proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE

FALL '18

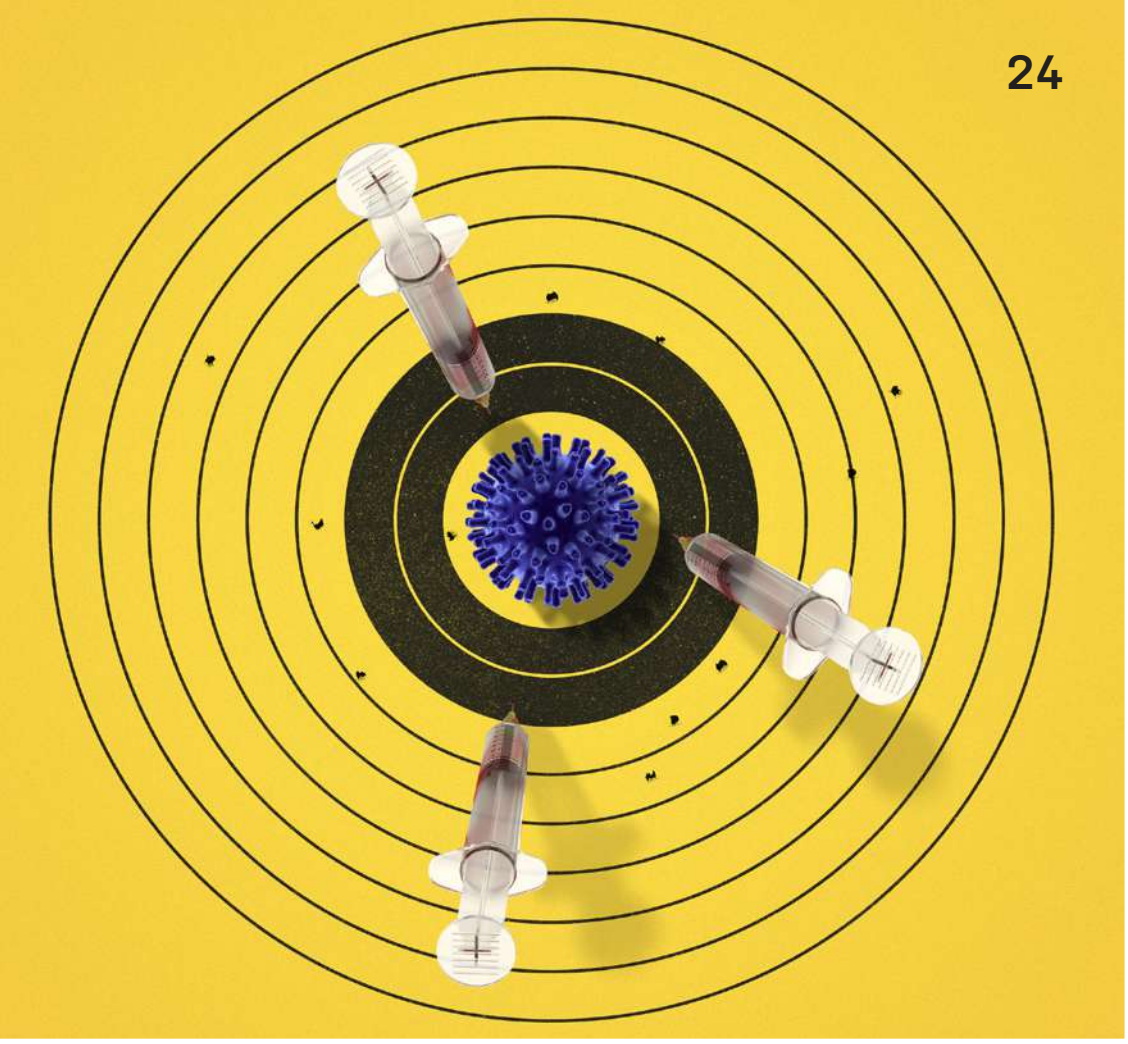
36 PAGES action-packed of thrills!

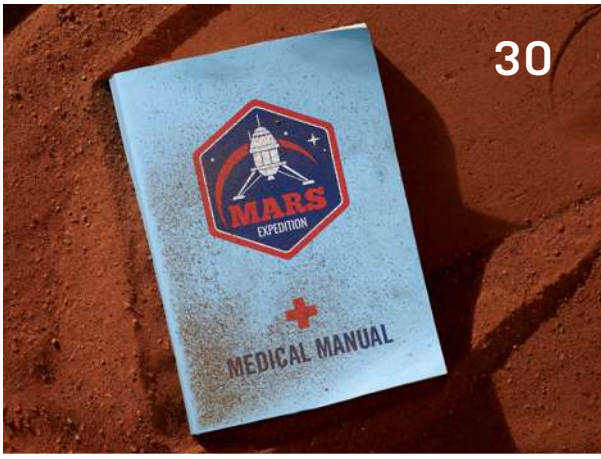
THE DEATH OF ANTIBIOTICS?

BACTERIA CONTINUE TO EVOLVE RESISTANCE TO THE BEST TREATMENTS WE HAVE. NEW HEROES ARE SORELY NEEDED. p12

HIBERNATION p18

MARS 911 p30





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FALL 2018

STAT

POST-OP

FEATURES

on the cover

Bacteria are becoming resistant to antibiotics at an alarming rate. While most efforts are focusing on changing patterns of antibiotic use, some labs are looking to develop entirely different weapons for combating infection. // Illustrations by Michael Cho

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.

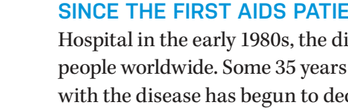
SINCE THE FIRST AIDS PATIENTS arrived at Massachusetts General Hospital in the early 1980s, the disease has killed more than 35 million people worldwide. Some 35 years later, the number of people newly infected with the disease has begun to decline, and now, taking a single daily pill can keep the disease at bay indefinitely.

In the United States, that remarkable advance in treatment has perhaps led to a false sense that HIV/AIDS is no longer a problem here. The reality: Of the 40,000 people diagnosed in 2015, a quarter of those cases had already progressed to AIDS, and fewer than a third of U.S. HIV patients receive care that meets current clinical standards.

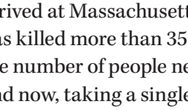
Making real progress will require further gains in the lab: new treatments, vaccines and ultimately a cure, as described in the article "An Endgame for an Epidemic." But it also necessitates improvements in the ways that health care systems deliver these miracles of science in the United States and around the world.

One such ambitious effort began in 2009 with the founding of the Ragon Institute of MGH, MIT and Harvard. The goal was to bring researchers together from across disciplines and specialties to create an effective HIV vaccine. Generous funding has supported nimble, innovative research, and the close cooperation among collaborating institutions has led to progress in following the mystery of how HIV eludes the immune system.

With a vast range of promising efforts underway in this country and abroad, more breakthroughs—better treatments, cures and prevention—will come. Among the hospital's collection of historical artifacts is a bottle of what was to become the revolutionary AIDS drug AZT, dating from 1986, when MGH was a site of a clinical trial for the drug. We look forward to the day when AIDS itself—and the story of science's triumph over it—is relegated to history.

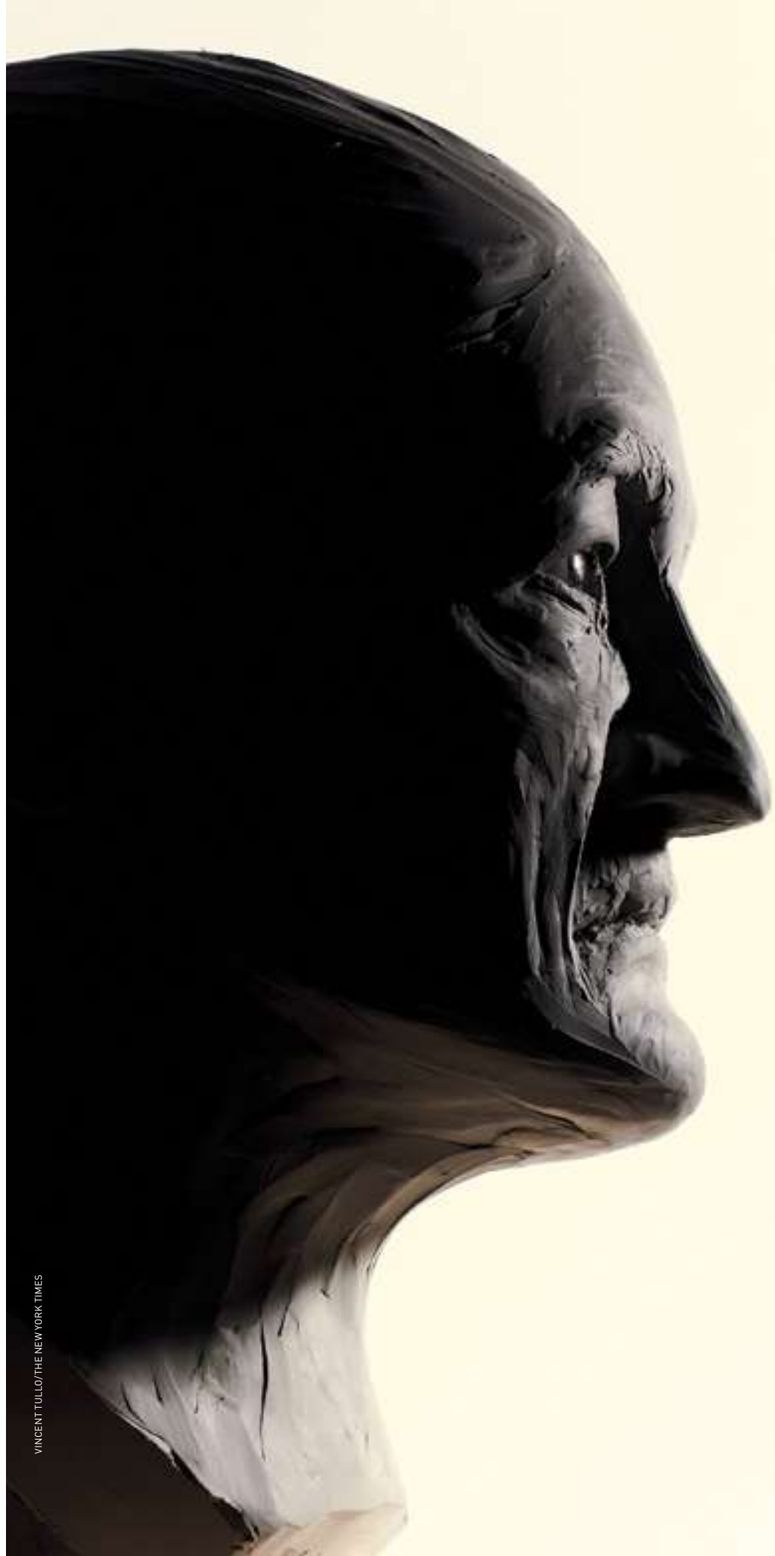


PETER L. SLAVIN, M.D.
President
Massachusetts General Hospital



TIMOTHY G. FERRIS, M.D.
CEO
Massachusetts General
Physicians Organization

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



VINCENT TULLO/THE NEW YORK TIMES

stat

FOCUS

Putting a face to unidentified remains requires both anatomical knowledge and an artistic hand. Sculptor Madison Haws began this bust with the bones of a woman who died anonymously in a home for the mentally impaired in Queens, N.Y. Haws started with a 3D-printed replica of the woman's skull, then built up layers of clay to recreate lost muscles and tissues. Genetic analysis of the remains allowed her to factor in racial and other physical factors.

Haws' work is part of a program offered at the New York Academy of Art, where she is a student. The majority of the skulls come from the Arizona desert, where many migrants perish attempting to cross the border. The aim is for these painstakingly rendered pieces to be recognized by friends or family, allowing them to put the dead to rest.

INTERVIEW

On Her Wavelength

Indoor light can affect health in good ways and bad. Photobiologist Mariana Figueiro wants to get patients the optimal exposure.

BY STACY LU

When you picture a hospital room in your mind's eye, it's bound to appear in sterile, bright tones. But the electric lighting responsible for that can have a negative effect on healing, says Mariana Figueiro, director of the Lighting Research Center at Rensselaer Polytechnic Institute in Troy, N.Y. Emotional well-being and the immune system are both closely tied to circadian rhythms, a roughly 24-hour clock in the human body that is wound, ultimately, by light.

Figueiro's research over the past 20 years shows that lighting can be a powerful ally in clinical care, especially for patients prone to sleep problems. Timed periods of bright light, for example, can help Alzheimer's patients regulate when and how much they sleep, increasing their wakefulness during the day and easing their depression and agitation. Recently, Figueiro collaborated with researchers at the Icahn School of Medicine at Mount Sinai in New York City on using bright lights to ease the side effects of cancer treatment.

RACHEL BRENNECKE FOR *PROTO*

Q: In the cancer trial, what role did lighting play?
A: We worked with people who had received stem cell treatment for myeloma or lymphoma, which are cancers of the lymphatic system. These patients are typically in the hospital for two to three weeks, and like all hospitalized patients, they get the same level of artificial light at all hours of the day and night. This lack of a robust, daily light-dark pattern can disrupt their circadian cycle, leading to sleep and mood problems that can impede their recovery in the long term.

So we placed light fixtures in their rooms to deliver ambient light at the wavelengths and amounts—brighter in the morning and dimmer at night—needed to synchronize their systems. Our preliminary data show that those who received treatment were less likely to develop depression, had reduced fatigue and maintained their sleep quality during treatment. Good sleep is very important, because we know that it reduces inflammation and bolsters your immune system.

Q: Is artificial lighting a common factor in depression?
A: Reduced exposure to natural light seems to magnify a lot of existing problems, such as the sleep disruption that can come with Alzheimer's or, yes, a tendency to suffer from mood disorders or seasonal depression. If you already suffer from circadian disruption, perhaps as a shift worker, you're going to be sleeping and awake at odd times, so there's a likelihood you're getting light at the wrong time. Many studies have shown that these populations are more at risk for depression.

Q: What lighting challenges exist in a health care environment?
A: The default setting is a constant level of brightness, 24 hours a day. It's a kind of white noise. There's a conflict, of course, because nurses and doctors need to see, while patients need to sleep. Yet frail people need to be exposed to a robust dark-light pattern. And neither patients nor staff have easy control over the different kinds of light they might need, either to sleep or to work.

Q: Is the technology getting better?
A: The new generation of light-emitting diode lighting has been great because these systems are very adjustable, effective and less expensive to run over time. LEDs let you light up an entire room with varied colors, wavelengths and intensity. You might adjust the light to a hue that helps the eye distinguish colors, which could help hospital staff make accurate visual diagnoses, then adjust levels to help patients sleep better—and do it all wirelessly.

