the time that issues with research funding were a major reason.

McDowell's work, on the role of the cytoskeleton in early left-right body patterning of frog embryos, may never have led to a Nobel Prize. But if he and great numbers of other young scientists continue to leave research because of limited opportunities, there will eventually be a day of reckoning. "If fewer of our brightest, most talented people get started as biomedical researchers over the next five to 10 years, we are going to find ourselves falling behind," says Michael Lauer, deputy director for extramural research at NIH, "and the next generation of great scientists simply won't be there."

> If young scientists continue to leave research because of limited opportunities, there will eventually be a day of reckoning.

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Biomedical research in the United States happens in a variety of settings: universities, medical schools, drug companies, hospitals and other research institutions. The focus of that research is broadly broken into three categories: Basic research looks at the underpinnings of biological processes and diseases; translational or preclinical research moves those findings closer to practical use in new drugs, treatments and medical devices; clinical research is done in conjunction with patients, often to test new drugs, and is normally supervised by physicians.

The scientists conducting this research may earn a living in several ways. Those who work in the pharmaceutical industry, which employs an estimated 142,000 research scientists in the United States, are paid directly by their companies. Graduate students and postdoctoral researchers may get stipends, and a tenure-track university position can provide a steady income.

But many research institutions rely on a "soft money" formula, where a hospital or university provides space, facilities and academic titles, while researchers are expected to use grant money from NIH or another source to pay their own salaries and those of postdocs assisting with their projects. For generations, the soft money approach has benefited researchers and society alike, says Orf. "It makes people very motivated to do great research and to write good grants," he says.

As the overall level of funding has dropped, however, healthy competition has descended into a darker cycle of high anxiety and "a state of hypercompetition," says Lauer. "We have an excess number of scientists vying for fewer dollars." Physicians in particular, long a key segment of biomedical research scientists, are applying for fewer grants these days, Lauer notes.

Although the stiffer competition for grants affects scientists of all ages, younger researchers have been steadily losing ground to their older counterparts. In 1998, researchers 35 and under captured 971 NIH grants, outpacing the 728 grants for those over 65. By 2014, grants to younger scientists had dropped to 762, while the older group had tripled its number, to 2,318.

And while the United States still leads the world in spending on biomedical research, other countries, eager to establish themselves as destinations for the best young researchers, are closing the gap. Less than a generation ago, the U.S. share of global spending on this research was as high as 80%. That has dropped to about 45%, according to a 2014 study by *The New England Journal of Medicine*. From 2007 to 2012, spending by Japan, India, Singapore, South Korea and China surged, with Chinese outlays jumping about 33%. At a time when China promises top prospects full-time salaries and several years of research funding, Hotez is already advising his students: "Be prepared to live outside the United States."

Congress has recognized the plight of young researchers as a national problem. As part of the 21st Century Cures Act, which became law in late 2016, NIH launched the Next Generation Researchers Initiative (NGRI) to become "more aggressive about funding investigators who are at earlier stages of their career," says Lauer, who is leading the effort. NIH is also looking to expand research training opportunities to new physicians during residency, in hopes of encouraging more of them to pursue research.

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It will take years to know whether the NGRI and other such efforts will have the intended effect. In the meantime, however, another NIH initiative—the National Center for Advancing Translational Sciences, established in 2012—may do more to generate jobs

for early-career scientists. The stated goal of NCATS is to help "reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline." That approach, with its promise of a clearer path to potentially marketable products, is drawing increasing support not only from Congress and private industry but also from teaching hospitals and other research institutions.

At MGH, for example, translational science has become a key part of the hospital's Research Institute, a recent effort to focus attention and support on the hospital's biomedical investigations. While MGH remains home to a wide range of basic research, "we knew we had to reduce our very heavy reliance on the federal government and also teach our investigators to think about how their work could become more translational," Orf says. Working with industry, MGH has launched partnerships for research on vaccines, immunotherapy, neurological disorders and a number of other frontiers. The hospital's Translational Research Center, meanwhile, has 18 hospital beds for industry-sponsored clinical trials.

In a separate effort, Partners HealthCare, founded by Brigham and Women's Hospital and MGH, launched Partners Innovation in 2008 to improve the bridge between basic and translational research groups and businesses, thereby accelerating laboratory discoveries and making them more accessible to pharmaceutical companies, device manufacturers and venture capitalists.

Those sources of financing, however, are much less likely to support basic and early-applied research. "The early-stage work is much more difficult to fund," says Patrick Fortune, a vice president of Partners Innovation. That's the obvious drawback to focusing too much on translational research—the basic science needed to understand the body and its many ills will be neglected. Even the most ardent supporters of translational science, including Orf and Austin, readily acknowledge that today's practical applications are made possible only by knowledge gained through decades of national commitment to arduous, time-consuming research into fundamental principles. And they warn of the potential consequences 20, 30 and 40 years from now if the country allows today's generation of bright young researchers to leave such investigations behind. As Austin puts it, "Without basic research, there's nothing to translate."

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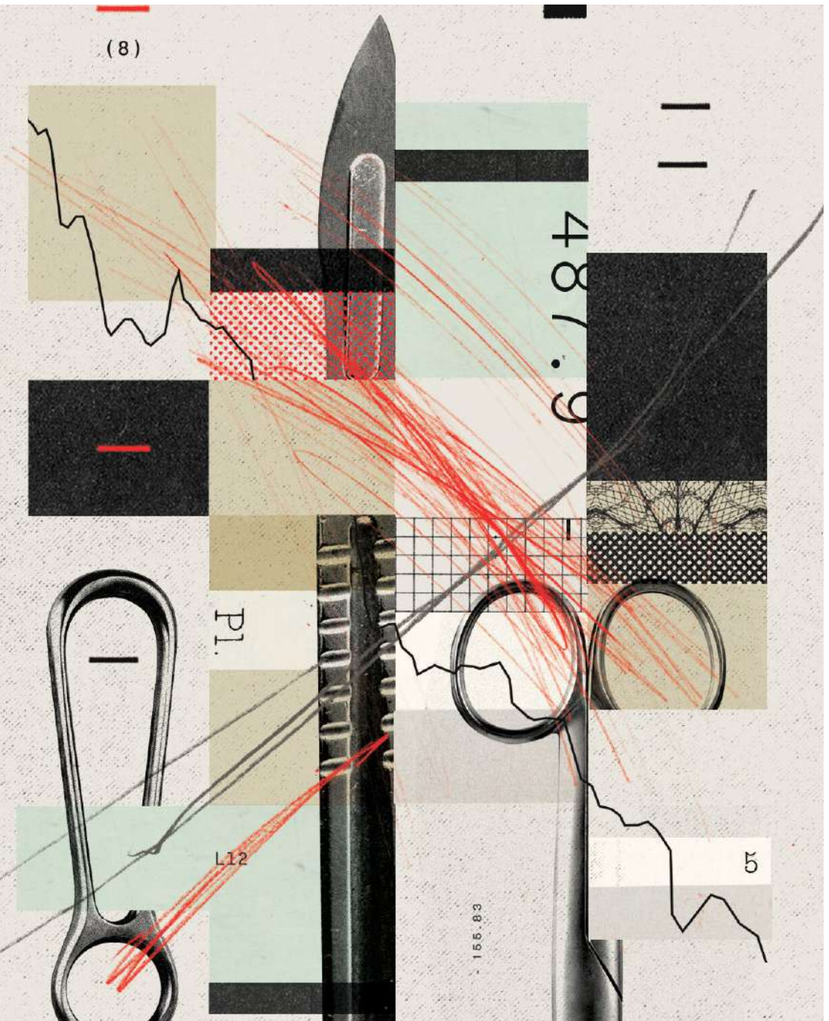
Amid dire predictions about the future, some young researchers assert that scientists themselves must be part of the answer—not just conducting research but also advocating greater public awareness about the importance of their work. In 2015 Devon Collins, a Ph.D. candidate at the Rockefeller University who studies neuroendocrinology, neurobiology and behavior, joined with two classmates—Avital Percher and Maryam Zaringhalam, both now molecular biologists—to launch a podcast called Science Soapbox, aimed at alerting Americans to the close connection between research dollars and public health.



Scientists tend to be more interested in lab work than in politics, says Collins, and as a result they often feel blindsided when opportunities dry up because of funding decisions made by politicians. "We didn't know who to be angry with," he says of himself and his colleagues. "So we took it upon ourselves to create a resource that helps us and other scientists have a deeper understanding of who's responsible for the decisions."

The podcast has evolved from a way to vent into a forum for trading ideas and solutions. "It was a good way to grab and engage people, for us as early-career scientists who are interested in policy and advocacy to meet people who are doing really amazing things," says Zaringhalam. The mission also includes bridging the divide between scientists and the taxpayers who ultimately finance most of their work. "The traditional way that Ph.D.s are trained doesn't include any kind of public-facing component," she says. "We're told to look down at our benches instead of looking out at society at large. We should think about where our funding comes from, which is largely from taxpayers, and think about what we owe them as our benefactors." All three founders of the podcast now intend to pursue careers in developing the policy that underpins and supports scientific research, a move that reflects both the opportunities and the challenges of coming of age as a researcher today.

Gary McDowell, who left his frog research behind in 2016, is now executive director and co-founder of Future of Research, an advocacy organization dedicated to supporting early-career researchers. Among his other efforts, McDowell is working on a National Academy of Sciences study to recommend ways for Congress and NIH to support next-generation investigators. McDowell hopes to fill in gaps in the understanding of how and why many postdocs become frustrated with the system and ultimately abandon research, as he did. "Postdocs are just this nebulous group of people that nobody really knows and can't identify easily, and many disappear through the cracks," says McDowell. Universities have a responsibility to educate graduate students about the realities of a career in research, he believes, and to track what people actually do with their education.

> As the level of funding has dropped, healthy competition has descended into a darker cycle of high anxiety.

McDowell and his Future of Research colleagues are especially interested in a cohort of researchers known as "doubling boomers," so called because they earned their degrees during the last period in which NIH funding doubled, six-year bursts of federal largesse from the late 1990s to the early 2000s. Those scientists, attracted in part by what they saw as reliable money to pursue their ambitions, entered from graduate school at a time when funding was still booming, and then emerged into a world that seemed anything but what they expected.

One such researcher, Needhi Bhalla, received her Ph.D. in biochemistry from the University of California, San Francisco, in 2002. "It was a great time to be in graduate school," Bhalla says. "You had the sense that lots of important questions were being asked. You had incredible freedom to answer some of those questions and go in whatever direction your research took you."

