SCIENTIFIC AMERICAN
Health & Medicine

ISSUE
No. 5
October-November 2019

The Nature Cure

A STUDY OF 20,000 PEOPLE SHOWS THAT THOSE WHO SPEND TIME OUTDOORS REPORT BETTER HEALTH AND MENTAL WELL-BEING

Plus:

WITH COVERAGE FROM nature

LIZ TORMES

Take It Outside

In this issue's cover story, Jason G. Goldman covers a massive research study of 20,000 individuals in England that found that 120 minutes spent in nature every week proffered marked benefits in health and mental wellness (see "The Nature Cure"). While the scale of such an undertaking makes the work significant, the results are likely to be met by some societies with little surprise. Take Denmark, where for more than half a century families have sent their children as young as three years old to so-called forest kindergarten to forgo classroom curriculum and play and explore each day outdoors, no matter the weather. Some research has shown that those kids get sick less often, can concentrate better and have improved motor skill development. Perhaps this latest finding won't spur the creation of "forest universities" or, sadly, "forest workplaces," but if ever there was a case to get outside and commune with nature, this is it.

Cassandra Willyard writes about a string of recent advances that have helped patients with spinal cord injuries regain mobility and functionality (see "First Steps to a Revolution"). And David Adam profiles anesthesiologist John Carlisle, who, in his free time, sleuths hundreds of peer-reviewed papers for misleading or falsified data. His work has led to the retraction of hundreds of papers (see "The Data Detective"). Good reads such as these are best consumed while lounging outside, preferably under a leafy tree.

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Health & Medicine

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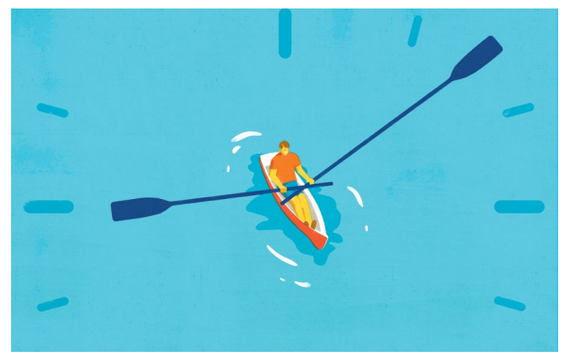

CHRIS GASH

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A study of 20,000 people shows that those who spend time outdoors report better health and mental well-being

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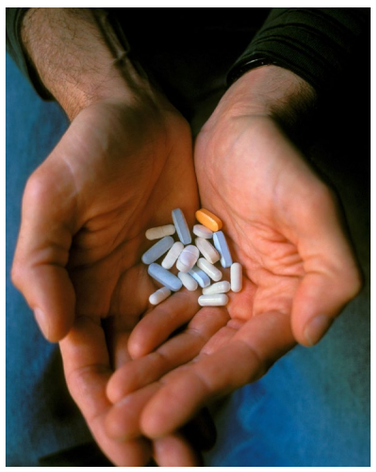

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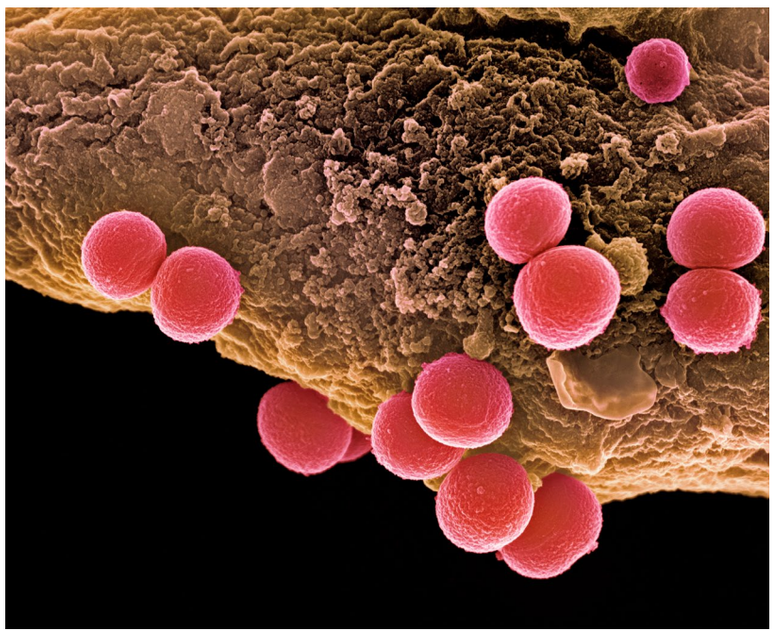

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CHRIS GASH

The Nature Cure

Mind and body benefit from two hours in nature each week

BY NOW IT'S ALMOST common knowledge that spending time in nature is good for you. Areas with more trees tend to be less polluted, so spending time there allows you to breathe easier. Spending time outdoors has been linked with reduced blood pressure and stress and seems to motivate people to exercise more.

"So it'll come as no surprise that there's research showing that spending time in nature is good," says University of Exeter Medical School researcher Mathew P. White. "I mean, that's been known for millennia. There's dozens of papers showing that."

"We get this idea. Patients are coming to us and they're saying, 'Doctor, how long should I spend?' and the doctor is saying, 'I don't really know.'"

So White and his team decided to find out by using data collected from nearly 20,000 people in England through the Monitor of Engagement with the Natural Environment Survey.

And their answer? Two hours a week. People who spent at least that much time amid nature—either all at once or totaled over several shorter visits—were more likely to report good health and psychological well-being than those with no nature exposure.

Remarkably, the researchers found that less than two hours offered no significant benefits. So what's so special about two hours?

"I have absolutely no idea. Really. We didn't have an a priori guess at what this would be, this threshold. It emerged. And I'd be lying if I said we predicted this. I don't know."

Even more noteworthy, the two-hour benchmark applied to men and women, to older and younger folks, to people from different ethnic backgrounds, occupational groups, socioeconomic levels, and so on. Even people with long-term illnesses or disabilities benefited from time spent in nature—as long as it was at least 120 minutes per week. The study is in the journal Scientific Reports.