Light manufacturers are also creating portable devices that allow you to measure the light spectrum wherever you are. At Rensselaer we've also come up with a circadian stimulus calculator so installers can calculate how much circadian-effective light people are already getting in a given place.

Q: What other health applications are you researching?
A: We're looking at metabolic disorders, which get in the way of how the body produces or processes energy. We started with mice, and have already shown that the patterns of light and dark that we associate with shift work can cause circadian disruption and decrease glucose tolerance. We're also testing long-wavelength red light, which has been shown to increase nighttime alertness, in nurses who do shift work.

My newest project is working with people who have suffered traumatic brain injury, which brings a high risk of developing a sleep disorder. The light for the control group is the usual dim and dingy setup, while our other subjects get bright ambient light. When I came in to check one installation, a patient told me, "I absolutely love these lights. I suffer from depression, and when those lights turn on I feel like a different person."

BY THE NUMBERS

Ice Cream

88

Pages in *De Sorbetti*, a Napolese treatise written in 1775 about the curative powers of frozen treats. The author, court physician Filippo Baldini, notes that cinnamon flavors dull pain, while chocolate elevates the mood.

10

Gallons of ice cream that poet Walt Whitman bought and distributed to Civil War wounded at Carver General Hospital in Washington, D.C. In the following decades, hospitals adopted ice cream as a palatable, calorie-rich food.

6

Tons of ReCharge strawberry ice cream manufactured in New Zealand in 2009. The dessert was engineered to have high levels of lactoferrin, a protein that showed potential as an adjunct to chemotherapy. While animal trials were promising, human trials have been inconclusive.

84

Days in succession that research subjects in Osaka, Japan, were asked to eat ice cream, some of which was infused with high doses of *benifuuki*, a form of green tea. Results showed a decreased risk of arteriosclerosis in the subjects consuming the substance. While drinking green tea directly may offer the most benefit, the researchers believed that incorporating the bitter substance in ice cream might make it more palatable to Western tastes.

20

Number of foods of varying textures and tastes offered to Danish seniors with dysphagia, or difficulty swallowing, in a 2018 study. The ones they found the most appealing had three qualities in common: They were frozen, cold and sweet.

INFOGRAPHIC

The Village Without Memory

In France, a home for people with dementia is designed from the ground up.

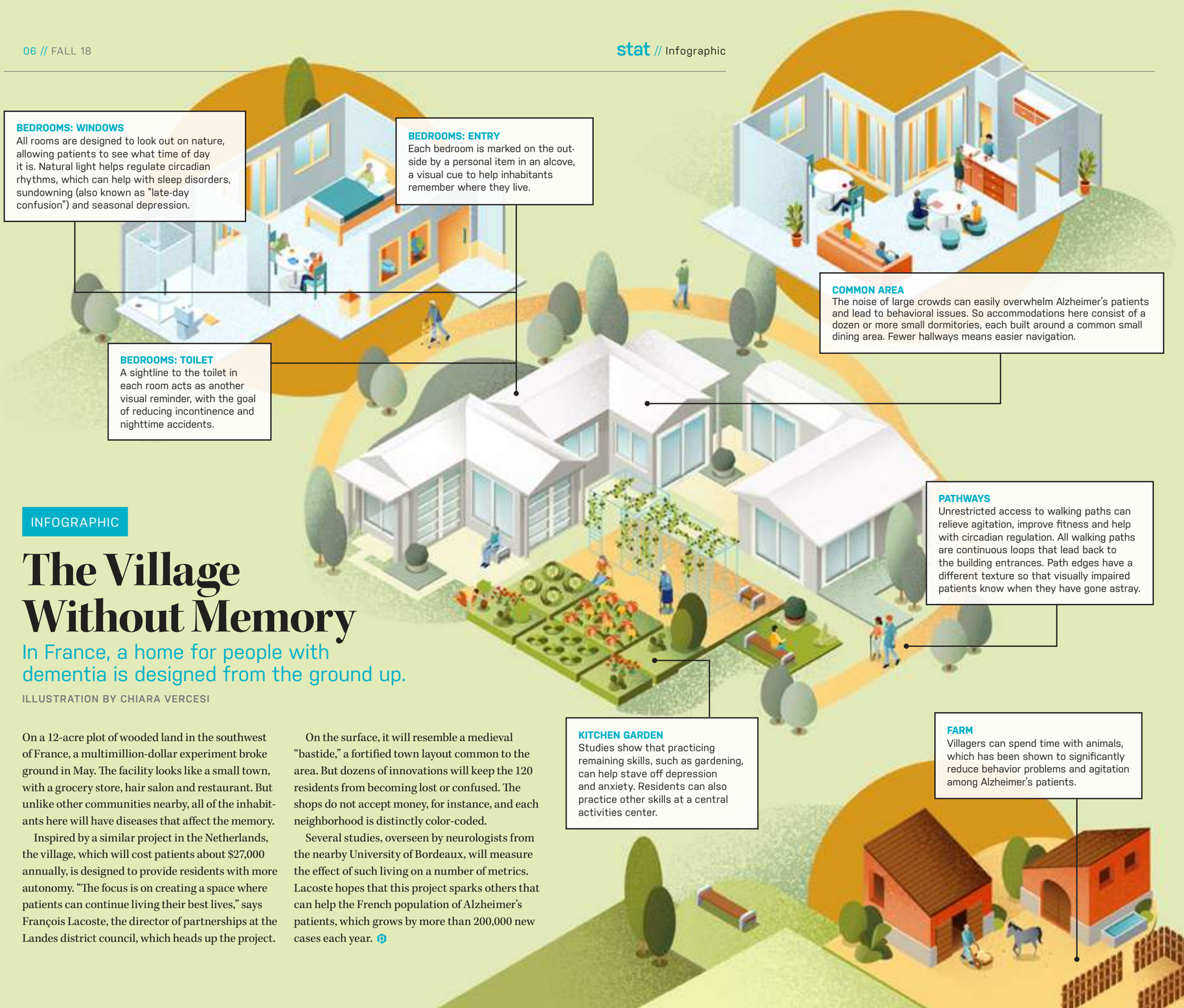
ILLUSTRATION BY CHIARA VERCESI

On a 12-acre plot of wooded land in the southwest of France, a multimillion-dollar experiment broke ground in May. The facility looks like a small town, with a grocery store, hair salon and restaurant. But unlike other communities nearby, all of the inhabitants here will have diseases that affect the memory.

Inspired by a similar project in the Netherlands, the village, which will cost patients about $27,000 annually, is designed to provide residents with more autonomy. "The focus is on creating a space where patients can continue living their best lives," says François Lacoste, the director of partnerships at the Landes district council, which heads up the project.

On the surface, it will resemble a medieval "bastide," a fortified town layout common to the area. But dozens of innovations will keep the 120 residents from becoming lost or confused. The shops do not accept money, for instance, and each neighborhood is distinctly color-coded.

Several studies, overseen by neurologists from the nearby University of Bordeaux, will measure the effect of such living on a number of metrics. Lacoste hopes that this project sparks others that can help the French population of Alzheimer's patients, which grows by more than 200,000 new cases each year.



VILLAGE DESIGNS PROVIDED BY NORD ARCHITECTS, COPENHAGEN; COLLAGE, SOURCE MATERIAL: GETTY IMAGES

CUTTING EDGE

The Houseplant Is In

Smart greenery may help detect harmful particles or organisms.

BY ALICE MCCARTHY

A fern or a ficus in the home has few responsibilities, apart from looking green and lovely. This cushy ride may be coming to an end, however. Researchers at the University of Tennessee are working to create houseplants that act as biosensors—organisms that can detect environmental contaminants in the air around them.

A team, led by C. Neal Stewart of the department of plant sciences, has been working for close to 20 years on engineering industrial plants that can report internal changes, mostly by means of fluorescent proteins visible to the naked eye. "The idea has been to make plants that are early detectors of their own diseases," Stewart says. The concept of working with houseplants in this way partly came from Stewart's wife, Susan, an interior designer.

In this model, the plant's stomata—microscopic holes in leaves that open and close—would constantly sniff in the air around them. If a contaminant were detected, the plant would change color or fluoresce. Stewart has been studying several common plants, including *Fittonia albivenis*, better known as the mosaic plant, and *Spathiphyllum*, the peace lily. Both have distinct colorations that can be genetically manipulated to become signaling mechanisms.

The Stewart laboratory has already made plants that can detect gamma radiation. In the future, he will work on plants that can detect toxins such as those released by harmful mold species, or common microbial pathogens. He imagines plants that could detect dangerous, drug-resistant bacteria might even find a home in a hospital setting.

"One could create a menu of plants with different sensing capabilities, tailored to the health considerations of the people in those settings," says Stewart. "The greenery we have in our lives would gain an additional function."

POLICY WATCH

Choosing Unwisely

Why is it so hard to eliminate waste, even when physicians agree on how to do it?

BY LINDA KESLAR

Eric Barbanel is passionate about cutting down on unnecessary care in his practice, and for him that begins with educating patients. "I have some who ask for an antibiotic before they even say hello," says Barbanel, a primary care physician at Crystal Run Healthcare in Middletown, N.Y. "Every time, I explain that antibiotics are useless against a cold."

Barbanel has been an outspoken champion of Choosing Wisely, a national campaign launched in 2012 that takes aim at unnecessary medical tests and procedures, listing the common ones and encouraging clinicians to limit their use. The initiative quickly expanded from its origin at the American Board of Internal Medicine Foundation and a handful of other medical organizations to encompass more than 80 groups. Collectively these expert panels have generated 550 recommendations about curtailing the use of various medical practices.

There's little doubt that such an effort is needed. According to the Institute of Medicine, nearly 10% of health care spending—well over $200 billion a year—goes toward low-value care. Yet six years after the launch of Choosing Wisely, it's struggling to make headway. A recent analysis in *Health Affairs* cited a study published in *JAMA Internal Medicine* in 2015 based on data from 25 million members of Blue Cross Blue Shield plans. Focusing on seven services on Choosing Wisely's list, the researchers found that the use of only two of them—imaging tests for uncomplicated headaches and cardiac imaging for patients with no troubling history of cardiac conditions—had declined. Three others remained near previous levels, and the last two actually went up. Other studies have shown similarly disappointing results.

> Nearly 10% of all health care spending—roughly $200 billion a year—goes toward low-value care.

"Choosing Wisely has been really successful in getting a national conversation going," says Jeffrey Kullgren, a research scientist in the Center for Clinical Management Research at the VA Ann Arbor Healthcare System in Michigan and a co-author of the *Health Affairs* article. "This is a paradigm shift in medicine, so widespread change may take a long time."

Moreover, some expensive and possibly unneeded practices aren't even on the Choosing Wisely list. An analysis in *The New England Journal of Medicine*, for example, suggests that many knee replacements and other joint surgeries may be unnecessary, and rack up millions of dollars in costs each year. But the American Academy of Orthopedic Surgeons has not added these procedures to its section of the Choosing Wisely list.

A separate study in *Health Affairs* surveyed physicians about Choosing Wisely and found that awareness of the effort had grown by only 4% from 2014 to 2017. In addition, although some doctors said they continued to provide low-value care because of patient demands, most said that they delivered such services "just to be safe." They didn't want to risk missing a serious diagnosis or to fail to live up to the "standard of care"—the metric by which they could be judged in a malpractice case.

Despite such concerns, however, some medical organizations have found success by applying Choosing Wisely's recommendations in a more targeted way. During the past three years, in a project funded by the Robert Wood Johnson Foundation, 14 health care systems have homed in on reducing specific items. Nearly all of those groups reduced antibiotic prescriptions for upper respiratory infections by 20% or more, for instance, and showed significant progress in cutting back on a handful of other measures.

To improve Choosing Wisely, Kullgren and his co-authors call for medical societies to work together to streamline overlapping recommendations and develop new lists that include tests and treatments that are more widely practiced. "We need a next set of recommendations that are clinically meaningful for more patients and would have a bigger bang for the buck," Kullgren says.

Until that happens, the program will continue to rely on the dedication of practitioners and health care systems to make choices about what care is truly needed. "It's become part of my routine to have these conversations with patients," says Barbanel, "and when I do that, 95% of the time they get it."

CHRIS GASH

MILESTONE

Doctoring on a Screen

Telemedicine made its first broadcast 50 years ago in an airport clinic.

BY PETER ANDREY SMITH

On Oct. 4, 1960, an Electra turboprop with 72 passengers and crew took off from Logan Airport in Boston, struck a flock of starlings and plummeted into the shallow waters of nearby Winthrop Bay. Gawkers flooded the scene, delaying emergency vehicles from reaching survivors. The death toll would climb to 62. The difficulty of getting to the airport led health authorities to build a new clinic right on site—a step that led in turn to the first sophisticated use of telemedicine.

While the airport clinic would be of limited use during another crash, it was invaluable for most of the emergencies that arose among the 12,000 employees at the airport or the 50,000 passengers that passed through daily. That said, there was rarely enough work to occupy a full-time physician.

Massachusetts General Hospital internist Kenneth Bird moonlighted as the first head of the new clinic at Logan. In 1967, after a particularly frustrating commute from the airport into the city, Bird was venting with his colleagues in the emergency department. According to Jay Sanders, who was then an ED resident, Bird started to spitball a new approach. "What if I bought two TV cameras and put one at Logan Airport and one here in the emergency room, and I began to examine patients over TV? What do you think?" Sanders, now president and CEO of the consulting firm Global Telemedicine Group, remembers saying it was the stupidest idea he'd ever heard.

By April 1968, Bird had secured a broadcast channel with the Federal Communications Commission's approval and began beaming audio-visual data between the airport and the hospital. At MGH, a physician sat in front of two television monitors, installed in a recessed desktop, and looked into a camera specially designed for low-light situations, which avoided the need to light up the emergency room like a television studio. At Logan, the doctor's image appeared on a 17-inch screen directly above a similar camera trained on the patient. Nurses could operate a separate telemicroscope to magnify and transmit images of urine or blood smears.

The so-called Logan station began to work out its kinks, and was soon producing research about what came to be known as telemedicine. Pathologists found they could make diagnoses using the black-and-white images from the remote cameras. They also found ways to transmit patients' pulse rate, blood pressure and EKG data. Not every obstacle was within their control, however. Transmission failed during heavy rain and snow, and became distorted in extreme cold.

COURTESY OF MASSACHUSETTS GENERAL HOSPITAL ARCHIVES

Many early critics of the system, such as MGH psychiatrist Tom Dwyer, were eventually won over. Dwyer had predicted that the technological interface would erode much of what was gained by seeing a patient face to face. But Dwyer found he could not only connect to patients remotely, but also that camera close-ups and other framing techniques could help reinforce his message.