Now 44 and an associate professor of molecular, cell and developmental biology at the University of California, Santa Cruz, Bhalla is among the fortunate few who have found an academic post and research funding—in her case, for investigations into cell division. Still, her career today is hardly what she imagined at the outset. Much of her time, she says, is spent not in the lab but trying to navigate an uncertain funding process.

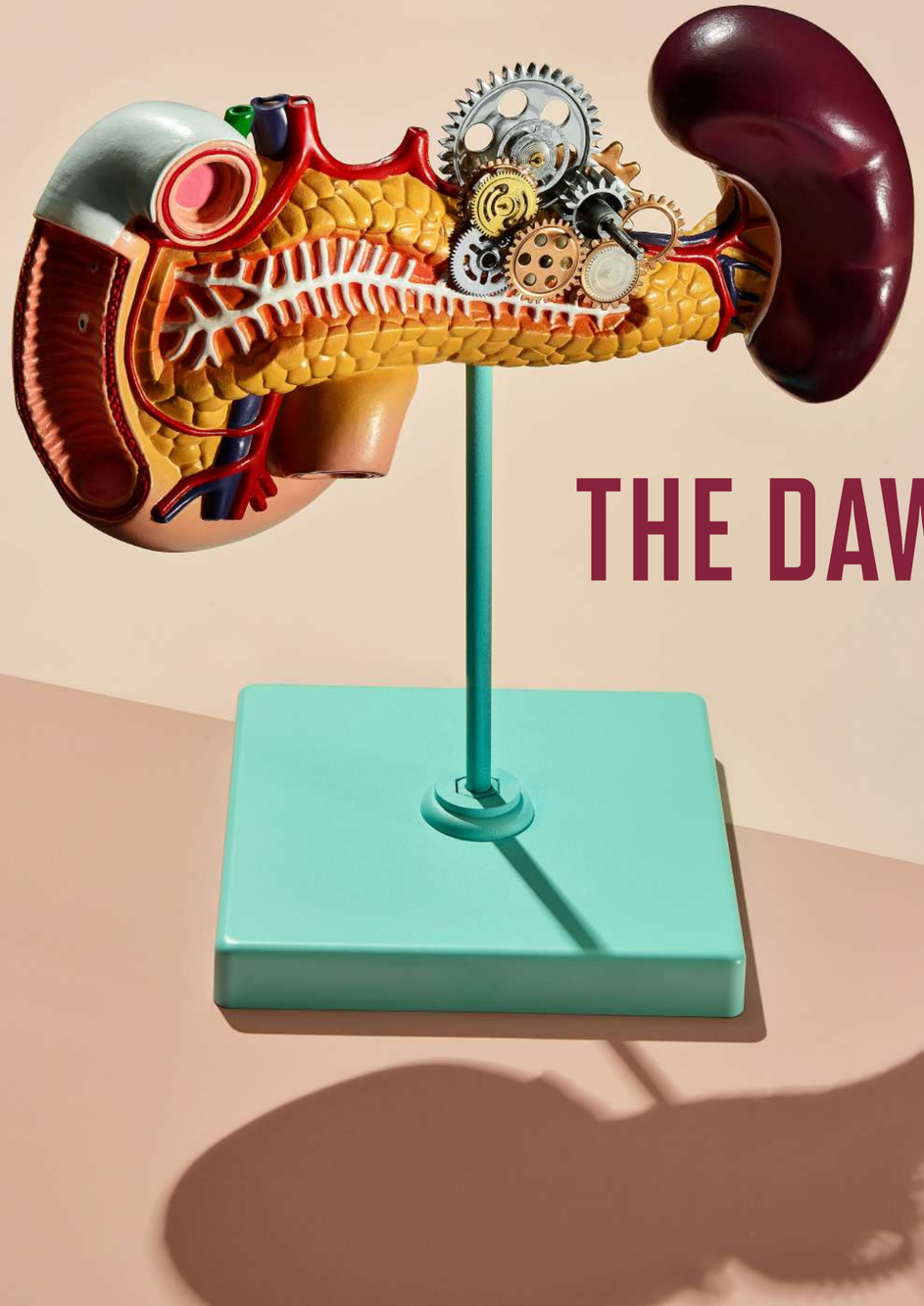
At times in her career, Bhalla has found herself thinking about what would happen if funding dried up and her lab shut down. Once she even considered chucking it all and teaching high school biology, and she has seen many talented friends drop out of research. "The people who do persist are going to be great scientists," she says. "I'm just concerned about the people we see *not* becoming research scientists and what that means for the direction of science."

Today, Bhalla says, researchers are in another kind of golden age, supported by remarkable technology, an unprecedented understanding of the basic building blocks of life, and an expanding potential to cure diseases. That's a world she's determined to be a part of, whatever it takes. "It's a hard time to be in science, but it's also such an awesome time to be in science," she says. "I don't want my concern to eclipse my wonder."

DOSSIER

"Agents of Change," by Virginia Gewin, *Nature*, October 2016. This article explores how three advocates for junior researchers are working to improve conditions for young scientists.

"A Generation at Risk: Young Investigators and the Future of the Biomedical Workforce," by Ronald J. Daniels, *Proceedings of the National Academy of Sciences*, January 2015. This article outlines the challenges that young scientists face, such as obtaining research grants, and offers proposals related to career paths, peer review and funding.



Type 1 diabetes means a lifetime of precise, constant self-treatment. Lapses can lead to disability or death. Has the time come to trust that treatment process to a machine?

THE DAWN OF THE BIONIC PANCREAS

In type 1 diabetes, the pancreas doesn't produce insulin, a chemical essential for regulating levels of sugar in the blood. This means that people with the condition walk a very narrow path to good health. They must monitor blood sugar levels scrupulously and inject insulin to keep it from soaring. But too much insulin can push blood sugar dangerously low, a condition known as hypoglycemia. Children too young to carry out that level of vigilance and judgment must rely on parents or caregivers, and failure to follow the regimen exactly carries a high cost. Those who have type 1 diabetes can expect to die as many as 13 years earlier than people without the disease.

Even patients who manage to maintain healthy blood sugar levels live with a kind of chronic angst. Kaitlyn Labbe was diagnosed with type 1 diabetes at age six, and she says that she rarely goes more than a few minutes without being reminded she has the disease. Labbe often struggles to sleep out of fear she could become hypoglycemic overnight, which in extreme cases may lead to "dead in bed" syndrome, a phenomenon that is particularly terrifying to parents of children with the disease. Some researchers estimate that it takes the life of about one in 20 type 1 diabetes patients under 40.

"It's always in the back of your mind," says Labbe, 35, who lives in Quincy, Mass. "You can't ever not think about your diabetes."

By Timothy Gower //
Photographs by the Voorhes

But for a few weeks in 2017, Labbe was able to let a machine do most of her thinking. For a study at Massachusetts General Hospital, she wore an artificial pancreas that automatically administered just the right amount of insulin to keep her blood sugar within a healthy range. "It was pretty amazing," says Labbe, who slept peacefully for the first time in decades while using the system. "It was a gift."

Doctors have been telling patients that the artificial pancreas was "just around the corner" for more than 60 years, but the quest to get there has been thwarted again and again. Now the model Labbe tested, created by a team led by Boston University professor of biomedical engineering Edward Damiano, is one of several in development that could, finally, fully automate glucose control. Three other groups, also funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), are conducting advanced clinical trials of automatic systems. That support comes on top of the more than $100 million spent since 2004 by the JDRF (formerly Juvenile Diabetes Research Foundation) on a dozen or so projects aimed at developing an artificial pancreas. Meanwhile, Medtronic's MiniMed 670G system, which the Food and Drug Administration approved in 2016, greatly reduces the need for user judgment, and the company is working on a next-generation device that will relieve even more of a patient's burden.

That's the point: to take the most unpredictable variable—the patient—out of the equation while also achieving reliable control of blood sugar. According to results of the landmark 1993 Diabetes Control and Complications Trial, led by MGH endocrinologist David Nathan, keeping glucose within a near-normal range, through intensive insulin therapy, reduces the risk of severe complications, including vision loss, kidney and heart disease, nerve damage and stroke.

Yet just one in three adults and one in five children with type 1 diabetes hit the blood sugar targets the American Diabetes Association recommends. "You can't do that without investing a tremendous amount of energy, and most people can't do it at all," says MGH endocrinologist Steven Russell, who collaborates with Damiano on the device they prefer to call a "bionic" pancreas.

A patient must check blood sugar on average 13 times a day to achieve the ADA's targets, Russell notes. Every five minutes, the device Labbe wore sent data about her glucose levels to an insulin pump, which was programmed to deliver just the right amount of the hormone into her blood. "It makes 288 decisions a day," says Damiano, "that you no longer have to make."

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Type 1 diabetes occurs when the immune system mistakenly attacks and destroys insulin-producing beta cells in the pancreas. As insulin levels diminish, cells are unable to convert blood sugar into energy, causing glucose levels to rise and damage tissues.

Until the 1920s, a diabetes diagnosis was a death sentence for most patients, who usually slipped into a coma and perished from ketoacidosis, in which the body burns fat for energy but poisons itself in the process. In 1921, Canadian physician Frederick Banting, assisted by American scientist Charles Best, first isolated insulin, derived from cow and dog pancreases. Today, thanks to that discovery, the roughly 1.25 million people in the United States who have type 1 diabetes can give themselves the insulin they can't produce, either injecting it with a syringe or using an insulin pump. (A far more prevalent kind of diabetes, type 2, which afflicts more than 20 million Americans, typically strikes adults and can often be controlled with dietary changes, exercise and oral medication. But some patients with type 2 also eventually require insulin therapy.)

The early hope that insulin would actually cure diabetes, however, didn't come to pass. Although many who began to take insulin after its discovery lived for years, a significant number developed vision loss, kidney disease and other serious complications related to tissue damage caused by poorly controlled blood sugar. Many children diagnosed with type 1 diabetes did not live past their 20s.

A chief problem, then and now, is knowing how much insulin patients should give themselves. Urine-based test kits that measured blood sugar became available in the 1940s, but they had questionable accuracy. Moreover, patients tended to use less insulin than they needed, wary of pushing their blood sugar too low. Also known as insulin or diabetic shock, hypoglycemia's steep drop in blood sugar can produce jitters, perspiration, hunger, rapid heart rate and loss of mental clarity, among other symptoms. (Hypoglycemia is responsible for thousands of emergency department visits each year in the United States.)