Although the findings are based on a tremendous number of people, White cautions that it's really just a correlation. Nobody knows why or how nature has this benefit or even if the findings will stand up to more rigorous investigation.

"I want to be really clear about this. This is very early stages. We're not saying everybody has to do 120. This is really to start the conversation, saying, what would a threshold look like? What research do we need to take this to the next step before doctors can have the true confidence to work with their patients? But it's certainly a starting point."

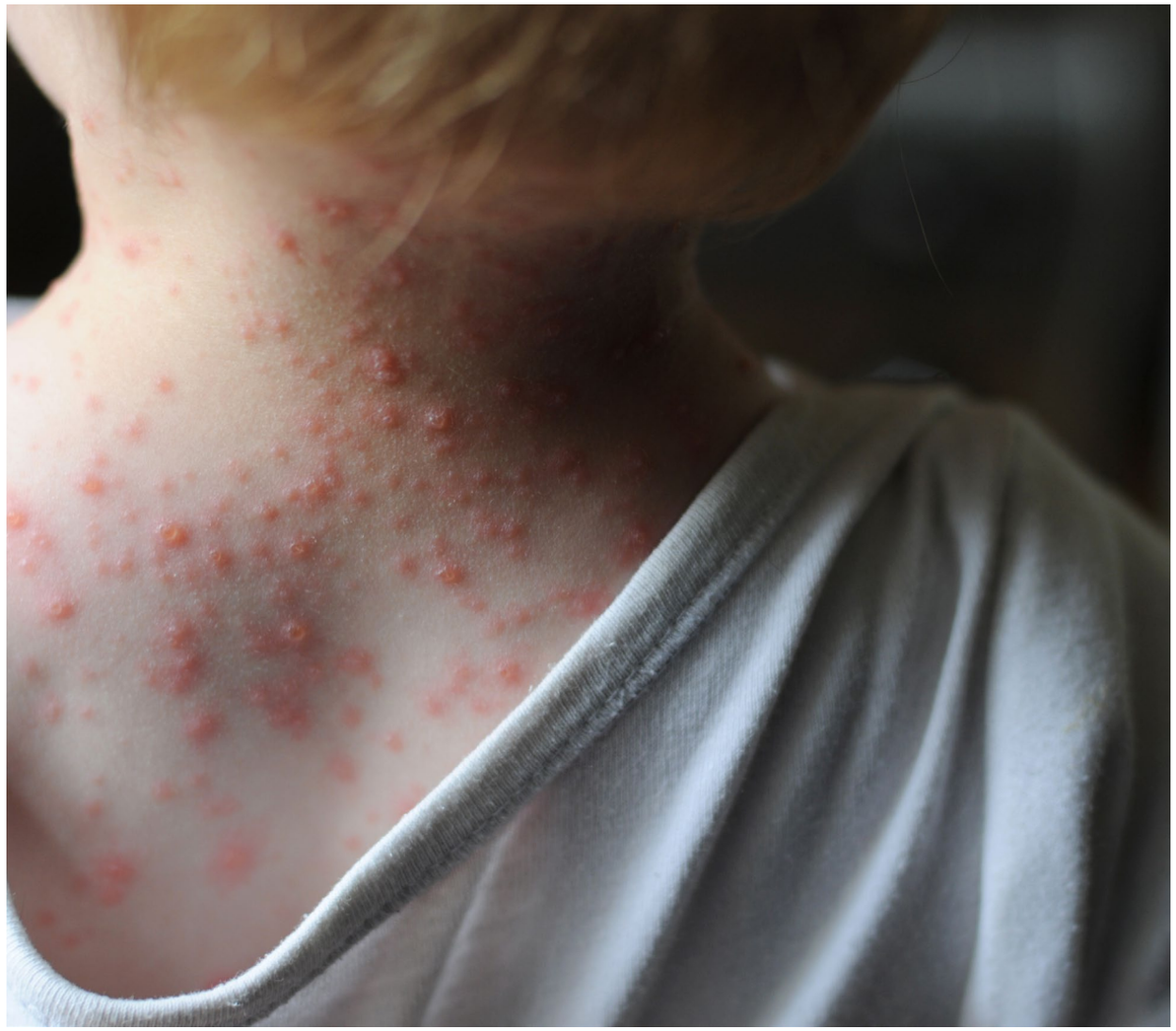
—Jason G. Goldman

Two for One: Chickenpox Vaccine Lowers Shingles Risk in Children

Immunization reduces the likelihood of a painful reemergence of the virus in kids

HEALTH ORGANIZATIONS recommend children receive the varicella vaccine at one year old to protect them against chickenpox, but the vaccine appears to have another benefit: it cuts the risk of shingles, a painful and potentially debilitating rash caused by the reactivated chickenpox virus, by more than half in children over two years old, according to a new study.

Approximately 38 per 100,000 children vaccinated against chickenpox developed shingles per year, compared with 170 per 100,000 unvaccinated children, researchers found. Furthermore, shingles infection rates were lower in children who received both recommended doses of the chickenpox vaccine compared with those who only got the first dose.



GETTY IMAGES

Chickenpox, a once common childhood virus that causes fever and a rash lasting up to a week, rarely causes death in children. Before the vaccine, two to three out of every 1,000 U.S. children who got the disease were hospitalized, and approximately 100 children a year died from it. It is often more severe in adolescents and adults.

Serious complications such as infection and brain inflammation can occur, as well as permanent scarring, but the bigger threat from chickenpox is what can happen years later. After an infection, the varicella virus remains latent in nerve roots and can reactivate to cause shingles, which typically strikes decades later and can

cause severe long-term nerve pain or vision loss. Formally called herpes zoster, the disease infects about a third of people who have had chickenpox, usually showing up in older adulthood, according to the U.S. Centers for Disease Control and Prevention. Shingles infection rates have been increasing for more than two decades. Although the risk increases with age, children can develop it as well, especially if their immune system is weakened.