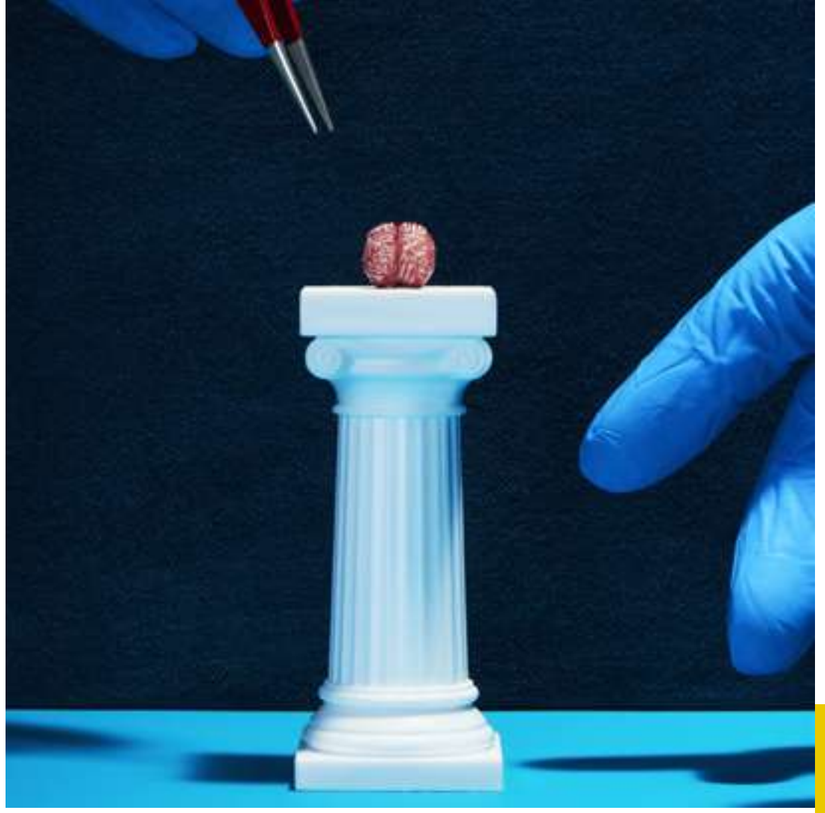
The Logan clinic closed in the 1970s because of cuts in federal funding. But by then, the Logan link had already paved the way for many things that are taken for granted today, such as remote diagnostic imaging, digital videoconferencing and the electronic transmission of medical records.

UPDATE

First Thoughts

Tiny models of the brain are becoming more complex. When should the ethicists step in?

BY BRANDON KEIM



ANDREW B. MEYERS FOR *PROTO*

When Thomas Hartung presented his neurological research at a conference in 2016, he expected the feedback to be technical, not philosophical. A toxicologist at Johns Hopkins University, Hartung was talking about his work with cerebral organoids, tiny assemblages of neurological tissue grown from human stem cells. His organoids would be used to test chemical safety, revealing harms that go undetected in tests on animals.

But one of the biggest reactions to his talk came in response to a chance comment. "I said our organoids are 'thinking,'" he recalls. By that, he meant that his organoids displayed spontaneous electrical activity, with neurons firing and stimulating each other.

A resulting tsunami of publicity anticipated a growing debate about the ethical implications of brain organoids, a powerful new tool for studying brains and their problems ("Tiny Marvels," Winter 2018). For many in the general public, Hartung's research conjured up an image from science fiction—a disembodied brain suspended in a vat—raising questions about selfhood, experience and the ethical boundaries of science. People wondered what kind of "thinking" the organoids could do, to which Hartung would respond: "They have nothing to think about."

Electrical activity in the current generation of brain organoids, including Hartung's, is far from the complex, sustained patterns found in human and other animal brains. Today's organoids possess neither perception nor memory, can't interact with the world outside of their containers and lack anatomical complexity. Hartung was quick to tell critics that although his organoids resemble brains, they are not minds.

That distinction, however, may eventually become harder to make. "We can't create that level of sophistication yet," says Christof Koch, president and chief scientific officer at the Allen Institute for Brain Science in Seattle. "But in a decade or more? We may get to the level of a simple mind, say that of a mouse."

While Hartung's organoids were no bigger than "a fly's eye," labs have rapidly made them larger and more sophisticated. In April, researchers at the Salk Institute in San Diego showed how they had transferred human brain organoids into mouse brains, which helped the organoids survive for as long as 233 days—much longer than previous methods. Researchers have learned to connect organoids with blood vessels, a critical step in enabling them to develop more complex structures. Soon brain organoids might be joined to hearts, eyes or other mini-organs.

"The closer the proxy gets to a functioning human brain, the more ethically problematic it becomes," wrote Nita Farahany, a bioethicist at Duke University, in an April *Nature* article that she co-authored with Koch and 15 other prominent ethicists and scientists. The authors warned that future organoids might be capable of experiencing "pleasure, pain or distress; being able to store and retrieve memories; or perhaps even having some perception of agency or awareness of self."

Such brain organoids would demand a profound re-evaluation of research practice, the authors said. What moral duties would they be owed? How should organoid tissues be disposed of? Would they be preserved in some way, like chimpanzees sent to live in sanctuaries after they were no longer needed for research?

Even now, some researchers worry that existing regulations may not be up to the task of dealing with this new, fast-moving field. In a cautionary paper published last year in the journal *eLIFE*, geneticists John Aach and George Church at Harvard Medical School recalled asking for guidance from their research oversight committee about a new technique they had developed that could have led to the connection of, for instance, a brain organoid to heart and eye tissue. That kind of complexity may approach that of a developing embryo, and "such entities might be morally concerning," they wrote.

But after careful study, the Harvard committee found that current federal guidelines didn't apply to this new work. A rule that actual embryos can't be grown past the age of 14 days, for example, was insufficient to regulate innovations that would allow brain organoids to reach much greater levels of complexity—potentially becoming, as Aach and Church designated them, "synthetic human entities with embryo-like features."

> Future organoids might be capable of experiencing pleasure, pain or distress.

In the *eLIFE* paper, Aach and Church called on the biomedical community to dive into the ethical and conceptual issues for such research, and argued against using timelines as a guide—depending, rather, on the presence of anatomical features concerned with physiological functions that are morally compelling. Marcello Massimini, a neurophysiologist at the University of Milan, and philosopher Andrea Lavazza at the International University Center in Arezzo, Italy, have proposed looking at electrical activity. They note that tests measuring neurological complexity are already in use, for example to determine whether a patient who appears to be in a coma may be conscious and aware. In the future, similar measures could be applied to assess brain organoids.

Hartung is preparing a bioethics course for medical scientists that will probe such issues, and Koch urges researchers and ethicists to look ahead to questions they could one day face. "We're still far away," he says, "but we need to think about it now so we can get ready to deal with the ethical issues."

SECOND OPINION

Fighting Fake News

"The Rise of Fake Medical News" (Summer 2018) paints a bleak picture of the state of medical information being shared on social media sites. While the spread of inaccurate medical information is undoubtedly a problem, the article rightly points out that it is not a new phenomenon. More research is needed to understand the diverse motives of the purveyors of inaccurate medical information to address its spread more broadly—rather than playing whack-a-mole with specific inaccurate stories as they arise.

But we have the ability to immediately mitigate the worst consequences of inaccurate medical news shared online, and the responsibility to address misinformation lies with all of us.

Expert organizations like the Centers for Disease Control and Prevention can rebut inaccurate posts without harming their credibility. Facebook has moved to using the Related Stories function to provide links to fact-checked sources about inaccurate news stories, which can reduce misperceptions. Everyday users can also work together to fact-check inaccurate content they come across by using their online connections.

Addressing inaccurate medical news online may not be simple, but it is possible if we each do our part.

Emily K. Vraga // Assistant Professor, Political Communications Minor Director, George Mason University, Fairfax, Va.

A New Use For Psychedelics

As discussed in "New Tools for Depression" (Summer 2018), it is undeniable that currently available treatments for depression are inadequate in alleviating symptoms for the majority of people. Investigating new approaches, other than daily dosing with drugs that target the serotonergic system, is crucial for discovering more effective ways to help the millions suffering from depressive disorders.

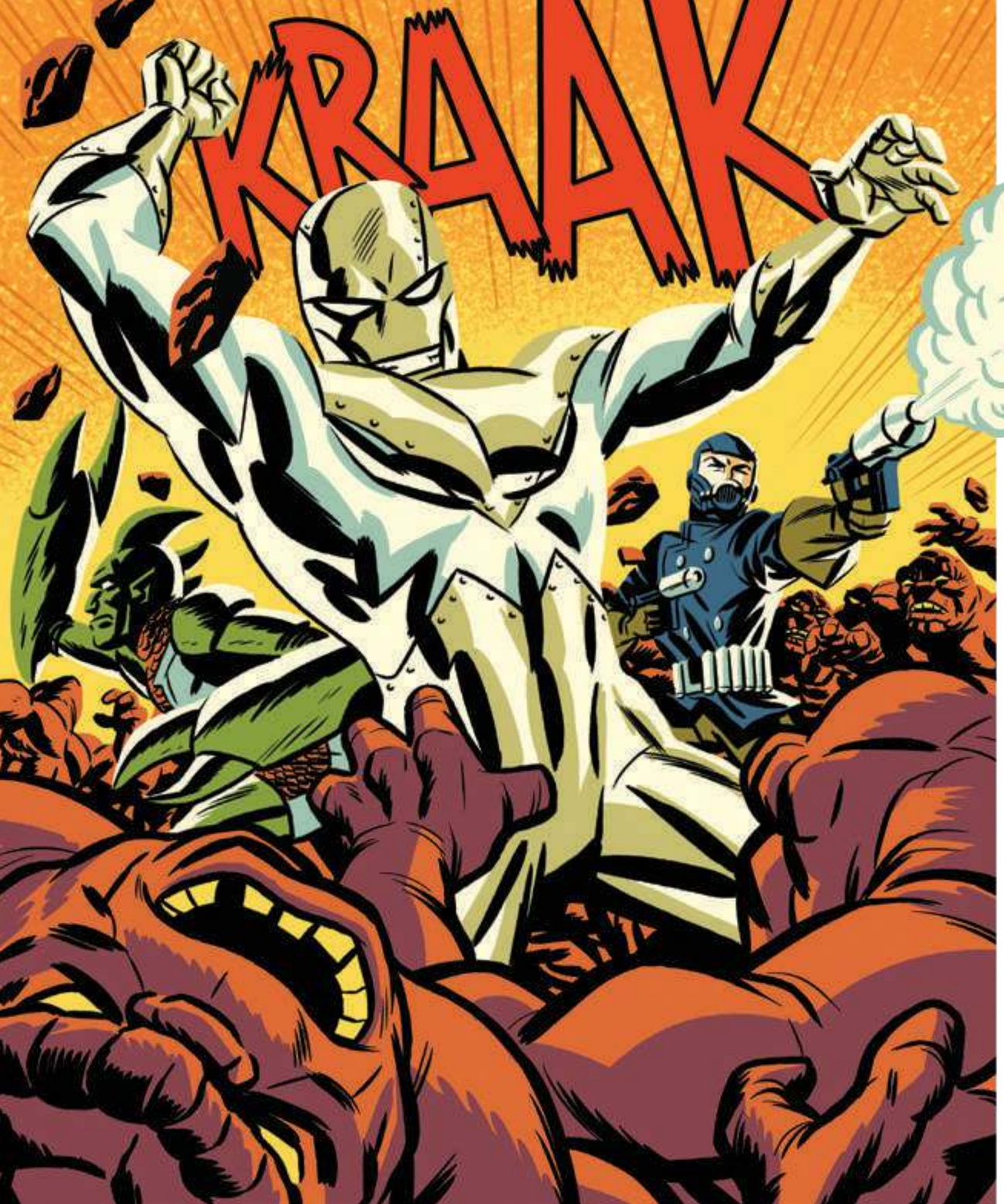
Two of the most promising drugs currently under study are ketamine and psilocybin. In clinical trials, psilocybin is administered with psychotherapy, which is thought to be crucial for the effectiveness of the treatment. Ketamine has been shown to rapidly reduce depression, but the effects last only three to seven days and require weekly dosing to maintain the positive outcomes.

An emerging group of therapists and psychiatrists, many of whom work on psychedelic-assisted psychotherapy trials, are advocating for combining ketamine with supportive therapy to work with a person while in an undepressed state. More research is needed, but these drugs and combo drug-therapy approaches are addressing the need for out-of-the-box solutions for depressive disorders.

Allison Feduccia // Co-Founder and Director, Psychedelic Support, Multidisciplinary Association for Psychedelic Studies, Santa Cruz, Calif.

MISSED THE LAST ISSUE?
All stories from *Proto*, Summer 2018, are available at protomag.com.

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

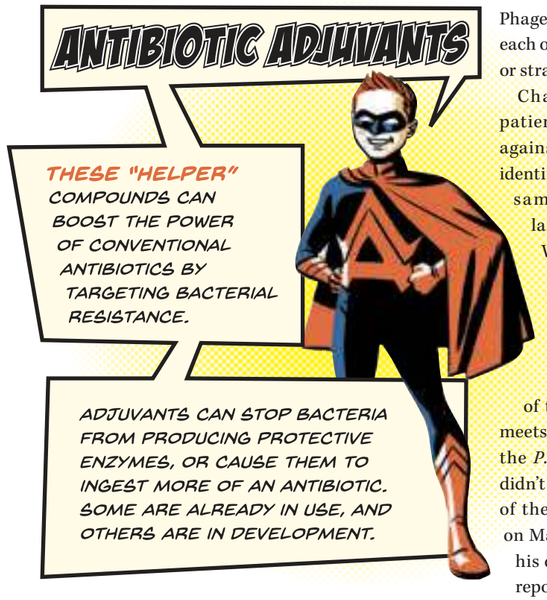


AS ANTIBIOTICS BEGIN TO FAIL, CAN OTHER TREATMENTS—SUCH AS MASS-PRODUCED ANTIBODIES OR TAMED VIRUSES—SAVE THE DAY?

NEW HEROES OF THE MICROBE WAR

BY TIMOTHY GOWER //
ILLUSTRATIONS BY MICHAEL CHO

The ominous future, in which antibiotics are powerless against the bacteria that threaten human health, may already be here. Hordes of antibiotic-resistant microbes mount attacks on the skin and in the gut, and many have overrun hospitals, where they can be lethal to patients with weakened immune systems. The bugs are particularly devastating when they attach themselves to implanted devices. Hidden inside the body, where they are able to multiply undetected, the bacteria can be almost impossible to eradicate. Often the only solution is for surgeons to remove the infected device and clean out the affected area—and hope that the infection hasn't spread too far.