By midcentury, the promise that technology might relieve patients of some of the burden began to be whispered in research circles, and in an address to the Endocrine Society in 1959, endocrinologist E. Perry McCullagh of the Cleveland Clinic made a bold prediction. "We are on the very threshold of an artificial pancreas," said McCullagh, who argued that medical equipment available at the time could be automated to control blood sugar and would eventually be miniaturized into a device the size of a paperback book.

McCullagh was overly optimistic about when the artificial pancreas would arrive. The pieces, however, slowly fell into place. In the 1960s, Arnold Kadish, an internist in California, produced the first portable insulin pump, which was worn like a backpack. By the early 1980s, there were pumps that could be clipped to a belt, and those available today are the size of a deck of cards or smaller. They include a computer and a refillable chamber for insulin that attaches with a cannula, or tube, that is inserted into the skin (usually the abdomen).

As insulin pumps have improved, so have options for accurately measuring blood sugar. The first glucose meters to use a drop of blood pricked from a fingertip became available in 1981, and that soon became the standard.

Continuous glucose monitors, which keep a constant watch on glucose levels, became available for research purposes in the early 1970s. The first wearable CGMs hit the market in the early 2000s, and while early versions were notoriously inaccurate, their precision has improved dramatically. A CGM is worn outside the body, but uses a tiny sensor inserted under the skin to detect blood sugar levels, which are displayed on digital readouts and updated every few minutes. A CGM will sound an alarm if glucose concentrations sink or rise too fast.

Yet CGM users often sleep through alarms, and even the most conscientious patients (and parents of patients) can err in choosing insulin doses based on CGM readings. Still, having wearable devices that could efficiently monitor blood sugar levels and deliver insulin meant that the pieces were in place to automate insulin delivery.

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When his 11-month-old son, David, was diagnosed with type 1 diabetes in 2000, Boston University's Ed Damiano gave himself a crash course in the disease and the technology available for controlling blood sugar. Tasked with constantly measuring his son's glucose levels and trying to give him just the right amount of insulin, he realized that what he needed was a computer algorithm—a set of rules designed to solve a problem—that could use data from a CGM to instruct an insulin pump on how to respond to the body's need for the hormone. The same system might also help regulate another pancreatic hormone, glucagon, which stimulates the liver to release glucose into the bloodstream when blood sugar levels drop.

DOCTORS HAVE BEEN SAYING THAT THE ARTIFICIAL PANCREAS WAS "JUST AROUND THE CORNER" FOR MORE THAN 60 YEARS.

Damiano enlisted a former graduate student, Firas El-Khatib, now a senior research scientist at Boston University, to develop such an algorithm. In 2006, Steven Russell, then a postdoctoral fellow at MGH, began collaborating with Damiano and El-Khatib after attending a talk Damiano gave at Boston's Joslin Diabetes Center about developing a bionic pancreas.

Russell was frustrated that so many of his patients, despite their best efforts, struggled to maintain healthy blood sugar levels. "People who are highly organized and think quantitatively, like engineers and accountants, do great with diabetes," says Russell. "Everybody else? Not so much." His goal, working with Damiano, was to create a tool all patients could use out of the box.

As Damiano and Russell worked on their system, several other groups pursued their own artificial pancreases. An important milestone came in 2009, when the European Union approved a Medtronic system that combined a CGM and insulin pump that automatically stopped delivering insulin when blood sugar dropped too low—a feature known as "Smart-Guard Suspend before low"—making it the first system to use data about glucose levels to alter the behavior of a pump.

"The FDA was nervous about having a machine take over administering a drug that was life-saving but could also be dangerous," says endocrinologist Richard Bergenstal of the International Diabetes Center in Minnesota who has led clinical trials involving patients who used the Medtronic system. It was an understandable concern. In an automatic system, both the CGM and glucose pump must be infallibly accurate. A glitch resulting in just a shade too much or too little insulin could dramatically plunge or spike blood sugar levels, with potentially fatal consequences. But in 2013, Bergenstal and colleagues published a study in *The New England Journal of Medicine* demonstrating that a system with the low-blood-sugar safeguard reduced the incidence of nighttime hypoglycemia by about 40%. That gave the FDA the further

evidence it needed to approve the system the same year, which became the first available in this country featuring an algorithm that made decisions about insulin delivery.

To improve further on that device, Bergenstal and Medtronic received permission to test a system that not only shut off insulin delivery when blood sugar was low but also gave more insulin when levels headed too high. Those trials led to the approval in 2016 of its MiniMed 670G system—currently the closest thing to an artificial pancreas on the market.

More than 30,000 people in the United States were expected to be using the 670G system by the end of 2017, according to Medtronic. "It eliminates 75% of the cognitive load of diabetes—if you let it," says Jason Gensler, 33, of Denver, who was initially uncomfortable trusting the device and frequently switched it to manual mode so he could adjust the pump's insulin output. But the 670G system's algorithm eventually "learned" how best to respond to his glucose levels, and now maintains the kind of tight control of glucose that the ADA recommends. Watching the device respond to changes in his blood sugar, he says, is "mind-blowing."

Will a machine ever really be able to mimic the human pancreas? "Pumping insulin under the skin is never going to get you exactly where you want to go," says Bergenstal, who notes that insulin produced by the pancreas starts working immediately, whereas injected insulin takes 20 to 30 minutes to begin acting on blood sugar. As a result, even the most conscientious diabetes patient experiences high blood sugar on occasion. Yet it may not be necessary for everyone to achieve what are commonly thought of as normal blood glucose levels. "Studies show that if we can get patients to stay in the target range 80% to 90% of the time, and not experience extremes, we have accomplished a lot," Bergenstal says.

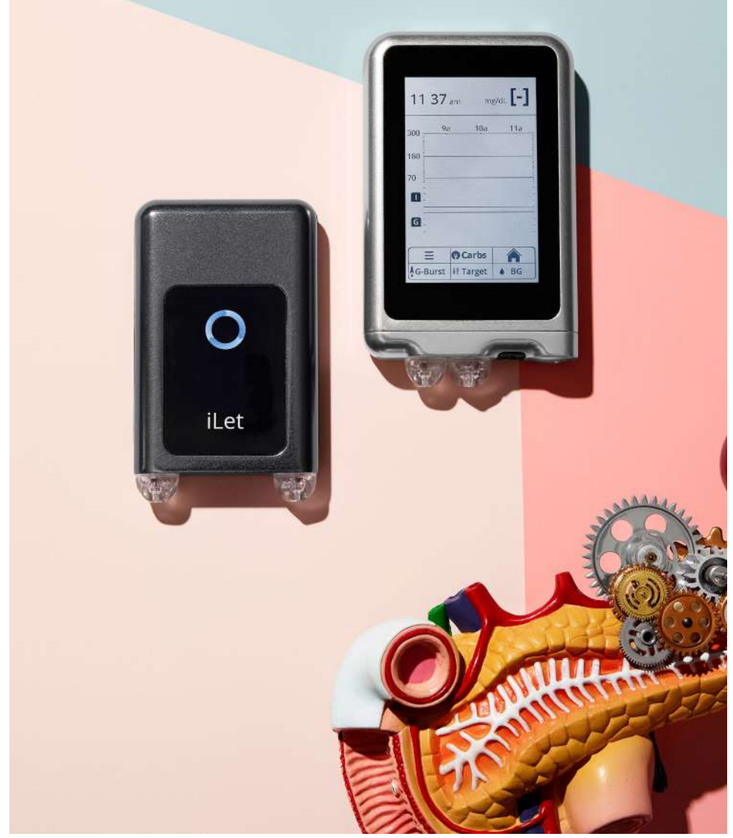
While it will be years before the long-term health benefits of using an artificial pancreas are evident, there's little doubt that keeping blood sugar in a normal range not only reduces the risk for common diabetes complications but also adds years to life. The 1993 Diabetes Control and Complications Trial found that aggressive insulin therapy lowers the threat of fatal heart attacks—a common cause of death in diabetes patients—by 57%.

Other developers, including Damiano and Russell, feel they've gone further, closely approximating the pancreas's remarkable ability to monitor and regulate glucose in the blood. The bionic pancreas technology they continue to test in clinical trials, now integrated into a device they call the iLet (a nod to pancreatic islets, clusters of cells that include insulin-making beta cells and glucagon-making alpha cells), gives users the option of administering extra insulin before meals, though there's no need to estimate how many grams of carbohydrates they'll eat. Instead, the iLet interface allows users to check off the type of meal—breakfast, lunch or dinner—and whether it will be small, typical or larger than usual. The system's algorithm adapts to what the user means by each designation and administers enough insulin to keep blood sugar in a healthy range. Moreover, if a user skips the premeal boost—as young people often do, Damiano says—blood sugar will rise, but only briefly, as the machine quickly detects the change in glucose levels and responds with a series of algorithm-selected doses of insulin.

A trial of the device done in 2012 by Damiano, El-Khatib and Russell was the first outpatient test of a fully automated insulin-delivery system. The researchers have shown that, compared with conventional therapy, it improves blood sugar control and reduces hypoglycemia in patients in a home-use setting, allowing them to go about their lives without restrictions on diet, exercise or driving, among other things. Beta Bionics, a company Damiano co-founded, plans to seek FDA approval for an insulin-only version of the iLet by the end of 2019, and within two years the company aims to offer a system with a glucagon pump, too, an addition that would help the device more quickly resolve episodes of hypoglycemia.

Some research is looking beyond the artificial pancreas to device-free methods for managing diabetes, such as "smart" insulin that works only when glucose levels rise too high. (See sidebar.) Other experimental approaches include implanting beta cells in protective capsules to prevent rejection and immunotherapy to preserve the pancreas's ability to make insulin. "The artificial pancreas is a bridge to a cure," says Aaron Kowalski, chief mission officer for the JDRF.

But that bridge is more than welcome to Kaitlyn Labbe and other diabetes patients who are ready to embrace a technology that will free them from the practical and psychological burden of managing diabetes. Labbe plans to get a Medtronic 670G as soon as the warranty on her current insulin pump expires, and when the iLet hits the market, she says, "I'll be first in line."



STILL NOT GIVING UP

Three efforts to cure diabetes—and make the bionic pancreas obsolete—show promise.