About 91 percent of U.S. children are vaccinated against chickenpox, according to the most recent National Immunization Survey data, but that does not necessarily mean they cannot get shingles. The chickenpox vaccine is made with the live attenuated (weakened) varicella virus, so "not surprisingly, it can also become latent after vaccination," explains Anne A. Gershon, a professor of pediatric infectious disease at Columbia University. "The virus has been altered so the vaccine rarely causes symptoms, but once you've been immunized and after the natural infection, you carry the virus in your neurons for the rest of your life," says Gershon, who wrote an editorial accompanying the new study, which was published in June in *Pediatrics*, and who was not involved in the work.

Previous research with small groups found conflicting results regarding shingles rates in children vaccinated against chickenpox, with lower rates in older children but higher rates in toddlers. In the new study, researchers analyzed the medical records of nearly 6.4 million children (ranging from newborns to 17-year-olds) who received care at six health care organizations in the West, Northwest and Midwest from 2003 to 2014. They looked at records from the child's birth or entry into the health system up until age 18 (or leaving the system), so any shingles infections after age 18 were not included. Half the children were vaccinated for at least part of the full study period; the other half were not.

The authors found that one dose of vaccine reduced shingles infection by 78 percent—except in young toddlers. Shingles rates were significantly higher in vaccinated one-year-olds than unvaccinated ones, although this increased risk for vaccinated children vanished by age two. The authors suspect the higher risk in toddlers "could be related to the developing immune system in very young children," says lead study author Sheila Weinmann, a senior investigator at the Center for Health Research, Kaiser Permanente Northwest in Portland, Ore.

That does not mean delaying the vaccine past the recommended age of one year for the first dose is wise, she added. The longer children go without the first vaccine dose, the more likely they are to catch the wild chickenpox virus—"and maybe even pass it on to young infants who are too young to get vaccinated," Weinmann says. "So it probably makes more sense to stick with the current recommendation." (Three of Weinmann's co-authors have received research funding for other studies from pharmaceutical company Merck, which manufacturers the varicella vaccine.)

Even unvaccinated children appear to be benefiting from the vaccine's use. Despite a brief shingles uptick in unvaccinated children from 2003 to 2007, overall rates in children declined by 72 percent from 2003 to 2014. Four years after the CDC began recommending the second varicella vaccine dose in 2006, shingles cases in unvaccinated children began dropping rapidly, likely because of herd immunity, Weinmann says. Herd immunity refers to the inability of a disease to travel easily through a highly vaccinated population. In this case, herd immunity's effect on shingles rates would occur by protecting unvaccinated children from developing wild chickenpox in the first place, thereby preventing shingles later on. As they grow older, however, unvaccinated children would remain susceptible to chickenpox (and therefore shingles).

"This study makes it clearer than ever before that the benefits of the varicella vaccine go beyond simply preventing chickenpox," says Nathan Boonstra, a general pediatrician at Blank Children's Hospital in Des Moines, Iowa, who co-hosts the podcast Vax Talk and was not involved in the study. "There's very good evidence now that the vaccine prevents a serious complication of chickenpox down the road, and shingles is really awful," especially because it can show up anywhere on the skin, including the face and eyes, he notes. This study's large population size and 12-year duration, as well as the big difference in infection rates it found, will also help doctors explain

the vaccine's benefits to parents, Boonstra says.

Two vaccines exist against shingles: Zostavax for adults age 60 and older and the much more effective Shingrix, approved in 2017, for adults age 50 and older. But it is not yet clear if children vaccinated against chickenpox will need a shingles vaccine in older adulthood. "We need to continue to follow a cohort of children who have been vaccinated and see what happens," Gershon says, although she expects shingles will be less of a problem for them. There are not much data on adult shingles rates in the study group yet because the CDC first recommended the vaccine in 1996, so the first generation to receive it is currently in their early 20s. Shingles becomes much more common after age 50.

Nevertheless, the fewer children who are getting chickenpox in the first place, the fewer are likely to develop shingles later on. "Because vaccination coverage in the population has been increasing over time," Weinmann says, "probably these [shingles] rates will continue to drop."

—*Tara Haelle*

The U.S. Opioid Epidemic Is Driving a Spike in Infectious Diseases

Researchers around the country are scrambling to understand these outbreaks but lack solid data on case numbers

Injection drug users who abuse opioids such as heroin are more susceptible to infections than other people.

SPENCER PLATT *GETTY IMAGES*

OPIOID ADDICTION kills tens of thousands of people every year in the U.S., and the trend shows no signs of slowing. Now public health officials are worried about a surge in bacterial and viral infections linked to opioid misuse that threatens to compound the crisis.

This surge includes an unprecedented rise in bacterial infections—including those caused by *Staphylococcus aureus*, a bacterium that's frequently resistant to antibiotics—and a spike in new cases of HIV and hepatitis associated with injecting opioids that risks undoing decades of progress in corraling these diseases.

Research groups around the country are working to understand, identify and treat these outbreaks. But the lack of solid data on the number of new cases, and where they'll crop up next, as well as stigma associated with drug use that can prevent people with infections from seeking early treatment, is hindering efforts.

"This is like HIV all over again," says Judith Feinberg, an infectious disease physician at West Virginia University in Morgantown, comparing the current crisis with the HIV epidemic that dominated U.S. public health efforts in the 1980 and 1990s. "People are stigmatized; they don't feel they deserve to live. They hear people say it's a lifestyle choice."

Over the past 20 years the use of opioids, including prescription pain medications, heroin and synthetic drugs such as fentanyl, has skyrocketed in the U.S. As of 2017, there were roughly 15 opioid-overdose-related deaths per 100,000 people in the country, compared with three

per 100,000 in 1999, according to estimates from the U.S. Centers for Disease Control and Prevention.

AN AFFAIR OF THE HEART

One type of opioid-related infection that researchers are grappling with involves diseased heart valves. Bacteria such as *S. aureus* can enter the bloodstream as a result of practices such as needle sharing or not cleaning the skin before injecting a drug. If the infection reaches the heart, it can damage the valves. Severe cases can require a heart transplant.

In an ongoing study, microbiologist Cecilia Thompson of the University of North Carolina at Chapel Hill is sequencing DNA from heart valves collected from people who have had surgery to replace diseased valves with artificial ones. Thompson found that valves taken from people who had injected drugs were more likely to be infected with *S. aureus* than were those of nonusers.