In one such case, the polyester graft used to repair an elderly man's damaged aorta was infected with *Pseudomonas aeruginosa*. This potentially deadly bacterium can cause pneumonia and other maladies, and in recent years it has become increasingly impervious to antibiotic therapy. The infection repelled repeated courses of treatment with traditional medications, and the patient's frail condition precluded replacing the graft.

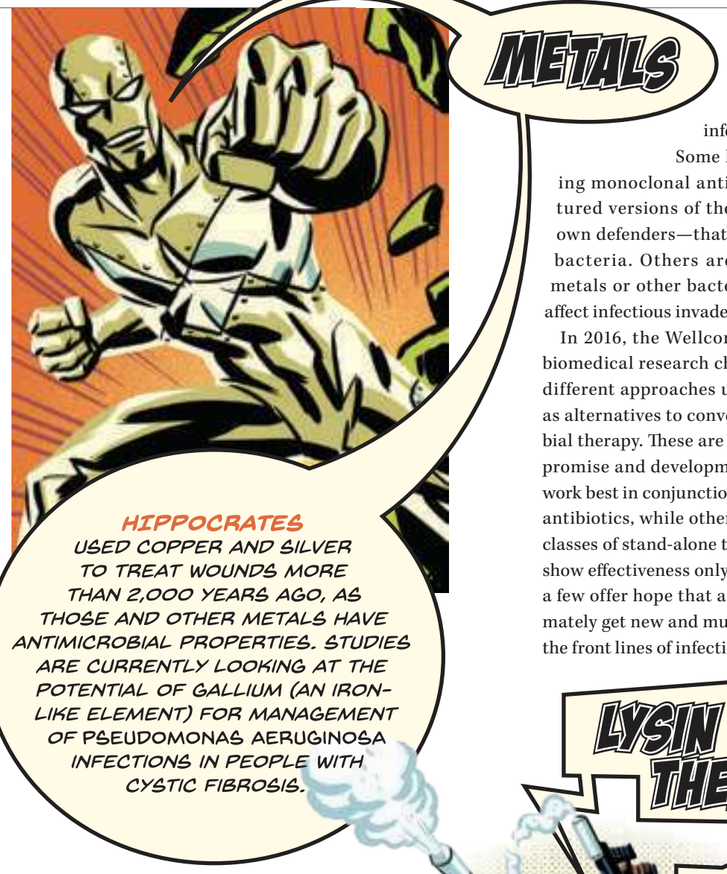
What options are available when antibiotics fail? After this man's physicians at Yale New Haven Hospital had tried everything normally at their disposal, they contacted Benjamin Chan, a microbiologist at Yale University who studies and collects bacteriophages—viruses that infect and destroy bacteria. Often known simply as phages, they're the most abundant organism on the planet, and are found in soil and bodies of water, especially pools of sewage and landfills that are thick with bacteria. Phages come in untold varieties, with each one targeting a particular species or strain of bacteria.

Chan tested a culture of the patient's *P. aeruginosa* infection against his library of phages and identified a few—found in a water sample from a Connecticut lake—that looked promising. With an OK from the Food and Drug Administration to make use of an emergency investigational new drug, doctors injected the phages— together with an antibiotic—near the site of the infection, where the aorta meets the heart. After the procedure, the *P. aeruginosa* disappeared and didn't recur during the final two years of the man's life. He died this year on March 8, the same day Chan and his colleagues published their case report in the journal *Evolution, Medicine, and Public Health*.

Antibiotics, one of the signature advances of twentieth-century medicine, have saved hundreds of millions of lives, and have made possible many other medical breakthroughs, such as organ transplants and complex surgeries. Yet decades of overreliance on and overuse of the drugs have led to a generation of bacteria that have evolved to evade this line of attack. Already, about 2 million Americans every year become ill as a result of antibiotic-resistant bacteria, and at least 23,000 die. Those numbers will almost certainly rise.

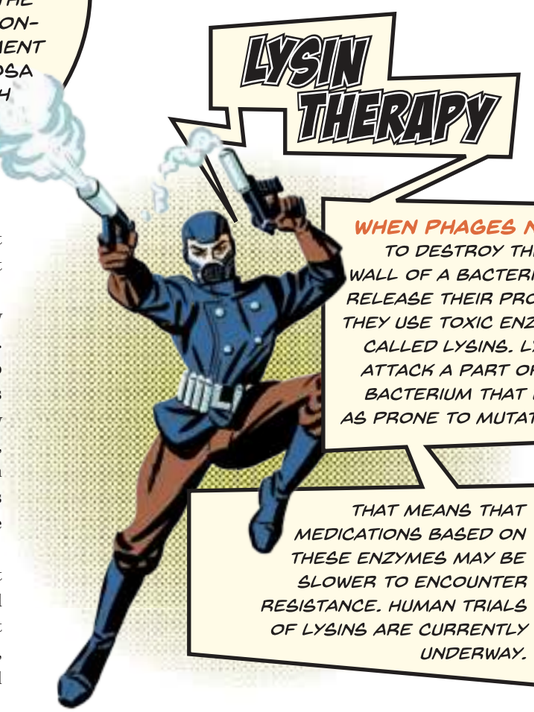
The ideal solution would be to develop new antibiotics that fight bacteria in novel ways. But few are in development, and most that do reach the market are simply modifications of older antimicrobials—making it relatively easy for bacteria to find ways around those, too. Without new solutions, the global death toll from antibiotic-resistant infections could exceed, by 2050, the number of people who die from cancer.

Most current strategies to prevent that dire scenario encourage wiser, more limited use of antibiotics. But an emergent effort is looking at entirely different therapies, including phages, that attack bacterial infections in new ways.



Some labs are investigating monoclonal antibodies—manufactured versions of the immune system's own defenders—that can target specific bacteria. Others are looking at light, metals or other bacteria, each of which affect infectious invaders differently.

In 2016, the Wellcome Trust, a British biomedical research charity, identified 19 different approaches under investigation as alternatives to conventional antimicrobial therapy. These are at various stages of promise and development, and some may work best in conjunction with conventional antibiotics, while others could create new classes of stand-alone therapy. While some show effectiveness only in limited settings, a few offer hope that antibiotics may ultimately get new and much-needed allies on the front lines of infection.



Bacteria multiply rapidly, and the genetic mutations that arise in each generation offer a chance of helping them ward off an antibiotic—for example, by producing protective enzymes or increasing the activity of proteins called efflux pumps that suck in and spit out the drugs. Bacteria may also share genetic material with one another, through a process known as horizontal gene transfer, which can also spread resistance quickly.

But if bacteria evolve rapidly, so do phages, their nemeses for billions of years. A phage injects its DNA into a bacterium and reproduces up to 100 progeny phages. To escape, the phage produces an enzyme called a lysin, which splits the bacterial cell wall, causing the bacterium to explode. The study of these bacterial enemies and their use to fight infection actually predated the development of antibiotics, but after the arrival of penicillin, first tested in humans in 1941, most physicians gave up on phages.

Still, doctors in the former Soviet Union and Eastern Europe, in particular, never stopped using them, and the Eliava Phage Therapy Center in Tbilisi, Georgia, treats the antibiotic-resistant infections of several thousand patients each year. Now that physicians in the United States have seen their potential, in part because of the recovery of Chan's patient and other high-profile successes, the study of phages has geared up.

One advantage of phages is that they hone in on specific bacteria. That trait forestalls diarrhea and other common side effects of treatment with conventional antibiotics, which may also kill healthy microbes in the gut and elsewhere in the body. And while bacteria can become resistant to phages, that may not be a problem if a phage is paired with an antibiotic, says Chan. He notes that *P. aeruginosa* resists antibiotics by increasing the activity of efflux pumps. When exposed to a phage, however, *P. aeruginosa* alters its efflux pumps to expel the virus—and that leaves the bacterium unable to defend itself against an antibiotic. "As far as we can tell, *P. aeruginosa* will be resistant either to a phage or to an antibiotic," says Chan. "It seems not to be both." He and his colleagues are studying whether similar phenomena occur in other species of resistant bacteria.

Before a specific species of bacteria can be treated, it must be tested against dozens of phages to find the right fit. "That's not a

practical way to treat patients," says Paul Grint, chief executive officer of AmpliPhi, a San Diego biotech company that supplied some of the phages used in other successful treatments. What's needed, he says, is a premixed phage cocktail that would work for most patients. To that end, AmpliPhi has identified a combination of three phages that Grint says has proved effective against 96% of multidrug-resistant samples of *Staphylococcus aureus*. The combination is now in early clinical trials for treating chronic sinus infections, and the company believes the drug could yield broader applications as therapy for bacteremia (blood infections) and endocarditis (infection of the heart lining). The future of phage therapy, Grint says, is "a vial you could pull out of the fridge" to fight most infections.

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Phages themselves depend on a potent weapon—lysins, the enzymes produced by the viruses that actually burst open bacteria to release their progeny phage. "Since half of the bacteria on Earth are killed by phages every two days, lysins may be considered the most effective bactericidal agent," says Vincent Fischetti, head of the Laboratory of Bacterial Pathogenesis and Immunology at Rockefeller University in New York City.

Fischetti and his colleagues have produced lysins from lysin genes acquired from many phages, including some found in New York's East River and a landfill on Staten Island, and they have shown that lysins can rapidly resolve pneumonia, *Clostridium difficile* infections (CDI), bacteremia and other bacterial infections in animals. Like the phages they come from, lysins target specific bacteria, so they don't kill healthy gut flora and cause gastrointestinal problems. Yet because lysins attach themselves to receptors on a bacterium's cell wall that are unlikely to mutate quickly, lysins are far less vulnerable to resistance than phages are. "Resistance will eventually occur, but it's going to take much longer than for conventional antibiotics," Fischetti says.

ContraFect, a biotech company in Yonkers, N.Y., is developing a lysin from Fischetti's lab that targets methicillin-resistant *S. aureus* (MRSA), which kills more than 9,000 people per year. Now the drug, CF-301, is being studied in conjunction with traditional antibiotics in a phase 2 trial of 117 patients with MRSA infections of the blood and heart valves. "In theory, the single dose of lysin will reduce the bacterial load in the infection," Fischetti says. "Then the patient's immune system and the antibiotic will mop up whatever's left."

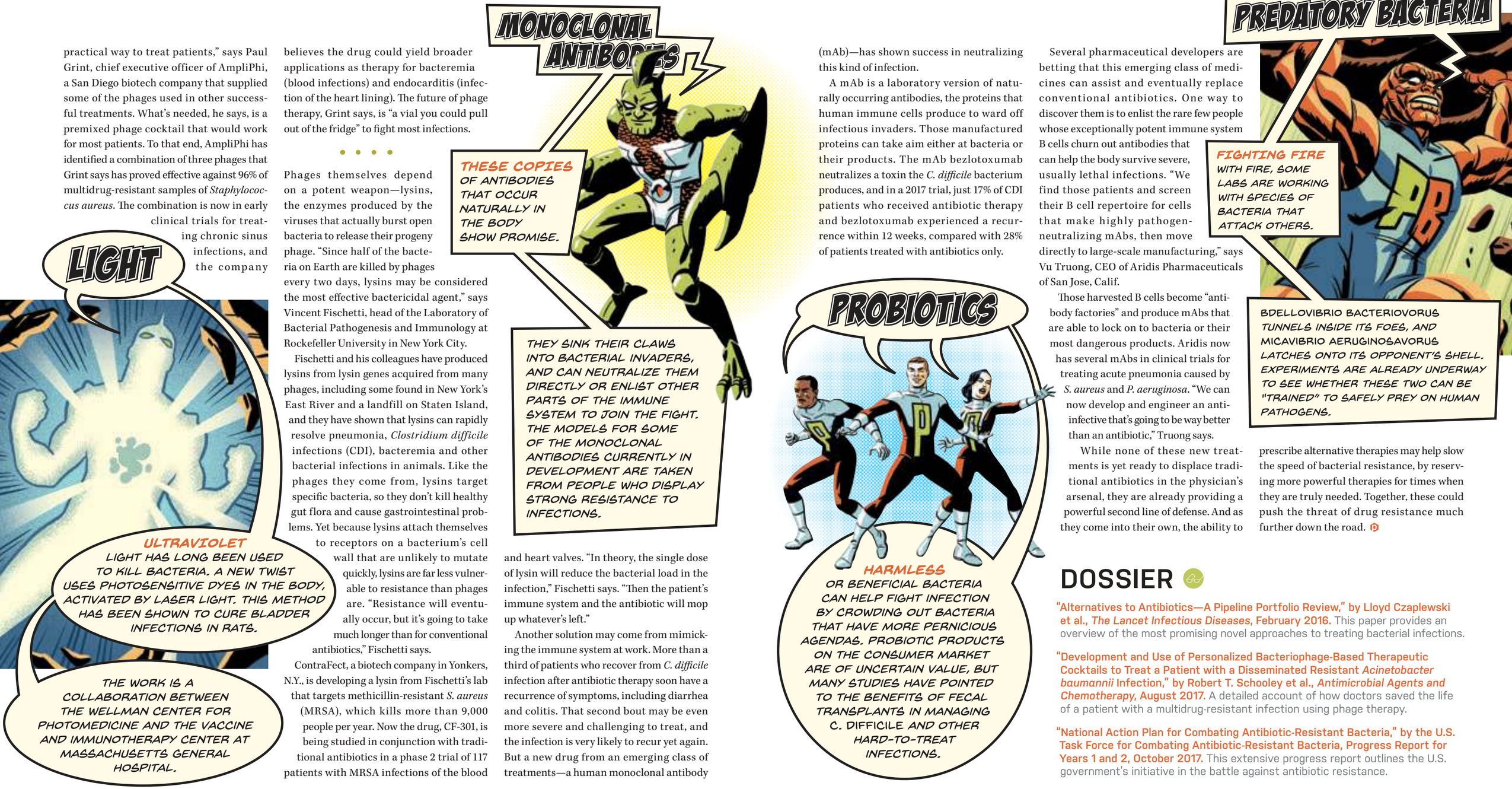
Another solution may come from mimicking the immune system at work. More than a third of patients who recover from *C. difficile* infection after antibiotic therapy soon have a recurrence of symptoms, including diarrhea and colitis. That second bout may be even more severe and challenging to treat, and the infection is very likely to recur yet again. But a new drug from an emerging class of treatments—a human monoclonal antibody (mAb)—has shown success in neutralizing this kind of infection.