Encapsulated beta cells

Surgeons can already transplant beta cells into people with type 1 diabetes to eliminate the need for insulin injections. But donor tissue is scarce, and recipients must take potentially dangerous antirejection drugs for life. Harvard scientist Douglas Melton and his colleagues are looking to overcome these obstacles. They create functioning beta cells from embryonic stem cells, eliminating the need for a donor. And those new beta cells are protected inside the body by barriers made of algae derivatives and other materials, which keep beta cells safe from attack by immune cells but allow insulin to pass into the blood. In one study, the manufactured beta cells maintained good glucose control for 174 days in mice, without the need for immunosuppressants.

Gene transfer

A healthy pancreas contains not only beta cells but also other cell types, including cells that manufacture essential digestive enzymes. What if these non-beta cells could be reprogrammed to produce insulin? Researchers at UT (University of Texas) Health San Antonio have cured diabetes in mice by doing just that, using an FDA-approved viral vector (or carrier) to transfer the genes essential to beta cell physiology into other pancreas cells. After that gene transfer, these cells produce insulin. Pulling off this trick in larger mammals is next, with human trials coming in as few as three years.

Vaccines

Various vaccines might be able to rein in the immune system attack that kills beta cells and causes type 1 diabetes. At Massachusetts General Hospital, immunobiologist Denise Faustman and colleagues are conducting a phase 2 clinical trial exploring a possible new use for the bacillus Calmette-Guérin vaccine—an inexpensive generic used to prevent tuberculosis. They hope it can reverse type 1 diabetes by eliminating the immune system's "bad" T cells that attack beta cells.

DOSSIER

"Coming of Age: The Artificial Pancreas for Type 1 Diabetes," by Hood Thabit and Roman Hovorka, *Diabetologia*, June 2016. This document provides a concise summary of how scientists have addressed the challenge of developing an artificial pancreas.

"Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes," by Steven J. Russell et al., *The New England Journal of Medicine*, July 2014. This study was the first to test an artificial pancreas in a real-world setting.

"How I Designed a 'DIY' Closed Loop Artificial Pancreas," by Dana Lewis, diyps.org. Blogger and diabetes patient Dana Lewis describes how her desperation drove her to build an artificial pancreas, which has been widely copied.

Chemical engineer Paula Hammond is working on a "gobstopper," a nano device with three layers: one that allows it to travel undetected, another that weakens the tumor's defenses and a third that releases a chemotherapy agent.

NANO ARSENAL

CANCER TREATMENT HAS BEEN WAITING FOR THE TINY, SMART PARTICLES THAT CAN SLIP THROUGH A TUMOR'S DEFENSES. HAS THEIR MOMENT COME AT LAST?

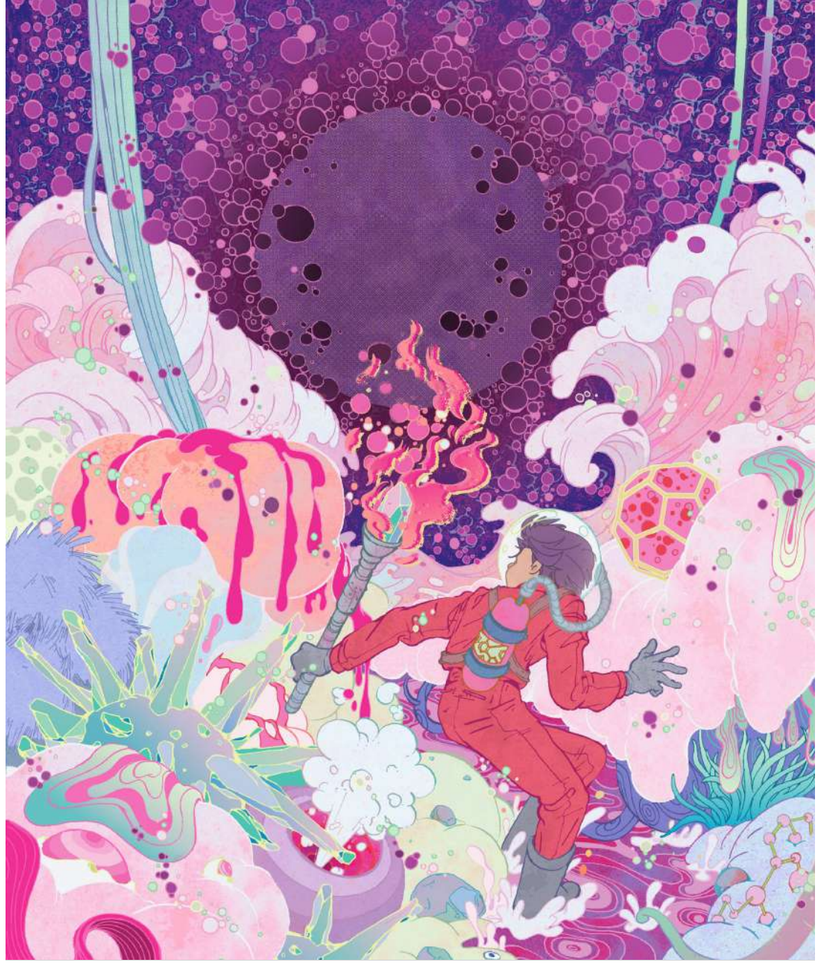
In 2016 several top cancer experts convened at a forum sponsored by Partners HealthCare to produce a report on the technologies that were most likely to transform cancer care during the next decade. Daniel Haber, director of the Massachusetts General Cancer Center, remembers the group talking about CRISPR gene editing, artificial intelligence to improve diagnosis and treatment plans, and immunotherapy techniques that incite the immune system to fight tumors. "At the end of the conversation someone said, 'What about nanotechnology?'" Haber says.

It's an open question. Among those experts, the consensus was that while nanotechnology, which in cancer treatment uses vanishingly minuscule particles to launch sneak attacks on tumors, may have promise for the future, that future has always felt just out of reach. Since the mid-1990s, when the first of a handful of nanotech cancer drugs hit the market, several have become standard parts of chemotherapy. Yet this approach to battling cancer has never proved quite as revolutionary as it was supposed to be. "For decades, everyone's been talking about this exciting research, and there's no doubt they're making some really cool particles," Haber says. "But we're still waiting for the breakthrough moment when we can say, 'This nanotech has a real impact in the clinic.'"

By Eliza Strickland //

Now that moment may finally be coming into view. At a time when gene therapy has been revived as a potent form of cancer treatment, a new approach would use nanoparticles, rather than viruses, to deliver strands of DNA or RNA to tumors. Other nanoparticles in development could be injected to rev up the immune system's ability to attack malignant cells. Researchers are experimenting with two ways to use gold nanoparticles—in one case, to reduce the collateral damage caused during radiation therapy while increasing effectiveness, and in another, as the targets of laser beams to help kill tumor cells. Iron-based nanoparticles, meanwhile, can be activated by magnetic fields to generate tumor-scorching heat.

At one hub of innovation, MIT's new Marble Center for Cancer Nanomedicine, researchers have taken aim at ovarian cancer with wide-ranging approaches, crafting nanoparticles designed to diagnose or treat the deadly disease. In their most intriguing work, they're collaborating on something new: a "theranostic" nanoparticle that can both diagnose and attack ovarian tumors. Such a potent particle would go well beyond the limits of today's cancer nanomedicines—and could finally demonstrate what can happen when cancer researchers think small.



A "theranostic" nanoparticle that combines Bhatia's nanosensors or Belcher's nanotubes with Hammond's gobstopper could simultaneously diagnose and treat cancer.

The first nano cancer drug approved by the Food and Drug Administration in 1995 was designed to make an existing treatment better, and the drug it would work with was a commonly prescribed chemotherapy, doxorubicin. Although doxorubicin can be effective at killing tumor cells, its noxious impact can hurt healthy tissues as well. Too large a dose can cause congestive heart failure, among other side effects, while a small dose may be overwhelmed by immune cells, which consider doxorubicin a foreign invader.

Yechezkel Barenholz, who was working at the Hebrew University Hadassah Medical School in Israel, and his colleagues came up with a nano packaging trick that addressed those problems. To get an idea of the scale at which they were working, consider that a human hair is about 100,000 nanometers wide. Barenholz's team put doxorubicin inside 100-nanometer particles made of lipid (fat) molecules, decorated on the surface with a polymer that attracted water molecules. That allowed each nanoparticle, packed with medication, to circulate in the blood in a surrounding cloud of water that shielded it from immune cells.

The clever packaging also reduced toxic side effects by using a quirk of tumor anatomy. In its rush to grow, cancer forms tangles of blood vessels, but those slapdash vessels are leaky. Barenholz's nanoparticles generally stayed in the bloodstream and avoided the heart and other organs, but when they reached the leaky blood vessels in the tumor, they slipped through those holes. When the particles reached the tumor itself, they released their chemo payload in a process related to that particular tumor cell's metabolism. This passive targeting system meant that a low dose of the drug could make a strong impact on tumors, yet with few side effects.

PREVIOUS PAGE: BRATISLAV MILENKOVIĆ; THIS PAGE: PAULO CAMPOS

"When we started, no one believed it would work," says Barenholz, now a professor emeritus of biochemistry and molecular biology at the Hebrew University of Jerusalem. But in 1995, after successful clinical trials, the FDA approved the nanodrug Doxil for treating AIDS-related Kaposi sarcoma; later, the agency extended its approved use to ovarian cancer and multiple myeloma, and in Europe doctors use it to fight breast cancer.

Like Doxil, all other existing cancer nanomedicines use specially engineered nanoparticles to transport an existing chemotherapy agent. And by some metrics, these first-generation nanodrugs have done well. They are widely prescribed and have been shown to limit toxic side effects.

Studies have found, however, that Doxil doesn't perform significantly better than the original doxorubicin drug at slowing cancer's advance or in prolonging patients' lives. Some analyses have questioned whether the passive targeting strategy, which depends on the circulating medication slipping through the unique apertures of a tumor, is effective, noting that the blood vessels that spring up around tumors may not be as porous as originally thought, and therefore may prevent large quantities of the nanodrug from reaching its target. While some researchers have tried to boost efficacy through new ways to administer the drug, such as in conjunction with focused ultrasound, others have looked to completely different approaches.

To make deeper inroads against cancer, nanotechnology may need to do more than simply miniaturize standard treatments. At the Marble Center for Cancer Nanomedicine, three research groups are working on particles that take more complex approaches to targeting tumors and delivering a wide variety of substances, including new kinds of diagnostic agents as well as cancer-killing therapies. Many of these efforts are focused on ovarian cancer, which is particularly deadly, with only 47% of those with the disease alive five years after diagnosis.