Thompson presented her results in June at the American Society for Microbiology meeting in San Francisco. But these are just the latest observations of what seems to be a worrying trend. In a study published in January, researchers found a 13-fold increase in heart infections among people who misused drugs in North Carolina between 2007 and 2017. Until 2013, surgeons in the state used to perform fewer than 10 operations to treat drug-related heart infections, compared with more than 100 in 2017.

Opioids themselves—rather than the method used to inject them—could also be making people more susceptible to infection. Another study, also published in January, looked at more than 25,000 people treated at veterans' health facilities between 2000 and 2012. It found that people who took medium or high doses of prescribed opioids for pain management—especially people with HIV—were significantly more susceptible to pneumonia. It's unclear why, but research in monkeys suggests that some prescription opioids, such as morphine, can suppress the immune system.

In response to these results, researchers are devising ways to improve the diagnosis and treatment of infections—whether they're bacterial, viral or fungal—in opioid users. Identifying the pathogen that is causing an infection is crucial to treating it properly. Thompson says that her group plans to use next-generation sequencing techniques, which can test for a wider array of microbes in blood and tissue samples than current methods, to help them with their work.

"People are stigmatized; they don't feel they deserve to live. They hear people say it's a lifestyle choice."
—Judith Feinberg

CATCHING THE CULPRIT

Even when researchers know what's causing an infection, the pattern of outbreaks associated with drug use may differ from that of non-drug-related ones. This makes it difficult to anticipate where infections will occur.

But a computer model developed by Georgiy Bobashev, a data scientist at RTI International, a nonprofit research institute in Research Triangle Park in North Carolina, and his colleagues simulates drug users and their social networks to predict the location of opioid-related HIV outbreaks. The program considers factors that include whom users know, the type of heroin available to them—which could affect the presence of pathogens—and their experience with the drug.

The social component to predicting these outbreak patterns is crucial, Bobashev says. People who used drugs during the height of the HIV epidemic in the 1990s learned safe injection practices, he says, but newer users are more likely to use riskier methods, such as sharing needles. "They don't have good practices, and they don't have good connections with people who have been injecting drugs for a long time," Bobashev says.

In an unpublished analysis, his group's model predicted that HIV outbreaks related to opioids would be concentrated within small geographic pockets, rather than spread over a wider area, as researchers would expect with non-drug-related outbreaks.

Data from real life bolster this result. Previous opioid-related HIV outbreaks, including one in 2014 in Scott County, Indiana, followed this pattern. And in March the West Virginia health department announced an outbreak in Cabell County caused by a spike in new cases of HIV acquired through drug use. Historically, sex was the primary mode of HIV transmission, according to the state's health department.

The key to preventing and stopping the rise in opioid-associated infections is to treat opioid use as a disease without stigmatizing people who misuse drugs, says Carlos Del Rio, a global health researcher at Emory University.

A working group at the U.S. National Academy of Medicine, which Del Rio is leading, has started to develop a strategy for integrating care for infections and opioid use. "The opioid epidemic is going to be to [young medical students] what HIV was to me," Del Rio says. "You'd better get used to it."

—*Sara Reardon*

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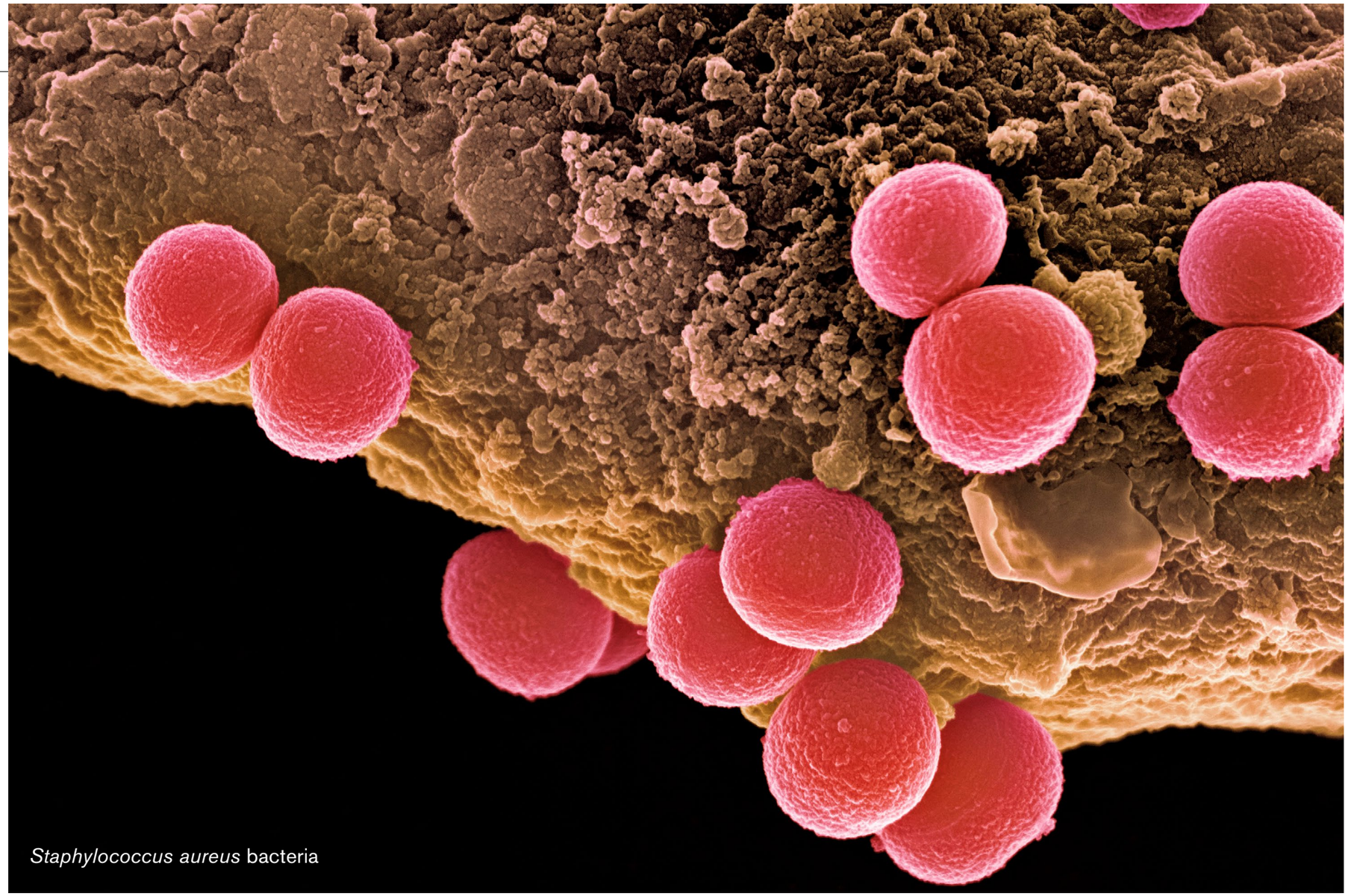