A mAb is a laboratory version of naturally occurring antibodies, the proteins that human immune cells produce to ward off infectious invaders. Those manufactured proteins can take aim either at bacteria or their products. The mAb bezlotoxumab neutralizes a toxin the *C. difficile* bacterium produces, and in a 2017 trial, just 17% of CDI patients who received antibiotic therapy and bezlotoxumab experienced a recurrence within 12 weeks, compared with 28% of patients treated with antibiotics only.

Several pharmaceutical developers are betting that this emerging class of medicines can assist and eventually replace conventional antibiotics. One way to discover them is to enlist the rare few people whose exceptionally potent immune system B cells churn out antibodies that can help the body survive severe, usually lethal infections. "We find those patients and screen their B cell repertoire for cells that make highly pathogen-neutralizing mAbs, then move directly to large-scale manufacturing," says Vu Truong, CEO of Aridis Pharmaceuticals of San Jose, Calif.

Those harvested B cells become "antibody factories" and produce mAbs that are able to lock on to bacteria or their most dangerous products. Aridis now has several mAbs in clinical trials for treating acute pneumonia caused by *S. aureus* and *P. aeruginosa*. "We can now develop and engineer an anti-infective that's going to be way better than an antibiotic," Truong says.

While none of these new treatments is yet ready to displace traditional antibiotics in the physician's arsenal, they are already providing a powerful second line of defense. And as they come into their own, the ability to prescribe alternative therapies may help slow the speed of bacterial resistance, by reserving more powerful therapies for times when they are truly needed. Together, these could push the threat of drug resistance much further down the road.



DOSSIER

"Alternatives to Antibiotics—A Pipeline Portfolio Review," by Lloyd Czaplewski et al., *The Lancet Infectious Diseases*, February 2016. This paper provides an overview of the most promising novel approaches to treating bacterial infections.

"Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails to Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection," by Robert T. Schooley et al., *Antimicrobial Agents and Chemotherapy*, August 2017. A detailed account of how doctors saved the life of a patient with a multidrug-resistant infection using phage therapy.

"National Action Plan for Combating Antibiotic-Resistant Bacteria," by the U.S. Task Force for Combating Antibiotic-Resistant Bacteria, Progress Report for Years 1 and 2, October 2017. This extensive progress report outlines the U.S. government's initiative in the battle against antibiotic resistance.

LESSONS FROM A LONG SLEEP

DURING A STROKE, A SUDDEN LACK OF OXYGEN IN THE BRAIN CAN CAUSE UNTOLD DAMAGE. WHY DO HIBERNATING ANIMALS EXPERIENCE NEARLY THE SAME PROCESS, WITHOUT INJURY?

BY CARRIE ARNOLD //

As August begins its slow fade into September in Alaska's tundra, Arctic ground squirrels (*Spermophilus parryii*) retreat into underground burrows to hibernate through the freezing winter. The squirrels' metabolism slows to near-zero; their hearts beat and their lungs inflate only once per minute; and their body temperature drops as low as 27 degrees Fahrenheit. Their brains, normally greedy for oxygen and glucose, receive almost no blood. Yet Arctic ground squirrels will emerge in spring undamaged, after cooling and warming themselves numerous times throughout their frozen sojourn.

A human who underwent such changes would die within minutes. But some researchers believe that understanding how the squirrels survive these oscillations in their metabolism could lead to new strategies for treating people who are having a stroke, in which blood also stops circulating to the brain. "The blood flow is so low in these hibernating animals that you'd think they *were* having a stroke," says Kelly Drew, a biochemist at the Institute of Arctic Biology at the University of Alaska Fairbanks, who has studied Arctic ground squirrel hibernation for more than 20 years. "But they have no signs of brain injury, which shows just how protective hibernation is."

It protects them in another way, too, shielding ground squirrels and other hibernating animals—ranging in size from diminutive Syrian hamsters to cave bats to Madagascar's fat-tailed dwarf lemur to massive grizzly bears—from harm when they warm up and blood flow resumes, which happens repeatedly during hibernation and again finally

in the spring when outdoor conditions improve. That also seems relevant to what occurs during a human stroke. Only some of a stroke's damage comes from the initial lack of blood, with a cascade of additional injuries occurring during "reperfusion," when warm, oxygenated blood returns to the tissues and immune processes kick into high gear.

Millions of years of evolution have given hibernators this seemingly miraculous ability to survive the equivalent of a stroke and its aftermath more than 30 times each year, all without signs of injury or distress. Hannah Carey, a physiologist at the University of Wisconsin, Madison, is another scientist who believes that solving the mysteries of how that happens might lead to treatments that could help prevent or reduce the harm to people who have a stroke. That includes 800,000 Americans each year, of whom 130,000 die as a result. "If we can tease out what is so special about hibernators, we might be able to apply that to medical treatments in humans," Carey says.

That quest to unravel what actually happens during hibernation isn't an easy one. For starters, the most common animal models in human medical research—including rats, mice and zebrafish—don't hibernate, so research on hibernators lacks the deep well of genetic and molecular data that has been built up from research on these model organisms. Moreover, some hibernators, such as the Arctic ground squirrel, don't breed well in captivity, which means new research subjects must be captured from the wild.

Working within these constraints, scientists have discovered that hibernation is far more complex than a long winter's nap. It affects every organ system in the body and doesn't have a simple on/off switch that can be flipped at will. Still, comprehending even small aspects of hibernation could ultimately lead to much-needed new stroke therapies, according to Sandy Martin, a molecular biologist at the University of Colorado. "It's not really that far-fetched to think that humans could make use of these mechanisms," she says.

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Diminishing hours of daylight, decreasing temperatures and a reduction in available food all can trigger hibernation, which on a fundamental level alters the expression of numerous genes, including those that protect cells from damage and others that assist in breaking down body fat for fuel. Hibernation brings metabolism almost to a standstill. Body temperature, pulse, respiration and blood flow all fall during this shutdown.

In this state, the mammals must rewarm themselves every few days, drawing energy from stored fat in significant quantities. Scientists still don't know exactly why these cycles of awakening happen, although they speculate that warming allows the animal to make needed cellular repairs that are impossible while sleeping. As temperatures rise and days lengthen, the animals wake up for good, skinny and starving, ready to find food and a mate. Hibernation ends as quickly as it began, reversing the physiological changes that occurred when they started hibernating. "A squirrel can go from freezing to normal in about two hours," Martin says.

This predictable and orderly process stands in stark contrast to the biological chaos that ensues when a person suffers an ischemic stroke. When human brain tissues are suddenly starved of blood and the oxygen it carries, neurons respond by releasing large quantities of neurotransmitters. These send rapid-fire signals through the brain's circuitry, setting off a chain of toxic events that can kill neurons even far from the site of the initial injury. "A tsunami of activity surges across the brain, sucking up oxygen it doesn't have and leaving a trail of dead cells in its wake," says Lee Schwamm, a neurologist and director of the Comprehensive Stroke Center at Massachusetts General Hospital. "The real problem is that there is insufficient blood supply to meet the demand."

To limit the impact of a stroke and its aftermath, time is of the essence—treatment can succeed only if symptoms are recognized quickly and a patient can be rushed to a hospital equipped to treat stroke patients rapidly and well. "Simply put, time is brain," says Ralph Sacco, chairman of neurology at the University of Miami and former president of the American Heart Association. To stop this cascade of destruction, physicians have three options—administer a drug called tissue plasminogen activator to break up the clot, remove it with clot retriever devices, or use both of the above treatments. These approaches can restore blood flow and a supply of life-saving oxygen to the brain. But the more time that has passed, the worse the ischemic and reperfusion injuries are when the blood returns, as the immune system unleashes immune cells called microglia that hurt healthy parts of the brain in their efforts to repair damaged tissue.

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Could lessons from hibernating animals help extend that golden hour? Perhaps, but only if researchers can pin down what exactly prevents those animals' brains from starving for oxygen in the first place, or figure out what protects them from reperfusion injuries once the blood returns. In an effort to answer that second question, Drew's team has spent nearly two decades hunting for protective mechanisms in a hibernator that underwent a stroke-like event.

She and her colleagues used a needle-thin probe to create tiny brain injuries—the closest simulation they could manage—both in Arctic ground squirrels that were hibernating and in those that were awake. Brain tissue in normal-temperature squirrels showed a cascade of damage and an inflammatory response in the tissue surrounding the probe, much like what happens to a person who has a stroke. But the intentional injury had significantly less impact in hibernating animals. Drew surmised that Arctic ground squirrels in this state are helped by some sort of neuroprotective compound.

Hjalmar Bouma, a pharmacologist and resident in acute internal medicine at the University of Groningen in the Netherlands, discovered what that compound might be—and is investigating it for clinical applications to protect against organ injury and conditions such as sepsis. As a medical student, Bouma had worked in the lab of Robert Henning, an anesthesiologist and pharmacologist at the university who was interested in hibernation as a way to protect organs during major surgery. For their experiments, Henning and Bouma used the Syrian hamster, a hibernating rodent native to the Middle East. The researchers compared hamster cells to kidney cells from rats as both sets of cells were chilled and rewarmed, simulating hypothermia and reperfusion.

The first clue about what set hibernating animals apart was olfactory. When Bouma and his colleagues opened the flask of the hamster's cell cultures, "the liquid reeked of rotten eggs," he says. Bouma guessed immediately that the smell meant the presence of hydrogen sulfide. All of those foul-smelling cells survived for 24 hours after being chilled and thawed, while only half of the rat kidney cells lived that long. When the researchers added hydrogen sulfide to the rat cells, the chemical blunted the harmful effects of reperfusion in those cells as well.

Bouma and others in Henning's lab spent the next several years investigating how hydrogen sulfide was involved in hibernation. They knew from the work of other

HAZEL DORMOUSE

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MADAGASCAR'S FAT-TAILED DWARF LEMUR

"IF WE CAN TEASE OUT WHAT IS SO SPECIAL ABOUT HIBERNATORS, WE MIGHT BE ABLE TO APPLY THAT TO MEDICAL TREATMENTS IN HUMANS."

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scientists that most mammals have only very small amounts of the compound, which acts as an antioxidant, counteracting the effects of "oxidative stress," in which harmful chemicals wreak havoc on DNA, proteins and other important molecules. Not coincidentally in this context, oxidative stress also causes much of the damage during reperfusion after a stroke, adding to the effects of an overactive immune response. But Syrian hamsters and other hibernators, including 13-lined ground squirrels (a cousin of the Arctic ground squirrel), produce hydrogen sulfide in abundance, and Bouma hypothesized that its purpose could be to protect cells from oxidative stress.

Other studies added credence to that hypothesis. In her lab at the University of Wisconsin, Carey found evidence of oxidative stress in hibernating 13-lined ground squirrels. Her team also found that some cells in the hibernator's body produce large numbers of protective proteins and reduce the synthesis of molecules that may increase stress to their cells—which may be part of the protection hibernators experience during the winter months.

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Can anything that hibernating animals do be translated into strategies for preventing or treating stroke in people? Some of the first attempts took perhaps the most obvious approach—reducing a person's body temperature to mimic the conditions under which hibernation occurs. But humans tend to shiver violently to maintain a normal body temperature, and shivering is a calorically expensive process that requires extra oxygen—just when, during a stroke, cells are oxygen-starved. Reducing body temperature thus puts an even greater strain on metabolism and could make stroke damage worse. Although hibernating animals do indeed experience hypothermia, that's the effect of a slowed metabolism, not the cause.

A second possibility would be to imitate the immune system changes that occur during hibernation. Bouma, studying European ground squirrels, 13-lined ground squirrels and Syrian hamsters, found that levels of infection-fighting white blood cells dropped by more than 90% during hibernation because of retention in lymph nodes and adhesion to vessel walls. Moreover, the researchers also noted that these white blood cells have a reduced function, leading to a broader immunosuppression that affected all parts of the immune system and which may, in addition to the effect of hydrogen sulphide, serve to protect against organ injury.

Tamping down the immune system might also help protect human patients, suppressing the collateral damage caused by overenthusiastic microglia immune cells, which attempt to clean up a stroke injury and hurt healthy cells in the process, says Mihai Podgoreanu, an anesthesiologist at Duke University. "Preventing this secondary injury would be hugely helpful," he says. But it could also leave patients at a higher risk of developing secondary infections.

Even if it were possible to isolate and reproduce some of the neuroprotective processes of hibernation—very large ifs at this point—Schwamm notes that "it is a leap of faith to think an injured human brain would have the same response as a 13-lined ground squirrel." He points to the scientific literature on stroke, which is littered with failed clinical trials of drugs that appeared effective in animals but didn't work in humans. Human brains are simply different, Schwamm says, and "the larger frontal lobes of people may simply not be amenable to hibernation."

In what may be the closest thing so far to a hibernation-inspired stroke therapy, John Hallenbeck, chief of the clinical investigations section of the National Institute of Neurological Disorders and Stroke, and Yang-ja Lee, his co-investigator, in November 2017 identified a potential drug that might help protect human brains.

Their discovery involves a cellular process called SUMOylation, which tags proteins with small molecules that, among other things, direct the proteins to their correct locations in a cell and alter how readily they can be recycled. SUMOylation modulates a variety of biochemical pathways, and this wide-ranging activity is part of what scientists think makes SUMOylation so advantageous. Indeed, previous studies showed that increasing SUMOylation in cells could protect them against damage from ischemia, a lack of blood flow and oxygen. Because they had observed that this beneficial process goes into overdrive in the brains of the hibernating squirrels, Hallenbeck and Lee wondered whether SUMOylation might be part of what keeps the animals from being harmed by the stroke-like conditions of hibernation.

Their next step was to look for a compound that could spur SUMOylation in human brains and perhaps limit the damage of a stroke. Hallenbeck and Lee used an automated process to comb through a library of more than 4,000 molecules. They found compounds that increased expression of the SUMOylating enzyme, and some that inhibited an enzyme removing such tags, including a selenium-containing molecule called ebselen that boosted SUMOylation in cultured rat neurons. When the researchers injected ebselen into the brains of healthy mice, the molecule enhanced SUMOylation and appeared to reduce the number of neurons that died from ischemia.

"For stroke treatment, it seems that studying hibernation was a good strategy," says Lee. The researchers now hope to replicate these results in human neurons.

A follow-up study published in January 2018 by Lee, Hallenbeck and colleagues revealed a potential mechanism for extreme ischemia tolerance in ground squirrels in which their brain cells cycled between two different biochemical states, giving them an extreme tolerance to stress.