One group is led by Angela Belcher, a relative newcomer to medical research. After years of breaking ground on nanomaterials for batteries and solar panels, in 2010 she joined MIT's Koch Institute for Integrative Cancer Research and threw herself into solving the riddles of ovarian cancer. Belcher's background, she feels, gives her a clear perspective on human anatomy and its quirks. "I'm a materials scientist, so I look at everything as a material," she says. "To me, all problems have material solutions."

Belcher, a professor in two MIT departments—materials science and biological engineering—believes there's a misperception regarding nanotech. "A lot of people think the great thing is that it's small," she says. "But what's really great is that when a material gets that small, its properties change." In that tiny world, objects have different optical, magnetic, electrical and mechanical attributes. Belcher explains that nanotech researchers can "tune" a material to get the properties and the outcomes they want.

RESEARCHERS HAVE TAKEN AIM AT OVARIAN CANCER, CRAFTING NANOPARTICLES DESIGNED TO DIAGNOSE OR TREAT THE DEADLY DISEASE.

Belcher's system uses nanoparticles as an imaging system that can help surgeons find tiny bits of residual tumor. "We've known for years that how well a patient does is directly related to the amount of tumor that the surgeon removes and the amount that's left behind," says Michael Birrer, who began working with Belcher when he was head of medical gynecologic oncology at Massachusetts General Hospital. (He's now director of the Comprehensive Cancer Center at the University of Alabama at Birmingham.) Tumor cells that aren't taken out can grow and spread, often with deadly consequences. With Belcher's nanoparticles, surgeons should be able to spot and remove tiny clusters of just a few cells, even when they're hidden behind other organs, thus preventing those seeds from growing into major malignancies. "Theoretically, we may be able to cure some patients," Birrer says. "This is some of the most exciting work I've ever done."

The crucial element is a carbon nanotube, a hollow structure made of sheets of carbon only one atom thick. At that scale, when the nanotubes are hit by near-infrared light with wavelengths of about 800 to 1,400 nanometers, they naturally fluoresce. That fluorescence isn't visible to the naked eye, but it can be easily recorded with optical equipment.

Introduced during tumor removal surgery, the nanotubes could light the way for surgeons. In a recent study using mice, a virus that binds to the outside of ovarian cancer cells was used to deliver nanotubes to the tumor sites. After the bulk of the ovarian tumors had been removed, the team projected near-infrared light onto the surgical site. The nanotubes illuminated minuscule tumor fragments—some as small as half a millimeter in

diameter—that the surgeons then removed. "We increased median survival time in animals by 40%, which gives us enough evidence to go on to human clinical trials," Belcher says. The team has already submitted a request to the FDA to conduct a small initial study in people.

Belcher hopes that the nanotubes might ultimately serve an additional function, as part of a noninvasive imaging system to screen women for ovarian cancer. The near-infrared light that causes the nanotubes to fluoresce can penetrate about eight centimeters into human tissue, so physicians could potentially shine the light through skin and flesh to look for fluorescence from nanotubes signaling the presence of cancer cells. Women whose ovarian cancer is detected before it has spread have a much better five-year survival rate of 93%. "That's the work I'm most excited about," Belcher says. "I want to find those early-stage tumors, and I want to increase the survival of patients with ovarian cancer."

NANOSENSORS COULD ALLOW DOCTORS TO DETECT CANCER AND PROVIDE TREATMENT MONTHS OR EVEN YEARS EARLIER THAN THEY DO TODAY.

The lab of Sangeeta Bhatia, director of the Marble Center, is also working on a diagnostic technique for ovarian cancer, but this one relies on chemistry. The researchers have devised a nanosensor that breaks apart in the presence of ovarian tumor cells and sheds fragments of itself. Those fragments are then filtered out through the kidneys and can be detected in a urine test.

The nanosensors accumulate in the tumor through a turbocharged variation of the targeting mechanism that first-generation cancer nanodrugs employ. Once the sensors have traveled into a tumor's leaky blood vessels, they use special targeting molecules to bind to receptors on the surface of blood vessel cells. That activates a cellular process that whisks the nanosensors inside the tumor's outer shell, where they can do their work. The sensors are particularly helpful because they respond to a specific enzyme that a tumor needs to grow blood vessels and to remodel neighboring tissue, steps that enable the tumor to spread. The enzyme "isn't just a random by-product of a tumor—it's something that can serve as a marker for growth and malignancy," says Ester Kwon, a former postdoctoral researcher in Bhatia's lab.

Small molecules called peptides on the nanosensor's surface react chemically with the enzyme, causing fragments of the peptides to break off. Those fragments float away, are captured by the body's filtration systems, and wind up in urine—in which they can be detected even at minute levels.

The nanosensors aren't yet ready to be tried in people. But in mouse studies, the sensors detected tumors smaller than five millimeters.

Like Belcher's nanotubes, this diagnostic tool could also be used as a screening method for ovarian cancer. Today, women typically don't get checked until they're exhibiting symptoms, which can range from abdominal pain and indigestion to constipation, diarrhea and vaginal bleeding. Moreover, current diagnostic tests aren't very sensitive. The average tumor detected by ultrasound measures about five centimeters in diameter, and the biomarkers used in blood tests enable oncologists to detect tumors as small as one centimeter. Researchers estimate that it can take as long as 10 years for a tumor to grow that large. Bhatia's technology could allow doctors to detect the cancer and provide treatment months or even years earlier than they do today. That difference could be lifesaving.

A third innovation from the Marble Center comes with an arresting moniker: the gobstopper, named after the multilayered hard candy. It's the result of an effort by Paula Hammond, who heads MIT's chemical engineering department, to perfect a process of layer-by-layer assembly that enables nanoparticles to carry several drugs between their strata. The gobstopper can then sneak those therapeutic agents past the body's defense systems and deliver them to an ovarian cancer tumor.

The outer layer of the gobstopper is a stealth layer; much as in the technique used by Doxil and other first-generation nanodrugs, its surface attracts water molecules, so the particle can avoid notice by the body's patrolling immune cells. Its outer coating also has a negative electrical charge that repels the negatively charged immune cells.

When the nanoparticle reaches a tumor, its middle layer releases an RNA molecule that weakens the tumor's defenses by turning off certain cancer-promoting genes. That assault sets up the tumor for a final blow when the nanoparticle's core releases a chemotherapy agent. "By building particles layer by layer, we've already made two compartments for drugs," Hammond says. "And we can get fancier."

The modular nature of Hammond's nanoparticles might also benefit either Belcher's light-responsive nanotubes or Bhatia's fragment-shedding nanosensors, by packing them into a layered particle that contains a chemo drug at its core. Hammond has ongoing investigations with both of those labs, work that could lead to a theranostic nanoparticle that simultaneously identifies ovarian tumors and hits them hard.

Such a combination, Hammond says, could yield rich information for oncologists. "With the nanotubes, we'd have a way of optically imaging the location of tiny tumors and treating them on the spot," she says. "Then with the second method, we can detect tumor activity with enzymatic activity, and can monitor the effects of treatment over time."

With the enzymatic detection method, says Bhatia, urine tests could also be used to track a patient's progress. If the signal decreased, the oncologist would know the tumor was shrinking. "You could assess the patient's response to treatment, alter the regimen if needed, and monitor for any chance of early recurrence," she says. That adaptive approach to treatment might offer patients relief from chemotherapy's harsh side effects. "We're trying to increase both survival *and* quality of life," Bhatia adds.

The Marble Center researchers, as well as others in this field of cancer treatment, are well aware that these medicines are sometimes characterized as futuristic solutions that are always about 10 years away. It's true, moreover, that these potential advances aren't yet close to routine clinical use—and some might not get there at all. But with truly innovative ideas now emerging from the nanoworld—ideas that don't just scale down existing treatments but take entirely new approaches—they see potential for real breakthroughs that will save patients' lives. The revolution in cancer care just might be nano-sized.

SEÑOR SALME

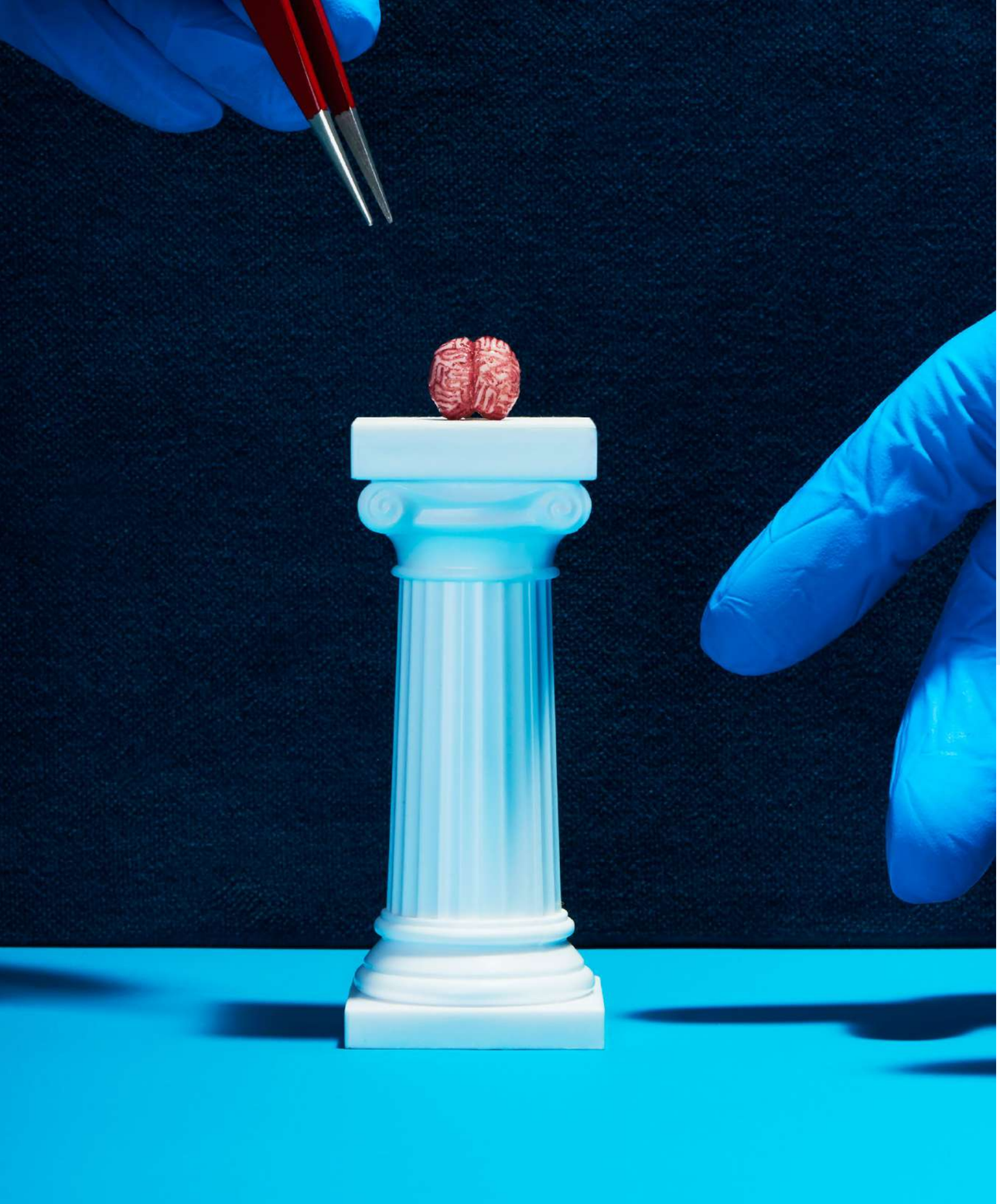
Angela Belcher's nanotubes are made out of hollow sheets of carbon that are only a single atom thick. The tubes can bind to cancer cells and, when hit with near-infrared light, fluoresce. In this way, a surgeon can illuminate any tumor fragments that are in danger of being left behind during a procedure.