Staphylococcus aureus bacteria

GETTY IMAGES

Mind the Staph: London Is Crawling with Antibiotic-Resistant Microbes

The bacteria are not a major threat, but they could transfer their resistance to more dangerous pathogens

LONDON IS TEEMING with bacteria—some of which have developed resistance to antibiotics. These microbes are mostly harmless, but if they do cause an infection, it can be hard to treat. And there is a chance that they could transfer their resistance to more dangerous strains, experts warn.

In a new study, researchers in England and their colleagues found that frequently touched surfaces—such as elevator buttons, ATMs and bathroom-door handles—can be reservoirs of drug-resistant *Staphylococcus*, or staph, bacteria.

The researchers collected 600 samples from locations throughout East and West London such as hospitals, public washrooms and

ticket machines, finding 11 species of staphylococci. Nearly half of the samples—including 57 percent in East London and about 41 percent in less crowded West London—contained bacteria resistant to two or more frontline antibiotics. Just under half of the staph found in hospital public areas was drug-resistant, compared with 41 percent in community settings, the team reported in August in *Scientific Reports*.

"Resistance genes and elements present in these bacteria can spread to human pathogens and result in the emergence of new [antimicrobial-resistant] clones," says Hermine Mkrtchyan, a senior lecturer at the University of East London, who headed the team that conducted the research. "Although these bacteria are nonpathogenic, the increased levels of antibiotic resistance that we found in general public settings in the community and in hospitals pose a potential risk to public health."

Should people be worried?

"So long as you wash your hands after going out into public areas, it should be fine," says Richard Stabler, co-director of the Antimicrobial Resistance Center at the London School of Hygiene & Tropical Medicine, who was not involved in the work. "I certainly recommend washing your hands after being out in London."

Despite the high ick factor of the idea of touching potentially dangerous bacteria in familiar settings, Stabler concedes that these species are commonly found on skin, so it is no surprise that they would be found in public places where people are constantly shedding skin and microbes.

These bacteria do not pose a real danger right now, Stabler says, because although some of them were resistant to two common antibiotics, they cannot evade the entire medical arsenal. "This is potentially a problem out there, but at the moment, it's still quite containable," he says.

Antimicrobial resistance is a major public health threat across the globe, Mkrtchyan notes. Every year more than 700,000 people die because of it, and the toll is predicted to rise to 10 million by 2050. Resistance means patients will stay sick for longer, which increases the cost of health care, Mkrtchyan says. "Our research highlights that general public areas (part of our everyday life) can be reservoirs for multidrug-resistant bacteria and alerts us that concrete global efforts are required to tackle the problem."

Mkrtchyan and her colleagues previously found similar drug-resistant bacteria in a study of London hotel rooms. They are now comparing the genes of the 11 species found in both studies to better understand how they evade drugs and the physical environments that support their development and transmission.

Knowing about the presence of antibiotic-resistant bugs is useful, Stabler adds, because public officials can utilize the information to prepare and guide treatment. "It's okay that they're out there," he says. "We have to live with them rather than trying to exterminate them—because that doesn't work."

The study is a somber reminder that the overuse of antibiotics has consequences, says W. Ian Lipkin, a professor of epidemiology at Columbia University's Mailman School of Public Health, who was also not involved in the research. Lipkin has found similar results in studies of rats and mice in New York City subways and apartment buildings. A 2015 study by another group found that nearly half of the bacteria, viruses and additional microbes that were collected from the city's subway system did not match any known organism.

Lipkin and others blame global antibiotic resistance on the overprescription of antibiotics for viral infections and other situations where they will not help, the problem of patients not taking their medications as prescribed and the vast overuse of antibiotics in farm animals. "The good news is that if we restrict the use of antibiotics to situations where they are truly needed, bacteria will regain their sensitivity to antibiotics," Lipkin says.

Lipkin notes that some antibiotic resistance exists naturally. Researchers have found resistant microbes in isolated caves, he says, suggesting that some bacteria have evolved to tolerate natural antibiotics. But humans have dramatically increased the prevalence of these microbes by using antibiotics inappropriately.

The findings are concerning but not a reason to panic, Lipkin says. Similar drug resistance has been found in other places for years. "It's just another call to be more sensible about how we use antibiotics," he explains. Still, "the fact that they're there at all means that they're capable of moving into people."

—Karen Weintraub

A Year In, the Second-Largest Ebola Outbreak Continues to Rage

Despite vaccination and treatment efforts, the epidemic in Central Africa has resulted in 1,700 deaths and counting

Health worker takes a days-old baby suspected of having Ebola to a treatment center in the Democratic Republic of the Congo.

JOHN WESSELS *GETTY IMAGES*

THIS SUMMER MARKS the anniversary of the current Ebola outbreak centered in the Democratic Republic of the Congo (DRC). First declared on August 1, 2018, in the nation's province of North-Kivu, it has sickened more than 2,500 people and killed close to 1,700—making it the second-worst outbreak after the one between 2014 and 2016 in West Africa, which sickened more than 28,000 people and killed more than 11,000.