Meanwhile, Bouma's and Henning's group in the Netherlands is beginning preliminary trials using treatments based on the effects of hydrogen sulfide to prevent acute kidney injury—during critical illness and major cardiac surgery. And Drew's team at the University of Alaska is starting its own trials. After several decades of exploring the processes of hibernation, Drew has homed in on the A1 adenosine receptor, a protein that is present throughout the bodies of ground squirrels, humans and other animals. Drew's previous work had flagged the receptor as a potential hub of hibernation, and when she activated it in Arctic ground squirrels, the rodents' body temperatures plunged far below normal. That makes the A1 adenosine receptor possibly useful as part of a stroke treatment, but activating it can also trigger dangerous heart arrhythmias. Now Drew is searching for molecules that can stimulate the A1 adenosine receptor in humans without creating cardiac problems.

Even as scientists begin to experiment with ways to use the processes of hibernation to treat strokes in people, most mysteries about how it works in animals remain unsolved. Still, those who are involved in this research have high hopes that greater understanding will come, and with it the ability to harness hibernation's power to protect human brains from the ravages of ischemia. Says Duke anesthesiologist Podgoreanu, "Maybe it's time we let Mother Nature inform us how things can be done."

MOST MYSTERIES ABOUT HOW IT WORKS IN ANIMALS REMAIN UNSOLVED. STILL, THOSE WHO ARE INVOLVED IN THIS RESEARCH HAVE HIGH HOPES.

EUROPEAN LESSER HORSESHOE BAT

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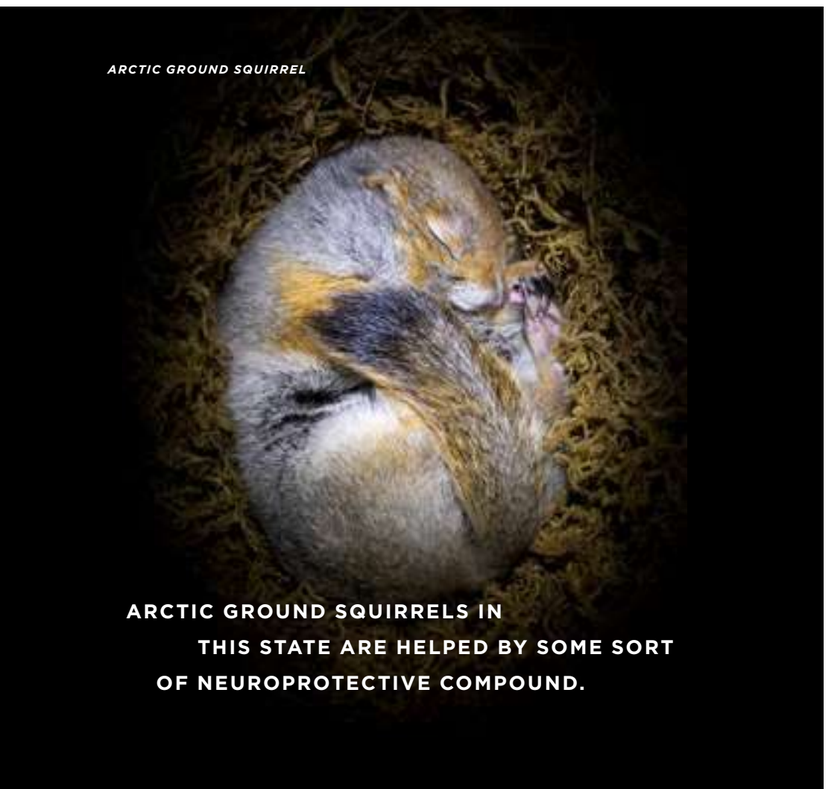

ARCTIC GROUND SQUIRREL

ARCTIC GROUND SQUIRRELS IN THIS STATE ARE HELPED BY SOME SORT OF NEUROPROTECTIVE COMPOUND.

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DOSSIER

"Induction of Torpor: Mimicking Natural Metabolic Suppression for Biomedical Applications," by Hjalmar R. Bouma et al., *Journal of Cellular Physiology*, May 26, 2011. This paper provides an overview of how scientists are planning to create a hibernation-like state in individuals with ischemia and other types of injuries.

"Neuroprotection: Lessons from Hibernators," by Kunjan R. Dave et al., *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*, February 2012. In this review, scientists discuss adaptations in mammals that may suggest therapeutic targets and strategies to protect the human brain.

***Winter World: The Ingenuity of Animal Survival*, by Bernd Heinrich, HarperCollins Publishers, 2003.** This book examines the clever strategies animals use to survive frigid temperatures, including hibernation.

The fight against HIV/AIDS has seen nearly four decades of breakthroughs and setbacks. Can the plague finally be stopped?

An Endgame for an Epidemic

In 1981, young men with remarkably low white blood cell counts began showing up in emergency rooms in Los Angeles, San Francisco, New York and other cities. The collapse of their immune systems led to devastating infections, and doctors could do little more than try to make these patients comfortable. Most of them died. Soon the condition was linked to other populations, and the research community began referring to the four Hs—homosexuals, heroin users, Haitian immigrants and hemophiliacs.

This new scourge soon gained a name—acquired immunodeficiency syndrome, or AIDS—and in 1983, researchers isolated its cause: HIV, the human immunodeficiency virus. The devastation of the disease would continue to expand exponentially, and those who had it were stigmatized by a terrified public. In response, a coalition of activists, policymakers and researchers launched the first World AIDS Day on Dec. 1, 1988. Their stated goal was to extend tolerance to those living with the disease, and to support initiatives that would stop the plague for good.

Three decades later, even after enormous progress, that quest remains incomplete. In many ways the epidemic seems under control, in large part because of medications that can turn HIV infection into a chronic condition. But not everyone has access to those drugs, and the number of new cases continues to grow. In 2016, there were 1.8 million new HIV infections globally and 1 million people died of AIDS. In the United States, nearly 40,000 people were diagnosed with HIV

By Anita Slomski //

Illustrations by Edmon de Haro

infection in 2015, and a quarter of those cases had progressed to AIDS. "Black gay men in southern states have a one-in-two chance of developing HIV, a rate comparable to that of South Africa, which has the highest incidence of HIV in the world," says Rochelle Walensky, chief of infectious diseases at Massachusetts General Hospital and former chair of the Office of AIDS Research Advisory Council at the National Institutes of Health.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) is counting on big strides in both prevention and treatment, and it has an ambitious goal for the near future: to end the AIDS epidemic by 2030. To achieve that, UNAIDS has established interim "90-90-90" treatment targets for 2020: 90% of people living with HIV will know they are infected by then, 90% who have been diagnosed will be on treatment and 90% of treated people will have had their HIV virus suppressed to a point of not being transmissible. At least 18 countries have stated that they have or soon will have achieved those milestones, most of them in Europe but some in Asia and sub-Saharan Africa.

Yet whether the rest of the world is able to get there, too—and whether the virus can be contained more completely—depends on advances still to be made. It will require research gains in how to control the disease in those who have it, and to prevent the uninfected from catching it along with a reinvigorated search for a cure, after decades of dead ends. And above all, the effort will require wise policy choices and continued funding at a time when many people seem to think this is a problem that has already been solved.

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HIV works by attacking a class of white blood cells—CD4-positive (CD4+)—that helps the immune system fight infection. After infiltrating the DNA of CD4+ cells, HIV replicates, infecting and killing those cells and rendering the body's immune system increasingly ineffective. Then, as HIV spreads, the virus mutates, constantly changing its genetic sequences and creating new variants that flummox the immune system's ability to recognize it as a pathogen.

Without treatment, the immune systems of people infected with HIV become weaker and weaker. AIDS is the final stage of HIV infection, when infections such as tuberculosis, pneumocystis pneumonia, Kaposi's sarcoma and other cancers take hold, or when the count of CD4+ cells falls below 200 per cubic milliliter of blood. The life expectancy of someone with AIDS at the beginning of the epidemic was about three years. Then, in the mid-1990s, came the first effective treatment: combination antiretroviral therapy, or ART.

In the United States, nearly 40,000 people were diagnosed in 2015.

Today's combination antiretroviral therapy packages three or more drugs in as little as one pill, which can suppress the activity of HIV to undetectable and intransmissible levels. "We now have extremely effective treatment for people who have access to it and are motivated to take a pill every day for life," says Steven Deeks, HIV researcher and professor of medicine at the University of California, San Francisco. "They can have a normal lifespan."

Still, committing to a lifetime of treatment, which in the United States currently has a price tag of about $380,000, is no small thing. "Continuing to take those pills through decades of midlife crises, losing health insurance, going off the wagon with substance abuse, getting burnt out by the whole thing—most people cannot sustain that indefinitely," Deeks says. Long-term ART can also cause bone and kidney problems, and people who have lived with HIV for many years tend to have accelerated aging and develop other diseases at a higher rate than the rest of the population. "The cumulative toxicity of the drugs we used prior to 2005 has taken a toll," says Paul Sax, clinical director of the HIV Program and Division of Infectious Diseases at Brigham and Women's Hospital in Boston. So while treatments exist that can keep HIV under control, there is plenty of room for improvement, with other approaches that could reduce the need for daily adherence while limiting the toll on the body.

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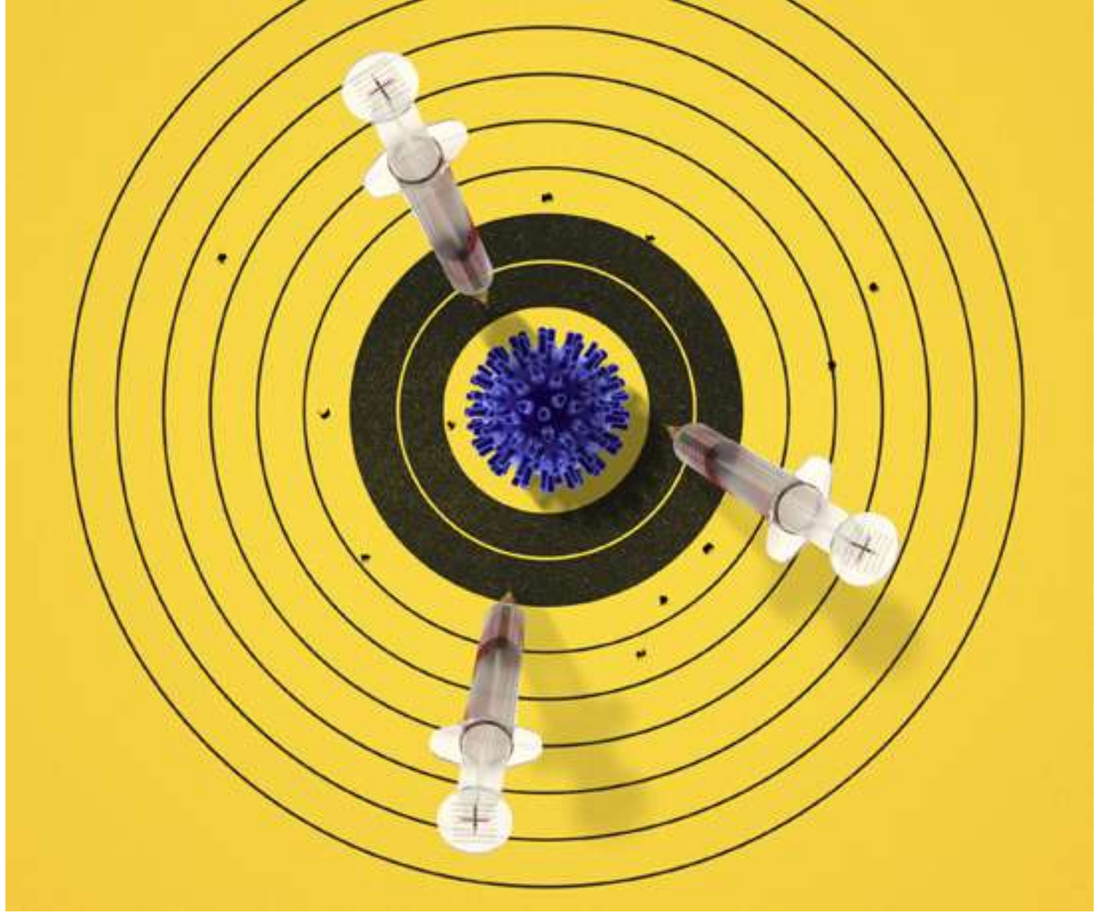
When people with HIV strictly adhere to the ART regimen, the possibility of transmitting the virus becomes vanishingly small, even when those infected with the virus don't use condoms or otherwise fail to follow HIV-prevention strategies. Yet not everyone with HIV is on ART, and in 2012, a new defense became available for those at risk of catching the disease. That pill, Truvada, contains two antiretroviral drugs and provides pre-exposure prophylaxis (PrEP). Men who take two doses of Truvada before a sexual encounter with an infected male partner and for two days after lower their chances of getting HIV. PrEP also protects women, but they need to take the pill for at least a week before and a week after sex, because the drug works more slowly to block HIV in the vagina and the cervix than it does in the rectum. The Centers for Disease Control and Prevention recommend that anyone at high risk for HIV take PrEP every day.

Not nearly enough people in this group do take it, however. In 2016, there were 77,120 PrEP users in the United States—a small fraction of the 1.2 million people at high risk of getting HIV, according to the CDC—and most of those who avail themselves of the treatment are middle-aged white gay men, among the at-risk populations least likely to contract HIV. "African-Americans, Hispanics and women tend to be left behind, and very few injecting drug users have ever heard of a pill to prevent HIV," says Dawn Smith, epidemiologist and medical officer in the CDC's Division of HIV/AIDS Prevention.



In any case, for women, a different approach to prevention—a vaginal ring that releases dapivirine, an antiretroviral drug, for a month at a time—may offer better protection. Tested in two advanced human trials in South Africa, Malawi, Uganda and Zimbabwe, the ring reduced the rate of HIV infection by 56% among women who used it consistently. "That compares with the first trials of oral PrEP, which reduced HIV infection by 44%," says Jared Baeten, vice chair of Global Health at the University of Washington's Schools of Public Health and Medicine in Seattle and an investigator on the pivotal PrEP and vaginal ring trials. The vaginal ring is currently under review for use in several African countries that have a high prevalence of HIV, while a vaginal ring that releases an antiretroviral for three months and one that includes a contraceptive are also being tested.

Even better than prevention, of course, would be a cure, and in 1997, at the breakthrough moment when the Food and Drug Administration approved the first combination antiretroviral treatment for HIV/AIDS, it appeared that a cure might also be within reach. But then a research team led by Robert Siliciano established that HIV infection created reservoirs of latent virus in the body.

Within a few days of infection, the virus hides itself, becoming latent in a particular type of CD4+ cell known as a memory T cell. Reservoirs of memory T cells with the DNA of HIV may reside throughout the body, particularly in lymph nodes, the spleen and the gastrointestinal tract, persisting indefinitely. Although ART can block HIV from replicating, it can't eliminate the latently infected memory cells, and if someone stops taking ART, production of HIV begins again, leading to a raging infection in as few as two weeks.