DOSSIER

"Mechanisms and Barriers in Cancer Nanomedicine: Addressing Challenges, Looking for Solutions," by Thomas J. Anchordoquy et al., *ACS Nano*, January 2017. The result of a workshop involving several dozen leading experts on cancer nanomedicine, this paper discusses the limitations of current cancer nanodrugs and the research necessary to advance the field.

"The Evolving Landscape of Drug Products Containing Nanomaterials in the United States," by Sheetal R. D'Mello et al., *Nature Nanotechnology*, June 2017. Researchers at the Food and Drug Administration examine data from more than 350 nanomedicines submitted for approval since the 1970s and identify trends.

"Plenty of Room at the Bottom," by Richard P. Feynman, lecture delivered at a meeting of the American Physical Society at the California Institute of Technology, December 1959. This lecture by the theoretical physicist Richard Feynman is often cited as the origin of nanotechnology. He challenged scientists to make machines and products that could interact with the world on the atomic scale.



ORGANS ARE CLAY MODELS, CREATED BY KIMBERLY CLOUGH/FAIRCHILD ART

TINY MARVELS

Researchers can now grow a small version of an organ from a single stem cell. The most exciting outcome might just be the brain in a dish.

By Cathryn Delude // Photographs by Andrew B. Meyers

Because the human brain is unique among animals, studies conducted in mice and other laboratory animals often aren't much help in predicting what will happen in people. Many neurological traits and diseases can't be accurately studied in mice—for decades the go-to animals for brain research—because the human versions involve cells and circuitry that are quite different in rodents or don't exist there at all. This problem has bedeviled researchers studying many brain conditions, and it was a particular barrier in research on microcephaly. A baby born with microcephaly has an abnormally small brain, which can contribute to severe neurological defects. But in mice with the condition, brain sizes aren't reduced in the same way.

In 2012 Madeline Lancaster, a post-doctoral researcher in the laboratory of Jürgen Knoblich at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences in Vienna, was trying another approach. Rather than breeding mice with the rare genetic mutation that can cause microcephaly, she would attempt to grow a tiny version of a human brain with that gene variant. If she succeeded, this so-called organoid—"a brain in a dish"—could give researchers a new window into how the condition unfolds in a developing human fetus.

An organoid is a simplified version of an organ grown from a single human cell. Organoids are small, typically about the size of the head of a pin, though some may grow slightly larger. For her brain organoids, Lancaster started with skin cells from a patient with microcephaly, which carried the gene known to cause the condition, and also from a healthy control. She "reprogrammed" these mature skin cells to become induced pluripotent stem cells (iPS), which can become any type of cell in the body. Then she coaxed these iPS cells to develop into tiny versions of her subjects' brains.

During the next two to three months, the cells began to organize themselves into layers and clusters of different cell types, paralleling what happens during the first eight to 10 weeks of human fetal brain development. Some cells differentiated themselves into various types of the nerve cells (neurons) found in several brain regions, while others remained "neural progenitors," creating a reservoir of potential neurons to be used later. Producing such self-assembling organoids "doesn't require any super-sophisticated

bioengineering," Knoblich told *Nature* in 2015. "We just let the cells do what they want to do, and they make a brain."

In the organoids that Lancaster had derived from a healthy person, the growth of the hindbrain slowed as the forebrain grew—reflecting what happens as a normal human fetal brain develops. Organoids grown from the cells of a patient carrying the gene for severe microcephaly, however, didn't grow as large because those brain regions didn't develop properly. Further research showed that too many neural progenitors in these organoids had become neurons early on, leaving the developing brain without the resources it would have used to enlarge the forebrain.

Lancaster and Knoblich published their work in *Nature* in 2013, at a time when microcephaly was still rare. But two years later the Zika virus outbreak hit, and physicians noticed that many women bitten and infected by virus-carrying mosquitoes gave birth to babies with microcephaly. To determine whether the Zika virus caused this, a number of independent teams of researchers—including two in Brazil and one at the University of California, San Diego—created brain organoids from healthy human cells and infected some of them with the Zika virus.

SINCE THE FIRST ORGANOIDS
were created less than a decade ago, their uncanny ability to mimic in miniature the development of real organs in the body has caused a quiet revolution.

Most of the Zika-infected organoids grew to barely half the size of their uninfected counterparts. The Zika virus also replicated the genetic defect in another way, depleting the progenitor cells and causing similar development problems to the ones that Lancaster had observed in Vienna. This experimental proof that the Zika virus caused microcephaly came quite rapidly, and other teams working with Zika have continued to use organoids to test therapeutic interventions and to probe why only some strains of the virus appear to result in the condition.

Since the first organoids were created less than a decade ago, their uncanny ability to mimic in miniature the development of real organs in the human body has caused a quiet revolution in many areas of medical research. Some of their most dramatic contributions, however, have come in studies of the human brain. "Organoids provide a great opportunity to study certain brain disorders that are overtly human, affecting the highest brain abilities that we have as human beings," says Paola Arlotta, a professor of stem cell and regenerative biology at Harvard University who studies the mammalian cerebral cortex.

Organoids may also break new ground in the pursuit of personalized medicine—treatments targeted to one person's genetic characteristics. Although organoids can also be created from embryonic stem cells, an organoid derived from a patient's own cells carries the complete genome of that person. While such a cluster of personalized cells is not a perfect replica of the organ that exists in that person's body, it can be experimented on and used to gauge the effectiveness of potential therapies, providing a powerful new tool to help researchers understand how diseases develop and how to treat them.

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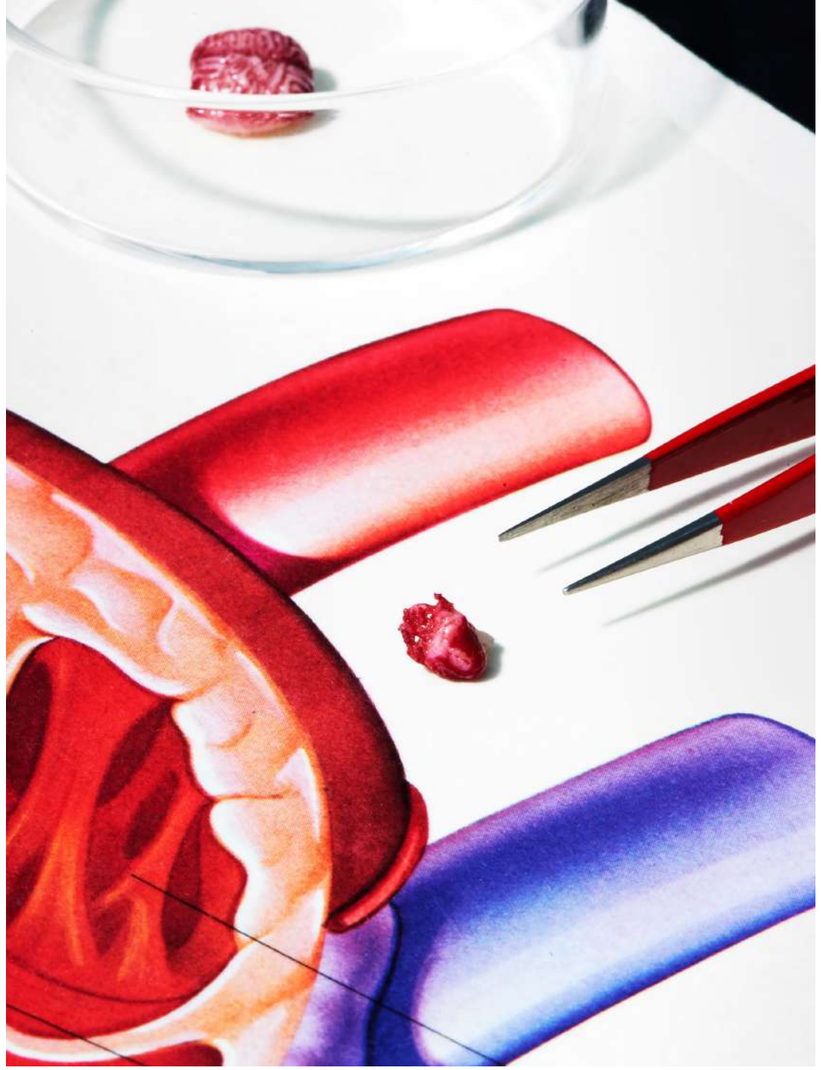
Hans Clevers at the Hubrecht Institute in Utrecht, the Netherlands, developed the first organoids from mice in 2009, and the first human organoids in 2011. At the heart of Clevers' work were adult stem cells, a type of cell that can replenish itself while also maintaining the ability to change into the many types of mature cells that a particular tissue or organ requires. For his experiments, Clevers used human intestinal stem cells that his lab had discovered in 2007.