On July 17 the World Health Organization declared the latest outbreak a public health emergency of international concern—its highest level of alarm. Following this designation, the World Bank released up to $300 million for global response efforts. But despite the availability of funding, vaccines and treatment, people continue to be infected and die from the disease—including in areas where it was once stamped out. It is also now hitting more populous regions; a second confirmed Ebola death has recently been reported in Goma, a city of two million residents and a major travel hub.

"One year after the outbreak, certainly, we didn't expect it to be still going on," says Michelle Gayer, director of emergency health at the International Rescue Committee (IRC), a humanitarian organization that has been responding to the outbreak in more than 70 health facilities. "It's killing more people than it should, despite vaccination and treatments. It's still going on, and it is affecting more women than previous outbreaks." Some 57 percent of those infected are women, and about 18 to 20 percent are younger than 18, Gayer says. The outbreak was initially clustered in the north, in cities such as Beni,

and then moved farther south, she says. Beni had been free of new cases for some time—but in July or so, more than half of them have been in that city, she adds.

This Ebola outbreak is the first in which a vaccine is being widely used. Made by Merck, the vaccine has not been commercially licensed but is being given under a "compassionate use" protocol because Ebola is often a fatal disease. Health workers have employed a "ring vaccination" strategy, vaccinating those who have come into contact with people infected with the virus and the contacts of those contacts. The vaccine is 97.5 percent effective. But not everyone can be vaccinated before they get sick, and many people hide their disease because of the stigma, Gayer says.

Violence has roiled the DRC for decades, but Gayer does not think it is directly driving the outbreak's severity. Health care workers have been killed—not as a result of the country's ongoing military conflict but rather out of a mistrust of the response and a lack of knowledge about the disease they are battling.

"I think it comes back to one piece, really, which is around community engagement and trust," Gayer says. "I think that's probably been the most critical factor." The problems are an inadequate understanding of what people's needs are among Ebola responders and a failure to engage with them in the right way, she says. If you have malaria or don't have clean drinking water, someone telling you to wash your hands or to be careful if you have a fever because you might have Ebola "is very confusing," Gayer notes. "We want to be making sure that we're not neglecting children who have pneumonia or women who want to deliver babies" while treating the Ebola outbreak.

Gayer's IRC colleagues regularly sit down face to face with groups of people in villages and towns affected by the epidemic, she says. They meet with women who want to know what happens if they are pregnant, for example. And they have invited community members to come to their clinics and help design the isolation structures for patients "so they don't look too scary," she says. People who have survived Ebola are also getting involved in helping treat patients.

But as new cases continue to crop up, an end to the outbreak remains elusive. "Right now we can say there are no clear signs of any significant slowing down," says Chandy John, president of the American Society of Tropical Medicine and Hygiene. He says the emergency declaration and the World Bank's $300 million will likely help, but more funding and support are needed. "If countries and organizations band together to get the needed funds, I think this epidemic can be contained," he adds. "On the other hand, the second case in Goma highlights the potential for spread beyond the current areas. So the need for additional work on the ground in all of these areas is urgent."

Gayer agrees: "I do believe that we will succeed, but it's going to take a long time," she says. "And there's no reason why the disease itself doesn't become endemic in the DRC. And that's something else that we have to deal with if that were to arise."

—*Tanya Lewis*

Editor's Note (8/6/19): This story was edited after posting to correct the figure for the percentage of those infected who are women and descriptions of causes of violence against health care workers.

Alarming Surge in Drug-Resistant HIV Uncovered

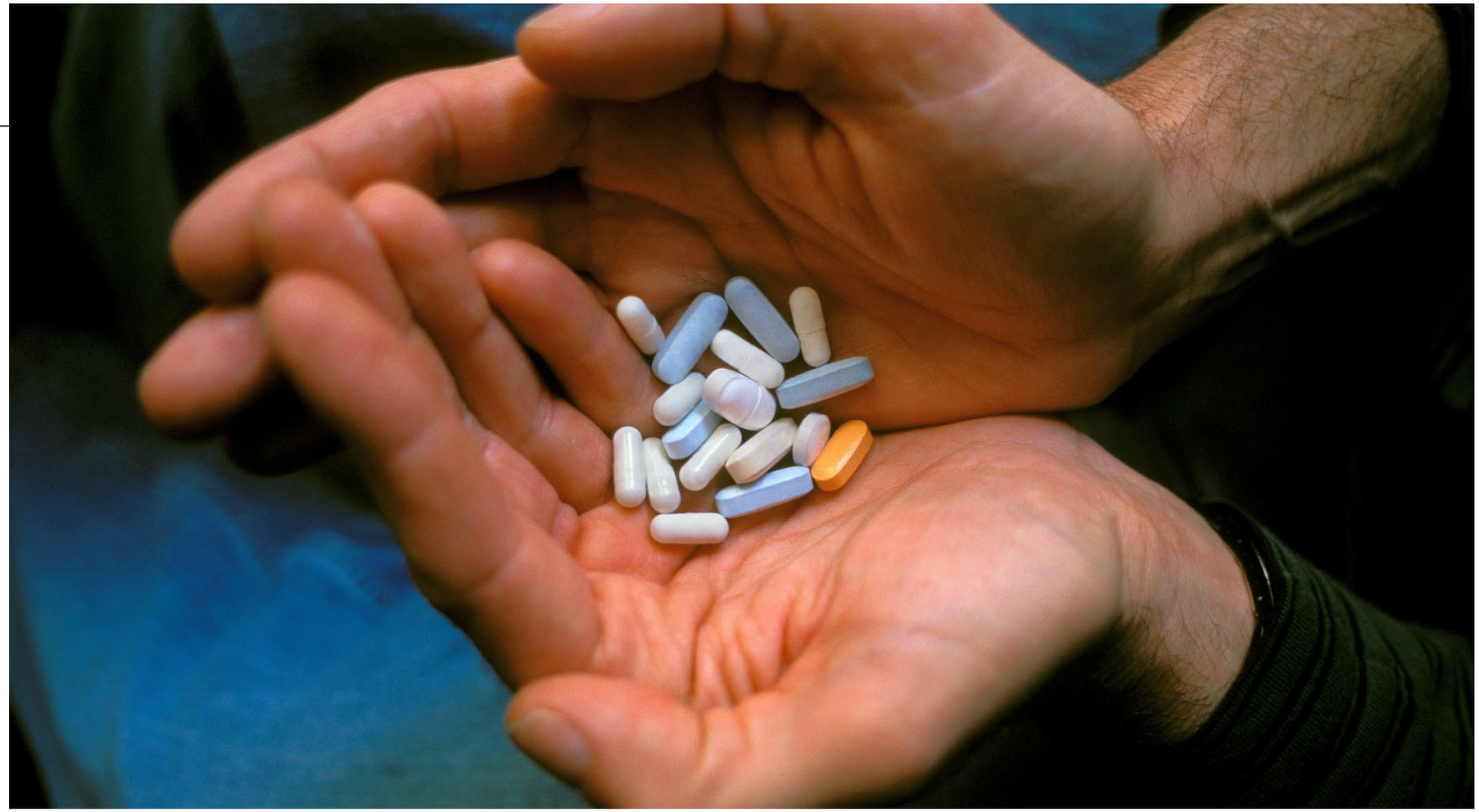
The drug-resistant form of the virus has been detected at unacceptable levels across Africa, Asia and the Americas