"Once we showed that HIV-infected cells would be present for life, it crushed much of the enthusiasm for a cure," says Siliciano, professor of medicine at Johns Hopkins Medicine in Baltimore. "For nearly a decade after that, the word *cure* became taboo because it falsely raised patients' hopes."

In 2009, however, American Timothy Ray Brown was pronounced cured of HIV. After taking ART for more than a decade, Brown was diagnosed with leukemia, and to treat the cancer, Brown received bone marrow transplants in 2007 and 2008 from a donor with a rare genetic mutation called CCR5 that provides immunity to HIV. Because Brown had stopped taking ART as part of his cancer treatment, his reservoirs of sleeping

virus should have been activated. Yet he had no detectable HIV in his blood, and physicians concluded that all of the virus, even in the reservoirs, had been eliminated.

Steven Deeks, who treated and studied Brown, says researchers aren't fully sure why Brown's bone marrow transplant cured him, but he suspects that a complication of the treatment might have killed all of Brown's cells harboring HIV. Still, the therapy almost killed him, too. "He was in and out of the hospital for years," Deeks says. "Brown has said that being cured was much worse than being treated for HIV."

Building on lessons from Brown's case, a team of investigators supported by the advocacy organization amfAR recently performed stem cell transplants, some from donors with the CCR5 mutation, to about 30 HIV-infected patients with cancer. "Even if they aren't cured, we believe we will learn a lot from these patients, such as whether there are some types of cells that more persistently harbor HIV," says Rowena Johnston, vice president and director of research for amfAR.

Another, perhaps more promising approach to a cure—known as "shock and kill"—uses a drug to activate the CD4+ T cells containing sleeping HIV so that the immune system can detect them and make them vulnerable to additional treatment. Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston, created a stir in the research community with preliminary results of monkey studies he presented at an HIV/AIDS conference this year. Rhesus monkeys infected with an HIV-like virus in Barouch's experiment started ART and then received an immune-boosting drug to stimulate and awaken the T cells with latent virus, followed by a potent HIV antibody that recruited other immune system cells to kill the infected T cells. After stopping ART, the virus did not rebound in five of the 11 monkeys that received the combination therapy, and in the other six monkeys, the virus was at levels 100 times lower than in untreated monkeys with HIV.

As potentially transforming as such a treatment might be, it's probably too early to risk trying it in people. "There's no way to know for sure whether the reservoirs of latent virus have been completely eliminated, so the idea of doing treatment-interruption studies in people is controversial," says Robert Siliciano. For now, Barouch is testing the antibody given to the monkeys in preliminary human trials.

Deeks, meanwhile, says he believes HIV could be cured through a kind of permanent remission rather than by eliminating reservoirs of the virus. His approach is to use a vaccine and other agents to revive an exhausted immune system to fight the virus, in part by reversing some of the chronic inflammation that HIV causes. Then another drug stimulates natural killer cells, a separate part of the immune system, to control the virus and force it into remission, allowing people to stop ART. "This is exactly the type of immunotherapy that is having a revolutionary effect in oncology, using drug research that was being done in the 1990s with HIV," Deeks says. There are now about a dozen clinical trials of HIV immunotherapy that are planned or underway.

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A vaccine against HIV would be another effective means of reducing and potentially eliminating infection with the virus. Its pursuit has inspired some of the most ambitious research efforts in the field, including the founding of the Ragon Institute of MGH, MIT and Harvard, which brings together specialists across disciplines and funds promising research across the globe. But vaccine development has been hampered by the enormous variability of HIV. A truly effective vaccine would prevent infection and the establishment of latent reservoirs. "These are huge hurdles," Barouch says. "But we are cautiously optimistic that these challenges can be solved."

Indeed, previous large-scale human trials of traditional vaccines against HIV have failed. Only one, using a novel "prime-boost" regimen, had any success, and it reduced the risk of infection by a modest 31% compared with a vaccine placebo among study participants in Thailand.

Today, however, there is renewed hope for a vaccine, with two large trials currently underway in Africa, one of which is testing a more robust version of the vaccine tried in Thailand. The other experimental vaccine was developed by Barouch, one of the founding members of the Ragon Institute, and theoretical biologist Bette Korber at Los Alamos National Laboratory. Funded by the NIH, the Ragon Institute and others, it has a unique "mosaic" design that combines pieces of different HIV strains from around the world. "The theory is that a mosaic vaccine will elicit immune responses against all the diversity that HIV exhibits so only one vaccine will be needed globally," says Bruce Walker, director of the Ragon Institute.

Both new candidates are prime-boost vaccines, which use two injections to increase the body's immune response. One injection delivers HIV genes in a harmless carrier and the second contains a protein found on the HIV surface, which doesn't mutate along with the rest of the virus. "Although vaccine-induced antibodies against the surface protein aren't very potent, they should be able to bind to the virus to either block infection or kill infected cells," says John Mascola, director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases.

The mosaic vaccine, now being tested in 2,600 women in sub-Saharan Africa, provided 67% protection in monkeys that received the vaccination and then were infected with a simian HIV virus. "This vaccine has the best results seen in animal models, and we'll know in two-plus years whether it works in humans," says Walker. Should the vaccine prove to be at least 60% effective in humans, "it would have a dramatic effect on the epidemic," Mascola says.

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The effectiveness of these research advances will ultimately depend on a coordinated global public health infrastructure, one that can quickly implement vaccines, treatments or cures. In 2003, President George W. Bush established the President's Emergency Plan for AIDS Relief (PEPFAR) to provide HIV testing and treatment to developing countries. Since then, the United States has invested more than $70 billion to fight HIV and AIDS, the largest commitment by any country to address a single disease. Most of that assistance goes to the countries in which HIV infections are not yet under control, and the investments have led to significant improvements, slashing AIDS deaths by half and decreasing new HIV infections by an average of 23% annually. PEPFAR, funded entirely by U.S. contributions, underwrites the cost of ART for more than 15 million people in developing countries, and U.S. HIV funding has averted an estimated 5 million AIDS deaths in sub-Saharan Africa alone.

The effectiveness of these research advances will ultimately depend on a coordinated global public health infrastructure.

Yet continued progress could be impeded by a decline in financial support. "HIV and AIDS funding began slowing around 2011, when the global financial crisis caused many countries to re-evaluate their priorities," says Gregorio Millett, vice president and director of public policy at amfAR and a former CDC researcher and senior policy advisor on HIV in the Obama administration. PEPFAR's funding has stayed constant since 2010 after dodging a large proposed cut by the Trump administration this year. Yet it will take even more money to meet goals for reducing HIV infection worldwide. "The only way to get viral suppression for more people with HIV is to put them on treatment, and that requires more investment," Walensky says.

She would like to see that happen, so that UNAIDS goals can be met and HIV and AIDS could finally be conquered. But she's also aware of how far the world has already come. "HIV has inspired tremendous global solidarity among governments, scientists and community activists," Walensky says. She also notes that the benefits of that effort have grown beyond the disease itself. The cure of hepatitis C directly followed from what researchers learned in treating HIV, and work on HIV vaccines has sparked development of better vaccines for other diseases. "The progress we've made in 20 years is unprecedented," Walensky says, "but we cannot stop now."

DOSSIER

"Do Less Harm: Evaluating HIV Programmatic Alternatives in Response to Cutbacks in Foreign Aid," by Rochelle Walensky et al., *Annals of Internal Medicine*, November 2017. This paper evaluates the extent of harm, including HIV transmissions and deaths, from various strategies to scale back international aid to HIV programs.

"HIV Infection," by Steven Deeks et al., *Nature Reviews Disease Primers*, October 2015. This article is a primer on the mechanics of how the virus infects cells, current treatments and the status of research to cure and prevent HIV.

"Making an Impact with Preexposure Prophylaxis for Prevention of HIV Infection," by Jared Baeten, *Journal of Infectious Diseases*, July 2016. Researchers liken PrEP to contraception, a primary care intervention with modest risks but the potential to have a dramatic and widespread health impact.

ASTRONAUTS ARE ALREADY PREPARING FOR THE LONG TRIP TO MARS. HOW CAN MEDICINE PROTECT THEM FROM THE DANGERS OF DEEP SPACE AND THE ACCIDENTS THAT ARE BOUND TO HAPPEN ALONG THE WAY?

140 MILLION MILES FROM HOME

BY ADAM BLUESTEIN

PHOTOS BY DWIGHT ESCHLIMAN

NASA wants to send astronauts to Mars by the 2030s. The private aerospace company SpaceX is even more ambitious, aiming for 2024, and on the engineering side, it's possible that the necessary spacecraft, launch rockets and guidance systems could be good to go by then. Preparing a crew, however, may turn out to be more daunting. Although people have been going into space for more than half a century, the longest anyone has stayed away from Earth is about 438 days, and no one has ventured farther than the Moon, a mere 239,000 miles away. A crewed mission to Mars would be an exponential leap, especially for the human body.

The first visitors to Mars will most likely spend one year or so in microgravity, pummeled by levels of interstellar and solar radiation no previous humans have endured, while riding in a cramped metal craft to a destination some 140 million miles from Earth. Unlike previous astronauts, who have enjoyed real-time communication with Earth and could return relatively quickly if a medical emergency arose, a Mars crew will soon be too far away to do either of those things. A communication lag of up to 21 minutes each way will require crews to be medically self-reliant in emergency situations, and they'll have to be able to diagnose and treat anything that comes up—physical problems such as broken bones and bacterial infections, but also depressed or delusional crewmates—without immediate guidance from the ground.

NASA's Human Research Program (HRP) investigates risks to astronaut health and performance during space exploration, and is working to pinpoint the medical dangers of an interplanetary journey. The group's latest "roadmap" for long-duration space exploration lists 34 health-related risks that include space-induced bone loss and vision problems, traumatic injuries and the potential for psychiatric disorders. "We look at a broad spectrum of conditions and take stock of our ability to manage them," says chief HRP scientist Jennifer Fogarty, who works at the Johnson Space Center in Houston.

But NASA cannot hope to complete its mission without help. Contributing to this massive effort are thousands of researchers in medical schools and hospitals, government agencies and the military. Together, they are working on solutions to the problems of human bodies in outer space, which remain one of the most substantial barriers to exploring Mars and beyond.

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On the ground, no one thinks much about the Earth's gravitational pull. But it actually plays a major part in many systems in the body, and living without it can cause a wide range of problems. Astronauts in low-gravity environments experience insomnia, motion sickness, back pain and nasal congestion as well as more serious neurological symptoms.

Without gravity's resistance, muscles gradually lose strength and endurance, and cardiovascular fitness declines. To avoid those problems, crew members on the International Space Station (ISS)—the orbiting experimental facility that is a joint project of several national space agencies—work out for at least 12 hours a week on specially modified stationary bicycles and treadmills that simulate the effects of gravity. But that equipment weighs more than 4,000 pounds and takes up about 850 cubic feet. The Mars gym will have to be much more compact, and the four astronauts on NASA's Exploration Mission-2—a three-week lunar "flyby" planned for 2023—will test a device called the ROCKY (for Resistive Overload Combined with Kinetic Yo-Yo) that is the size of a large shoe box, weighs 20 pounds and can be stowed in about 1 cubic foot. Crew members will use it like a rowing machine for aerobic exercise and to perform strength-training exercises with as much as 400 pounds of resistance.

Other teams are looking at drugs that might help astronauts keep their muscle tone. Recent studies on mice aboard the ISS tested a myostatin inhibitor made by Eli Lilly that could reduce atrophy in muscles, a treatment that was developed for patients on Earth with muscular dystrophy, ALS or other muscle-wasting diseases.

Astronauts in microgravity are also likely to lose bone mass, about 10 times as quickly as someone with osteoporosis, leading to an increased chance of fractures. In space, the thigh bone, for example, loses an average of about 1.5% of mass each month, adding up to a 10% loss during six months in space—and recovery on Earth can take three years or more. To counter that risk, preflight genetic testing might one day be used to reveal an inherited propensity to suffer bone loss, leading to extra preventive measures during interplanetary transit. Measuring bone density en route could flag crew members with higher rates of bone loss and help them take extra precautions. These travelers might get calcium and vitamin D supplements, perhaps coupled with bisphosphonate medications used on Earth for osteoporosis treatment.

IN SPACE, THE THIGH BONE LOSES ABOUT 1.5% OF MASS EACH MONTH.

Vision degradation is another peril of microgravity, and has affected six in 10 astronauts on long-duration missions on the ISS, according to a 2011 study published in the journal *Ophthalmology*. On Earth, intraocular pressure (fluid pressure inside the eyeball) and intracranial pressure (pressure within the skull) balance to make the eyeball round. But in microgravity, intracranial pressure increases, flattening the back of the eyeball and pressing on the optic nerve. This can cause distortions in vision, including farsightedness, among other problems, which can persist after return to Earth. "The eyes are essentially a pressure release valve for the head," Fogarty says. "In microgravity, the whole system is thrown for a loop."

One source of this problem is the roughly two liters of blood that shift from the legs toward the head during spaceflight, making the face look puffy and potentially adding to vision problems. Most interventions—including thigh bands, compression pants and a vacuum sleep sack—are designed to keep blood in an astronaut's legs. But cerebrospinal fluid, a clear liquid in the brain and spinal column that buffers the brain from changes in pressure, also plays a role. A 2016 study by University of Miami researchers found that astronauts returning from months in orbit had significantly higher volumes of cerebrospinal fluid near the eyes.

Dozens of research groups are working on the space vision problem, testing eyes of mice in the ISS lab and of human volunteers under conditions approximating microgravity. Researchers need to parse multiple interrelated causes and effects, Fogarty says. "We might need four or five countermeasures, and if we interfere without completely understanding the problem, we could make a bad choice."

Radiation, meanwhile, may pose an even greater risk and limit the amount of time humans can safely spend in space. A 180-day flyby of Mars would expose astronauts to an average radiation dose of about 300 millisieverts, about 100 times the average exposure of a person in the United States during the same period of time—and more than 15 times the annual limit for workers in nuclear power plants. A landing mission lasting 860 days would subject astronauts to radiation of 1.01 sieverts, increasing their lifelong excess cancer risk by about 5% and raising the specter of other health problems. Acute radiation sickness can result in vomiting and fatigue, and long-term radiation exposure can mean a greater likelihood of heart disease and may damage the central nervous system.