Researchers had developed the technologies needed to create organoids years before—how to grow cells in culture, how to isolate stem cells from human tissue, and how to coax the stem cells, undifferentiated and immature, to become specific types of cells at later stages of development. But when such cells were grown in a laboratory dish, they adhered to the flat surface of the liquid medium they were grown on, spreading out in a thin layer. Confined to two dimensions, the cells couldn't form the integrated structures of developing tissue.

Previous research had shown that if cells are grown in a medium called Matrigel—firm enough to support cells above a dish's flat surface and pliable enough for cells to reshape as they grow and multiply—cells are able to develop in three dimensions as they would in the body, assuming the various shapes, layers, compartments and relationships within a particular organ. Clevers added his intestinal stem cells to this gel, and also introduced chemical growth signals that encouraged the stem cells to begin maturing. The intestinal organoids that grew from these elements developed several of the singular characteristics of that tissue type, including small knobby protrusions (crypts) that in full-size intestines serve as receptacles for stem cells.

Meanwhile, others in Clevers' lab were using similar techniques to grow organoids of the stomach, pancreas, prostate, breast and liver. Researchers elsewhere quickly adapted the methodology to create additional organoids—of the eye, lung, heart and brain—and their associated diseases, including cancers. Researchers now have modeled the majority of human organs, and organoids are being used to study everything from normal development and basic biology to a plethora of disorders.



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What sets organoids apart as a research tool is their inherent humanness. Conducting experiments on tissue that is very similar to the kind found in the body helps researchers in many specialties, but nowhere so much as in studying brain diseases, especially those for which treatments have long eluded researchers. "We've learned a lot about the brain from mice, but I think we can all agree that mice and humans are very different," says Li-Huei Tsai, a neuroscientist at the Picower Institute for Memory and Learning at MIT who studies the neurobiology of Alzheimer's disease. A number of promising drugs for Alzheimer's have, for instance, worked in mice, but when they reach clinical trials with humans "an astonishing 99% of them fail, and it has been 15 years since the last treatment, memantine, was approved," she says.

There's also a wide gulf between what seems to work in mice and what actually helps people who have neuropsychiatric disorders, says Steven Hyman, director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard. "Our most effective treatments in psychiatric disease were discovered serendipitously more than a half century ago," Hyman says. "And despite decades of research in mice, we still don't know how they really work."

Not only can organoids potentially offer a better model for human disease, they can also be surprisingly easy to coax into being. Given the correct chemical prompts, cells follow their internal instructions and spontaneously organize themselves. "We kept them healthy, and without giving them many instructions on what kind of cells they should become they produced many of the cells present in the human brain and achieved the formation of complex tissue," says Arlotta, describing the brain organoids she used in research published in *Nature* in May 2017.

For that study, Arlotta was looking at a stage of brain development later than the one studied in the microcephaly and Zika experiments, which modeled only what happens early on during pregnancy. So she modified the Lancaster system to allow her organoids to survive and develop in culture for longer than anyone else—more than nine months.

During gestation, a human brain generates the kinds of cells and circuits needed to carry information. Neurons, the main communicators, form connections with other neurons via structures called dendrites, which receive the incoming electrical signals used to communicate information within and beyond the brain, and axons that pass along the message to the next cell across synapses, the gaps between cells. "These long periods of development in the dish allow many types of cells to form and mature. Importantly, neurons acquire properties of mature cells, most notably dendritic spines, the structures that form on dendrites and receive synapses," she says.

Arlotta is now using this system to study organoids derived from patients with autism spectrum disorder and other psychiatric

illnesses as she searches for their underlying mechanisms.

Yet while autism begins during brain development, and it makes sense that a developing organoid could serve as a model, looking at diseases that affect people toward the end of their lives would seem more difficult. Many scientists, concerned about the finite lifespan of organoids, questioned whether they would be useful for research on conditions of aging.

For a 2014 study, Rudolph Tanzi, director of the Genetics and Aging Research Unit at Massachusetts General Hospital, Doo Yeon Kim, assistant in neuroscience at MGH, and their team were able to create an organoid that they called "Alzheimer's in a dish." In this three-dimensional culture, grown from human stem cells converted into neurons harboring genetic mutations known to cause the inherited, early-onset form of the disease, the researchers observed some of the characteristic features begin to develop. Plaques made of the protein amyloid were on the outside of cells, and they triggered tangles of a second protein, tau, within neurons—just as they were in the dissected brains of people who had Alzheimer's. This work was published in *Nature* in November 2014 and earned the researchers a Smithsonian Ingenuity Award in 2015.

Building on that work, for a 2016 study in *PLOS One*, Tsai's lab used cells from three patients with an inherited form of Alzheimer's as well as cells from two healthy people to create brain organoids. Within two months, those derived from the Alzheimer's patients began secreting high levels of amyloid protein, which clumped together in the spaces between neurons, resembling the formation of plaques in a fully formed brain. Within three months, the neurons in the organoids also had formed tau aggregates, further bolstering the hypothesis that amyloid plaques precede tau as Alzheimer's disease develops.

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Once Tsai's lab had discovered that organoids could acquire Alzheimer's-like traits, they moved on to another puzzle: Could those characteristics be prevented or treated? Researchers exposed another set of organoids derived from the same Alzheimer's patients to experimental compounds known to prevent the secretion or accumulation of amyloid, and they discovered that the plaques didn't form. (The compounds have not yet been developed for therapeutic use in people.)

That work underscores a chief benefit of all organoids—that they can be used to try out potential therapies, with results that are likely to be similar to what would happen in people when a treatment advances to human clinical trials. Moreover, because organoids can be grown quickly and in huge quantities, researchers can interrogate them repeatedly and mercilessly. How does a particular treatment affect human tissues? Is it toxic? If a suspected disease gene is inserted into the starter cells, what happens to the organoids' development and function? If organoids are cultivated from people who share a diagnosis for a complex disease—diabetes, Alzheimer's, schizophrenia, heart failure, celiac disease—will there be differences in how the cells from different people develop, and how the organoids respond to the same drug?

Because organoids are easy and relatively inexpensive to grow and can be created from a particular person's cells, they might also be extremely useful in personalized medicine, helping tailor a treatment the way some cancer treatments can be targeted to the genetic makeup of a tumor. As organoid techniques improve, researchers will be able to screen a compound on the very patient they are trying to treat, and test the efficacy of new and existing drugs on a patient's own cells. "It will be revolutionary," says Arlotta.

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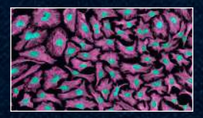
In drug development, however, the remarkable complexity of organoids can sometimes be a distraction. As their cells begin to organize into larger structures, organoids may begin to diverge in important ways from each other, becoming individualized much as a particular person's organs do. With diversity

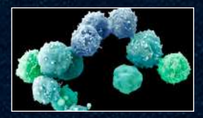
[1951] TOM DEERINKCK/NIH; [1998] STEVE GSCHMEISSNER/SCIENCE PHOTO LIBRARY; [2003] MATT SPINDLER/GLADSTONE INSTITUTES; [2007] SHINYA YAMANAKA, KYOTO UNIVERSITY; [2011] CLEVERS GROUP/HUBRECHT INSTITUTE; [2012] IMBA/JÜRGEN KNOBLICH; [2015] KATERYNA KON/SCIENCE PHOTO LIBRARY; [2016] PASCA LAB/STANFORD UNIVERSITY SCHOOL OF MEDICINE

THE RISE OF THE ORGANOID

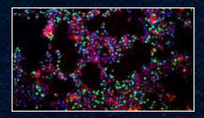
Learning how to grow these tiny, rudimentary organs required a long series of discoveries, with contributions by a global contingent of research teams.



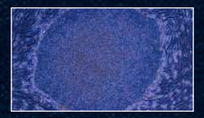
1951 A lab at Johns Hopkins Hospital in Baltimore keeps a strain of human cancer cells alive and propagating indefinitely outside the body. Repeating this feat with normal cells proves more difficult.



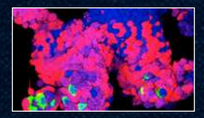
1998 Researchers at the University of Wisconsin isolate human embryonic stem cells, which renew indefinitely outside the body and can become the precursors to different tissue types.



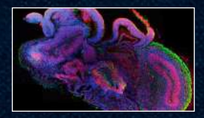
2003 Adult stem cells are isolated from the human mammary gland. These can also self-renew and differentiate into breast cell lineages. They are maintained in a 3D culture using Matrigel.



2007 A team at Kyoto University in Japan show how to make embryonic-like cells from human skin cells, obviating the need to use human embryos and reinvigorating human cell culture research.

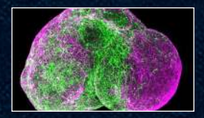


2011 Hans Clevers at the Hubrecht Institute in the Netherlands grows human intestinal organoids using stem cells. They mirror key structural and functional features and can be used to model several disorders.



2012 At the Austrian Academy of Sciences in Vienna, a group produces the first brain organoids. They use the tissue to study microcephaly, a disease that in humans causes abnormally small heads and brains.

2015 Following the Zika virus outbreak in South America, several teams of researchers use the Austrian method of creating brain organoids to determine if and how the virus causes microcephaly.