HEALTH AUTHORITIES HAVE uncovered an alarming surge in resistance to crucial HIV drugs.

Surveys by the World Health Organization reveal that in the past four years, 12 countries in Africa, Asia and the Americas have surpassed acceptable levels of drug resistance against two drugs that constitute the backbone of HIV treatment: efavirenz and nevirapine.

People living with HIV are routinely treated with a cocktail of drugs, known as antiretroviral therapy, but the virus can mutate into a resistant form.

The WHO conducted surveys from 2014 to 2018 in randomly selected clinics in 18 countries and examined the levels of resistance in people who had started HIV treatment during that period.



BRUCE FORSTER *GETTY IMAGES*

More than 10 percent of adults with the virus have developed resistance to these drugs in 12 nations. Above this threshold, it is not considered safe to prescribe the same HIV medicines to the rest of the population because resistance could increase. Researchers published the findings in July in a WHO report.

"I think we have kind of crossed the line," says Massimo Ghidinelli, an infectious disease specialist at the Pan American Health Organization in Washington, D.C.

Overall, 12 percent of women surveyed had a drug-resistant form of HIV, compared with 8 percent of men.

Particularly concerning, says the report, is the high level of resistance in infants with HIV in sub-Saharan Africa. Between 2012 and 2018 about one half of newly diagnosed infants in nine of the countries in this region had a form of HIV that was resistant to efavirenz or nevirapine, or both.

The causes of drug resistance remain elusive, says Silvia Bertagnolio, an infectious disease physician at the WHO in Geneva, Switzerland, and co-author of the report. But drug-resistant HIV might develop when people interrupt treatment, she suggests.

For example, many women living with the virus might have taken antiretrovirals during pregnancy to prevent their babies from becoming infected but stopped after delivery. The WHO recommended this practice until 2015, when it suggested that pregnant and breastfeeding women use the drugs for life.

The prevalence of resistance in people who restarted efavirenz and nevirapine after interrupting treatment was much higher (21 percent) than in first-time users (8 percent).

People living with HIV might go on and off the drugs for several reasons. Stigma plays a huge part, Bertagnolio says; they might not want to be seen picking up their medicines. Drug shortages at clinics could also contribute, the report noted.

In response to the evidence, the WHO has recommended that countries use dolutegravir, which is more effective and tolerable than other therapies, as the go-to HIV drug. The likelihood that the virus will develop mutations and, eventually, resistance is lower with dolutegravir than with other antiretrovirals, says Roger Paredes, an infectious disease physician at the Germans Trias i Pujol University Hospital in Barcelona. "We have to encourage a worldwide transition to dolutegravir," he adds.

Bertagnolio agrees but calls for caution. If treatment delivery is poor or patchy, resistance could emerge. "We don't want to find ourselves in the same situation we're in."

—Emiliano Rodríguez Mega

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Anorexia May Be Linked to Metabolism, a Genetic Analysis Suggests

A large, correlation-based study identifies eight genome regions associated with the eating disorder

ANOREXIA HAS ONE of the highest mortality rates of any psychiatric disorder, and scientists are still perplexed by its causes. Now, however, a new study has examined the genomes of tens of thousands of people and identified eight chromosome locations that may increase vulnerability to the illness. Some of these locations have been linked to metabolic problems—suggesting that the causes of anorexia may not be purely psychological.

Anorexia nervosa, as it is officially known, is an eating disorder primarily associated with an extremely low body mass index (BMI), usually accompanied by an aversion to eating and a distorted body image. It affects about 1 to 4 percent of women and 0.3 percent of men. Previous studies in twins suggest it has a 50 to 60 percent heritability, meaning 50 to 60 percent of the variability of the traits associated with anorexia can be explained by genetic differences among people, with the remainder linked to the environment or other influences. One of the disorder's most insidious features is that many patients are able to restore their body to a normal weight but have trouble keeping the pounds on.

"We all know how hard it is to lose weight. Yet somehow [people with anorexia] have this capacity to get down to a dangerously low weight and stay there," says study co-author Cynthia Bulik, a professor of eating disorders at the University of North Carolina at Chapel Hill and the Karolinska Institute in Sweden. "It has been explained psychologically—but it would take such an enormous amount of willpower to do that."

In treatment centers, patients can be nourished to a healthy BMI, Bulik says, but "we send them back out, and their weight just starts dropping like a stone again." The trend seems almost the inverse of obesity, in which patients can lose weight quite easily, but it often returns. "We don't know what the mechanism is here yet," she says. "It's just something that we've seen clinically for years but haven't thought about as potentially [involving] opposite ends of the same underlying process."

GETTY IMAGES

Bulik and her colleagues published a study in 2017 that analyzed the genomes of about 3,500 people with anorexia. In it, they identified the first chromosome location, or locus, to be correlated with the disorder, hinting at a possible metabolic link. Their new study analyzed dozens of data sets containing a total of nearly 17,000 people with anorexia and more than 55,000 healthy controls. The subjects were from 17 countries, and all of them had European ancestry.