Reducing these risks will require better shielding methods for spacecraft, and new ways to prepare, protect and repair the human body. Various types of radiation are known to damage DNA, causing cells to mutate in ways that can lead to cancer and other problems. Fogarty notes that understanding genetic vulnerabilities could eventually help identify those most at risk of harm from radiation—revealing a heightened likelihood of developing particular kinds of cancer, for example—and prompt closer monitoring or additional countermeasures for those astronauts. Scientists in the Harvard Consortium for Space Genetics, in the department of genetics at Harvard Medical School, are developing ways to assess and combat genome damage from radiation.

New drugs may also become available. Cellular damage from radiation stems from the formation of reactive oxygen species, also known as free radicals. Molecules that remove free radicals—antioxidants—are a first line of defense. WR-2721, an antioxidant drug used to treat acute radiation exposure, can be toxic and has other undesirable side effects, but another drug, PrC-210 (aminothiol), still being tested, appears to offer the same benefits with fewer adverse effects.

Much of the space radiation research is conducted at the NASA Space Radiation Laboratory, part of the Brookhaven National Laboratory on Long Island, N.Y., where scientists can simulate what an astronaut would experience during a two-year mission to Mars and test the effects of radiation on cells, tissue and DNA. But the future may hold a laboratory farther afield. NASA Gateway, a space transit hub and research station planned for Moon orbit, where space radiation is in full effect, could be ready as early as the 2020s.

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Whereas microgravity and radiation will be givens for any Mars voyage, preparing for other medical problems calls for more speculation—and a tough calculation of which supplies to pack and protocols to prepare. A catastrophic accident or an acute medical condition requiring emergency care could severely hamper a Mars mission, says Kris Lehnhardt, an emergency room physician and deputy element scientist in the Exploration

Medical Capability group of NASA's HRP. Lehnhardt's group examines how often particular medical conditions have happened on previous space flights, compares them with their frequency on the ground and runs many thousands of computer simulations to find the top 100 things most likely to go wrong. "Then we look at what it would take to treat each condition," he says. "From there we develop a resource list."

Once astronauts land on Mars, where gravity is roughly a third of what it is on Earth, and start exploring, "people are going to be falling a lot," Lehnhardt says. "You can try to protect the most fragile spots, like the wrist." Fractures may happen anyway, so his team plans to include pain medication or sedation and splinting materials, and for more complex fractures, it will map out the best ways to address the injury.

For an emergency that calls for something major—open abdominal surgery, say—the options will necessarily be limited. Such an operation would require a prohibitive amount of equipment and would be complicated by microgravity, which makes it difficult to create a sterile operating enclosure and, with other objects possibly floating into view, to maintain a clear field of vision for surgery. Lehnhardt imagines surgery would be attempted only as a last resort, factoring in the unique considerations of every risky action in space. "You have to ask which things you can do without and what conditions you may treat partially or not at all, either because it's not serious or because it's futile," he says.

A mission to Mars would need a physician on board, Fogarty says, and that doctor would complete training modules in several specialties—even learning to do things such as dental extractions. Other crew members would be trained in first aid and basic life support and would most likely do in-flight computer-based simulations to maintain proficiency.

For less urgent problems, crews could consult with the ground, though it could take up to 42 minutes to transmit an image or question to Earth from near Mars and receive an answer. As an alternative, astronauts probably will have access to an artificial intelligence decision-support system that will consider crew members' electronic medical records—constantly updated with vital signs—including blood pressure readings, exercise routines, carbon dioxide levels and their most recent medical conversations with the ground. Automating medical systems will be important, whether it's the crew doctor or another team member performing a procedure. "We know that the more a person needs to think about, the easier it is to miss a step," Lehnhardt says.

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Behavioral health issues could be among the most perplexing on a Mars journey. It's very difficult to know what will happen to a group of people confined indefinitely to a small space, isolated from normal social interactions and extraordinarily far from home. Neuropsychological challenges could include anxiety and depression or more serious complications, such as hallucinations and psychosis.

Cosmonauts on Soviet space stations in the 1970s were the first humans to be away from Earth for six months or more, and some of them showed significant signs of psychic distress, leading to the termination of several missions. And whereas crews on the ISS, during stays lasting around six months, have managed to avoid major mental issues, they have been helped by close proximity to Earth.

"They have lots of interaction with the ground and plenty of work and experiments to do," says Gary Strangman, director of the Neural Systems Group at Massachusetts General Hospital and an innovation specialist with the Translational Research Institute for Space Health at Baylor College of Medicine in Houston. On a round-trip in which each leg will take several months to a year, however, with the signal from home becoming ever more distant, a Mars crew will be much more isolated.

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Astronauts will be screened carefully for major mental disorders and antisocial tendencies, and planners will try to assemble a crew with compatible personalities to work together through months of boredom and whatever emergencies occur. Even then, however, individual sensitivity to the stresses of spaceflight will vary, particularly on such an extended voyage, says David Dinges, professor of psychiatry at the University of Pennsylvania, who led a scientific team at the National Space Biomedical Research Institute.

ASTRONAUTS WILL BE SCREENED CAREFULLY FOR MAJOR MENTAL DISORDERS.

To get an idea of what problems might arise, researchers study the behavior and performance of people who work in very isolated conditions on Earth—submarine crews and Antarctic researchers, for example. NASA also operates space-analog research stations in remote locations on land and under water. At the Johnson Space Center's Human Exploration Research Analog facility, volunteer crews are sealed inside a three-story mock spaceship for trip simulations of six weeks or more.

During the longest of the three Mars 500 simulations, which were conducted between 2007 and 2011, a six-person international crew lived and worked in a 550-cubic-meter "spaceship" in Moscow for 520 days. The men in this experiment, who performed daily maintenance work, scientific experiments and exercise, were isolated from Earth's light-dark cycles, temperatures and seasonal conditions. They received limited food and water, had to deal with simulated emergencies and experienced communication delays similar to those of a Mars mission. "In that crew of six, two coped really effectively, and the other four experienced a variety of behavioral health problems," says Dinges, who has published two papers analyzing the crew members' behavioral changes. Those included mild to moderate depression, stress and physical exhaustion, conflicts with other crew members and with ground control, and altered sleep patterns. Two of the men accounted for 85% of the behavioral health issues.

Sleep problems can be particularly debilitating. Recent astronauts have averaged only about six hours of sleep a day—a level that can lead to cognitive and neurobehavioral deficits—and the lack of a daily cycle of light and dark can add to the toll. On a trip to Mars, blue-enriched LED lights like those recently installed on the ISS can be adjusted to enhance alertness or promote sleep, and sleep aids may help maintain a circadian rhythm of sleep and wakefulness. It will also be important for astronauts to get regular downtime to bolster mood and performance.

Because time delays won't permit real-time conversations with a psychologist on Earth, Dinges and others are working on technology to perform behavioral and performance assessments. Having astronauts write in a digital diary, for example, could create a record of their thoughts and mental states while also serving as self-therapy. Dinges and his colleagues are also developing computerized tests to help the astronauts size up their own emotional processing, spatial orientation and risk decision-making, among other cognitive factors. "We'll have algorithms to give crew members a sense of their own profile, along with countermeasures for any deficits they discover," Dinges says. Those could include antidepressant medications, behavior modification exercises or even a chat with an artificial intelligence "therapist."

A voyage through space, like any venture of exploration, comes with a measure of risk that no amount of planning can eliminate entirely. Those preparing the Mars mission are doing their best to mitigate psychological and physiological harm, but they also recognize that on launch day, much will be out of their hands, Fogarty says. "We look at the Human Research Program as an occupational health program," she says, one in which thousands will have lent their expertise to minimize threats, provide protection and outline responses to any possible emergency. Together, they hope to have everything in place for those whose occupation takes them 140 million miles from home.

DOSSIER

"Psychological and Behavioral Changes During Confinement in a 520-Day Simulated Interplanetary Mission to Mars," by Mathias Basner et al., *PLOS One*, March 2014. This study examines the behavioral and psychological reactions of crew members during an Earth-based simulated mission to Mars.

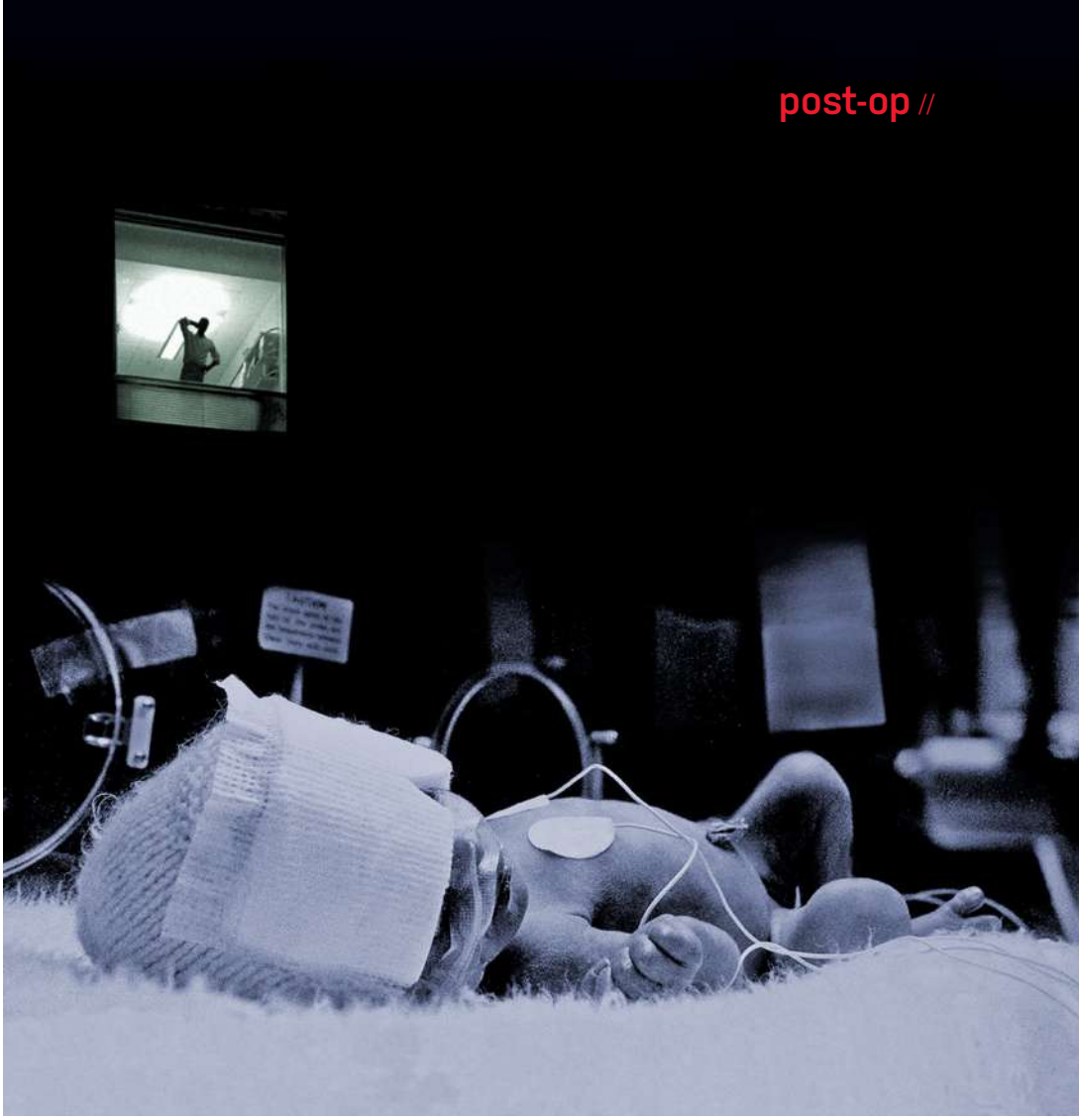
The NASA Human Research Program Evidence. Part of NASA's Human Research Roadmap, this resource provides a collection of evidence-based risk reports for individual risks of long-term space travel.

***The Habitat*, by Gimlet Media, April 2018.** This podcast series documents the real-life experiences of a six-person crew in a simulated mission to Mars on a remote Hawaiian volcano.

FIRST PERSON

Out of Reach

BY JEREMY BLACHMAN



We sit by our son's incubator in the neonatal intensive care unit, wondering if today will be a day we head home smiling, crying or, worse, don't head home at all. Mostly we are rooting for boredom in the NICU. A boring baby is one day closer to leaving.

My son was born at 29 weeks gestation, just 1 pound, 15 ounces. Other parents post happy pictures of their newborns on Facebook, meeting siblings and being held by grandparents. Our baby was whisked off to the NICU before I could even say hello. The first time I saw him, he was more wires and tubes than baby, and even if he could have cried, I wouldn't have heard it over the monitor alarms.

We had been through this before with his brother, born at 28 weeks and now four years old. In some ways, that experience made our return to the NICU easier. We knew that a baby can make it through and thrive. But in other ways, a second round added a dimension of cruelty. We knew what we were in for—a future of hand sanitizer, the fear of transmitting any illness to his weak system and, worst of all, a separation made more poignant by knowing what we were missing.

His older brother has taught us what it is like to hold your child and protect him. We can't give our younger son that same visceral assurance. The cutting truth is that the nurses and doctors are far more important to his care now than we are. Separated by a plastic box, by the CPAP mask, the feeding tube, the IV line, the ever-present, brain-scrambling noises of the NICU, it is hard to feel like I am his father.

I watch the nurse lift the lid to adjust one of his many tubes and hear a sound coming from inside the incubator. "Is that him?" I ask her. It could have been my son's cry, or someone else's, or just a sound from another machine. "It is," she says, and then the incubator lid is back down.

My wife and I hold him when we can, and sometimes we're allowed to change his diaper and perform other minor feats of parenting. But we also leave every afternoon, to get back to our four-year-old and to sleep in a home with an empty crib waiting. Here in his world, we are the visitors. Here, a strict set of rules takes precedence, rules that make us nervous, even dangerous outsiders.

A few days after his birth, I caught a cold. I stayed home for almost two weeks, long after the symptoms were gone, to make sure I wasn't taking any risks. The day I returned to the NICU—the first time I held my son skin to skin—I coughed, and immediately panicked. What if I was still contagious? What if I had just introduced a virus that was going to kill my child? I couldn't sleep that night from worry. It was three more days before I felt comfortable enough to hold him again.

How do you bond with a child you're afraid to touch? I try to find ways to be a father to my new son—talk to him, get to know his rhythms. I want to reassure him that this won't last forever. Someday, I whisper to the Plexiglas, you won't live alone in a box, poked and prodded, with parents who leave every afternoon. Someday there will be books, laughter, music and hugs. Someday I will be the father you need and deserve.

My boy is one of the lucky ones, growing bigger by grams and longer by millimeters. After two months, they tell us he'll be coming home soon. It can't happen quickly enough. He is overdue in knowing what it is like to be a member of our family. It will be a relief, finally, to hold him and not have to let go.

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