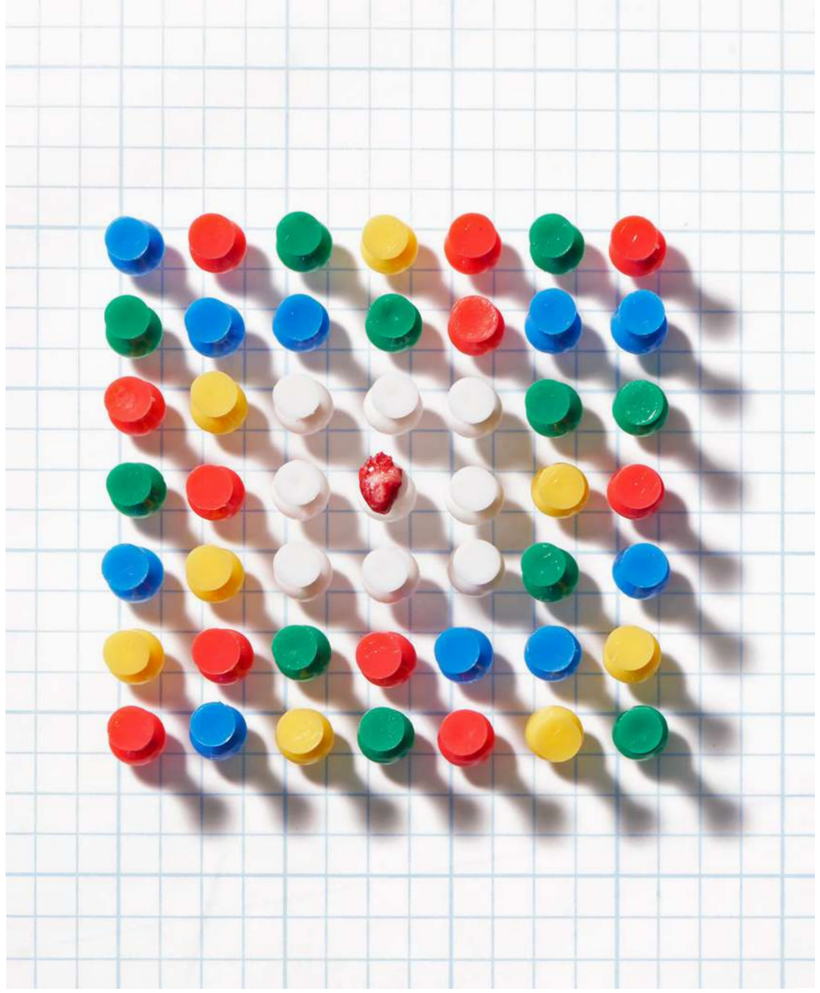
2016 Neuroscientists use organoids to model later stages of brain development, and show that multiple brain organoids can be fused to replicate more complex functions.

comes unpredictability, and that's a problem for testing new treatments, a process in which standardization and reproducibility are essential.

One way around that problem is to work with another kind of 3D cell culture known as a spheroid, which hasn't yet gone too far down the path of development and still contains mostly identical, similarly differentiated cells.

Much of the work geared toward drug discovery and testing uses spheroids. Lee Rubin, professor of stem cell and regenerative biology at Harvard University, employs them to study spinal muscular atrophy (SMA), a neurodegenerative disease affecting children that is similar to amyotrophic lateral sclerosis (ALS) in adults. "Because I'm interested in developing therapeutics, I need a system that generates billions of human neurons that have the particular mutations for this disease," he says. Those neurons need to be identical to each other, and to achieve that consistency, Rubin and his colleagues are willing to sacrifice some of the structural complexity they could get with more fully formed organoids. He can control what the spheroids' cells become—muscle neurons or glial cells, or even muscle or gut cells—by adding particular chemical cues to the medium in which they grow. But because the spheroids were created from a cell carrying the SMA gene, all of the cells, of whatever type, also have that mutation.

Rubin first used spheroids to confirm that, as expected, motor neurons die if they have the disease mutation. "But we also discovered something surprising," he says. Researchers had assumed that the SMA gene, essential for the survival of motor neurons, affected only that particular type of neuron. But the SMA mutation also generated defects in the other tissue cells—for muscles, gut, lung and thyroid—he derived from the iPS cells they used. That suggested that children with SMA might also suffer other problems affecting muscle tone or digestion, for example, that hadn't been known or discussed.



To find out whether this lab finding applied to children with SMA, Rubin collaborated with Isaac Kohane, who chairs the department of biomedical informatics at Harvard Medical School, to search some 60 million electronic medical records. They identified about 500 children with SMA and found that they did indeed have the kinds of problems the stem cell work had predicted. No one had connected those symptoms with the underlying genetic condition because those other problems didn't involve motor neurons.

"By studying cells in vitro we discovered new information and pathologies that were true in actual patients," Rubin says. "This back and forth between human and laboratory studies is leading to new ways of thinking about treating these kids." For example, knowing that the SMA mutation causes debilitating muscle weakness, researchers might be able to target treatments to address that problem even if they don't have a therapy that would affect the motor neurons themselves.

Rubin and Kohane believe that using models derived from human stem cells in conjunction with electronic medical records could provide a wealth of information about the subtypes of complex diseases, perhaps leading to individualized treatments.

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As powerful as both spheroids and organoids have become, they can't accomplish everything scientists might wish for. "We're excited but cautious," says Guoping Feng, a neuroscientist at MIT who studies neuropsychiatric disorders. For example, brain organoids so far can feature only relatively young neurons, and some genes that scientists would like to study don't become active until much later stages of brain development. Diseases such as adult-onset diabetes, kidney failure, heart disease and cirrhosis of the liver afflict fully mature organs and so may be hard to model. (That's not always the case, as the organoid work on Alzheimer's suggests.)

More generally, organoids aren't completely faithful to what happens in a human body, in which, figuratively speaking, no organ is an island. The heart depends on lungs for oxygen, and lungs depend on the beating heart for blood. "Also in real life, organs have an epithelial lining, a vascular component, connective tissues and immune cells, none of which can yet be replicated in their normal physical arrangement in organoids," says Donald Ingber, founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University. Most diseases also have an inflammatory component in which the body's misdirected immune responses contribute to the sickness, and organoids don't have that either.

Ingber prefers "organs-on-chips," another modeling approach that lines microchips with human cells—or, more recently, human organoids. He can connect a liver-on-a-chip to a gut-on-a-chip, for example, via blood vessel channels to give a better approximation of the interactions that occur in the body. Still, organoids are easier to engineer and less expensive than organs-on-chips. This may make organoids more suitable for rapid, high-volume screening of potential treatments in drug development and the practice of personalized medicine. Even then, Ingber notes, "you need to know how the drug crosses in and out of the bloodstream across the blood vessel wall, and from one tissue and into another tissue"—something organoids can't yet test.

That ability may come in the next frontier of organoid development, as researchers look to culture various types of stem cells together to create organoids that incorporate additional features. For example, adding endothelial cells of blood vessels to the initial cells of a culture might enable organoids to spontaneously create a working vascular system.

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Researchers are also beginning to "fuse" different organoid types to approximate the kinds of linked systems Ingber achieves with organs-on-chips.

Not so long ago, the advent of powerful genomic tools and genetic engineering techniques made it seem that studies involving mice engineered to carry human disease genes would be the best approach for exploring human disorders, superior to looking at cells isolated in a laboratory. Now, however, the ability to grow these three-dimensional cellular models may begin to challenge the supremacy of mouse models in research. Organoids allow researchers to conduct revealing human studies in an out-of-body sort of way.

"We need a range of models to learn about the connections among genes, molecules, cells, synapses and circuits in normal and abnormal cognition and behavior, and to help us understand the risks of particular patients," says the Broad Institute's Steven Hyman. Although he is talking about neurological disorders, the message applies broadly across the field of medicine. "Ultimately, we have to get a human model for human diseases so that we can expand human experimental biology in an ethical way and ensure that better, safer drugs get to patients faster," he says. Tiny organoids in the lab are bringing researchers closer to that model.

DOSSIER

"Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids Through Activation of the Innate Immune Receptor TLR3," by Jason Dang et al., *Cell Stem Cell*, August 2016. This study uses recently developed techniques for growing brain organoids to discover how the Zika virus causes microcephaly in infants.

"The Boom in Mini Stomachs, Brains, Breasts, Kidneys and More," by Cassandra Willyard, *Nature*, July 2015. This article provides an overview of the wide-ranging applications of organoids.

"Modeling Development and Disease with Organoids," by Hans Clevers, *Cell*, June 2016. This article outlines how organoids can be used to model various human pathologies "in a dish" and how patient-derived organoids may be able to predict drug response in a personalized manner.

FIRST PERSON

This Side of the Scale

BY HANNAH MATTHEWS

I launch into the list of food I've eaten in the past day: "Oatmeal with blueberries and skim milk, a spinach salad with salmon, a protein bar and an apple with some nonfat Greek yogurt." Hunched on the exam table in my paper gown, my eyes fixed on the floor. I haven't met my meal plan requirements, and I know my doctor is going to scold me for it.

My friends and family had been urging me to seek treatment for anorexia nervosa, and I was under no illusion that the process would be easy. For years I had been wrestling with disturbing thoughts and behaviors about food. I believed certain foods were "bad" or "toxic" if they weren't raw or organic; and I would obsessively count the calories I consumed and burned, as often as two or three times an hour. I also became extremely agitated if I couldn't plan a meal exactly.

The result had been steadily eroding health: My period stopped, I faced cardiac problems, and I walked through life in a fog of dizziness caused by malnutrition.

My therapist took a gentle approach in our sessions together. She would reach for my hand to comfort me and have tissues ready for when I started to cry. (I cried a lot.) My nutritionist is also tender with me. But with my internist, who we'll call Dr. Cooper, it is different. Every Wednesday afternoon when I enter that sunlit waiting room, I feel like a misbehaving child walking into the principal's office.

My appointments always start the same way: I step on the scale backwards so that I can't see my weight—that information can send me into a tailspin of anxiety and depression. Then comes the "intake," which involves my running down the list of what I have consumed in the past 24 hours. I feel ashamed when I haven't eaten enough to meet my prescribed goals, which is most of the time, and Dr. Cooper has no interest in letting me off the hook because of a few tears.

"Doesn't your meal plan call for full-fat dairy instead of nonfat?" Dr. Cooper begins today, peering over her glasses with a stony expression.

"Yes," I say, my cheeks burning.

For six weeks this is exactly how all of my appointments with Dr. Cooper go—the silence, then the steady admonishment. "Promise me you'll gain another pound," she says. "You can do better." Over the weeks, her unwavering pressure has set me in a rebellious mood. She couldn't possibly know, I think. This is harder for me than she could ever understand.

Today she looks at my chart and frowns a little. "Your weight is down again," she announces with characteristic brusqueness. "I'm worried about you."

As she pulls her clipboard onto her lap, I catch a glimmer of something on her wrist that I haven't noticed before. It is a bracelet with a silver charm etched with two curved lines. Very few people would know what they mean. I know that they represent a heart and also suggest the curves of a woman in full health. I also know that this is the symbol of an eating disorder and that most women who wear them have come through treatment. Someone had given me one on a necklace.

I wonder. Is she a survivor, too? I review our conversations in a new light. Maybe she was challenging me in a way that her own doctors had. If she had been on my side of the scale before, she must know exactly what kind of grit it takes to push this insidious disease out of my thoughts. Maybe she thought that what I need, what she had needed, was a little tough talk.

I don't know the answer. But I work up a smile for her today, one of my first. "Thank you for pushing," I say, "I'm trying. I am. I do want to get better."

COLLAGE, SOURCE MATERIAL: GETTY IMAGES