This time the researchers identified eight genetic loci linked to the disorder, although Bulik says there

are likely hundreds. Some of the eight were associated with psychiatric illnesses—but others were associated with metabolic traits, even after the researchers controlled for BMI. This result suggests the risk of developing anorexia may be linked to metabolic factors, the researchers report in the study, which was published in July in *Nature Genetics*.

"There's no question that this is an extremely important study and is aiming to take state-of-the-art methods and use them to examine the genetic risk factors that may be at the base of the challenging disorder of anorexia nervosa," says Evelyn Attia, a professor of psychiatry at Columbia University Irving Medical Center, who was not involved in the work. The findings are correlational, however, and do not conclusively prove that metabolic factors are among the causes of the disorder, Attia notes.

Nevertheless, the study's conclusions increase our understanding of genetic contributors to anorexia. Pharmacogeneticists may be able to use them as a starting point to develop new treatments, Bulik says. "Right now we have no medications effective in treatment of this illness," she says. "We're starting at zero."

Attia agrees that learning more about the genetics involved is a helpful first step toward therapies. "We're in the early phase of using these genetic results to directly inform new treatments," she says. But she adds that understanding more about what contributes to the development of this complex illness—notoriously hard to treat despite being known for centuries—is "tremendously exciting."

Environmental influences are also thought to play a role in anorexia's development, but they are difficult to measure. Dieting is a known risk factor—most people who diet, however, do not go on to develop the disorder. "Most of us, when we get hungry, we feel worse. And we get kind of grumpy and irritable and start foraging and do whatever we can to find food," Bulik says. Yet "people who are predisposed to anorexia often say that they feel sort of irritable and anxious at baseline, and starvation actually makes them feel better." Understanding this paradox would go a long way toward improving treatment, she says.

Anne Becker, a professor of global health and social medicine at Harvard Medical School, has conducted studies of body image and eating disorders among women in Fiji. Becker traveled to the archipelago nation in the early 1980s, describing its strong food culture and lack of weight stigma. She went back in 1995 and 1998—before and after television became widespread in the country—and noted a striking increase in the number of girls who reported "purging" themselves to look more like women they saw on TV.

Becker says science still has an incomplete understanding of how social norms, food insecurity and social determinants of poor health affect vulnerability to the disorder. She praises Bulik and her colleagues for their rigorous study of the genetic factors involved, adding, "I hope, in the future, that such studies can also encompass more global diversity and, especially, populations in the global south, which have been neglected in eating disorders research."

Environmental factors may contribute to the pursuit of thinness at the core of anorexia nervosa but do not, by themselves, cause eating disorders, Attia says. Currently in Western society, "we are in an environment flooded with images of idealized thin bodies," she says "[yet] rates of anorexia nervosa in Europe and North America are relatively low and have not changed much in recent years." The social context may simply increase the risk of eating disorders such as anorexia among individuals who are biologically susceptible to them.

To look deeper, Bulik says she and her team plan to increase the size of their study sample and to diversify it by including more people of African and Asian ancestry. Although their latest paper had a large number of subjects, it was still relatively small by the standards of such genetic-association studies. And there are many other eating disorders besides anorexia whose genetic involvement has yet to be explored.

But this study is an important step. "For now this [research] actually gives an explanatory model to a lot of patients and families who have just been perplexed by this illness for a long time," Bulik says. "It can be really encouraging when they're on that difficult path of recovery and really need that kind of help."

—Tanya Lewis

First Steps to a Revolution

Electrical stimulation has promised huge gains for people with paralysis. Now comes the hard part–getting beyond those first steps

By Cassandra Willyard

Rob Summers has a complete spinal injury that doctors said would prevent him from walking.

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Cassandra Willyard is a science journalist based in Madison, Wis.

ROB SUMMERS WAS FLAT ON HIS BACK AT A REHABILITATION institute in Kentucky when he realized he could wiggle his big toe. Up, down, up, down. This was new—something he hadn't been able to do since a hit-and-run driver left him paralyzed from the chest down. When that happened four years earlier, doctors had told him that he would never move his lower body again. Now he was part of a pioneering experiment to test the power of electrical stimulation in people with spinal cord injuries.

"Susie, look, I can wiggle my toe," Summers said.

Susan Harkema, a neurophysiologist at the University of Louisville, sat nearby, absorbed in the data on her computer. She was incredulous. Summers's toe might be moving, but he was not in control. Of that she was sure. Still, she decided to humor him. She asked him to close his eyes and move his right toe up, then down, and then up. She moved on to the left toe. He performed perfectly.

"Holy shit," Harkema said. She was paying attention now.

"How is that happening?" he asked.

"I have no idea," she replied.

Summers had been a university baseball player with major-league ambitions before the vehicle that struck him snapped all the ligaments and tendons in his neck, allowing one of his vertebra to pound the delicate nerve tissue it was meant to protect. Doctors classified the injury as complete; the motor connections to his legs had been wiped out.

When Harkema and her colleagues implanted a strip of tiny electrodes in his spine in 2009, they weren't trying to restore Summers's ability to move on his own. Instead the researchers were hoping to demonstrate that the spine contains all the circuitry necessary for the body to stand and to step. They reasoned that such an approach might allow people with spinal cord injuries to stand and walk, using electrical stimulation to replace the signals that once came from the brain.

So, when Summers intentionally moved his toes, Harkema was dumbfounded.

Prevailing wisdom has long held that spinal cord injuries represent severed connections between the brain and the extremities. For decades researchers have focused on repairing those connections, for example, with stem cells. But findings from Harkema's group and other laboratories suggest that some connections remain intact, even for people with the most severe damage. Electrical stimulation seems to help to amplify the messages being sent across the injury and to reestablish these links.

The surprise awakening of Summers's nerve connections is part of a string of advances that has invigorated research into spinal cord injuries. Last year labs in Kentucky, Minnesota and Switzerland made headlines with a spate of case studies. Stimulators that were originally designed to treat chronic pain have now helped about a dozen people with paralysis to wiggle their toes, flex their legs or walk with support—for up to one kilometer in some instances.

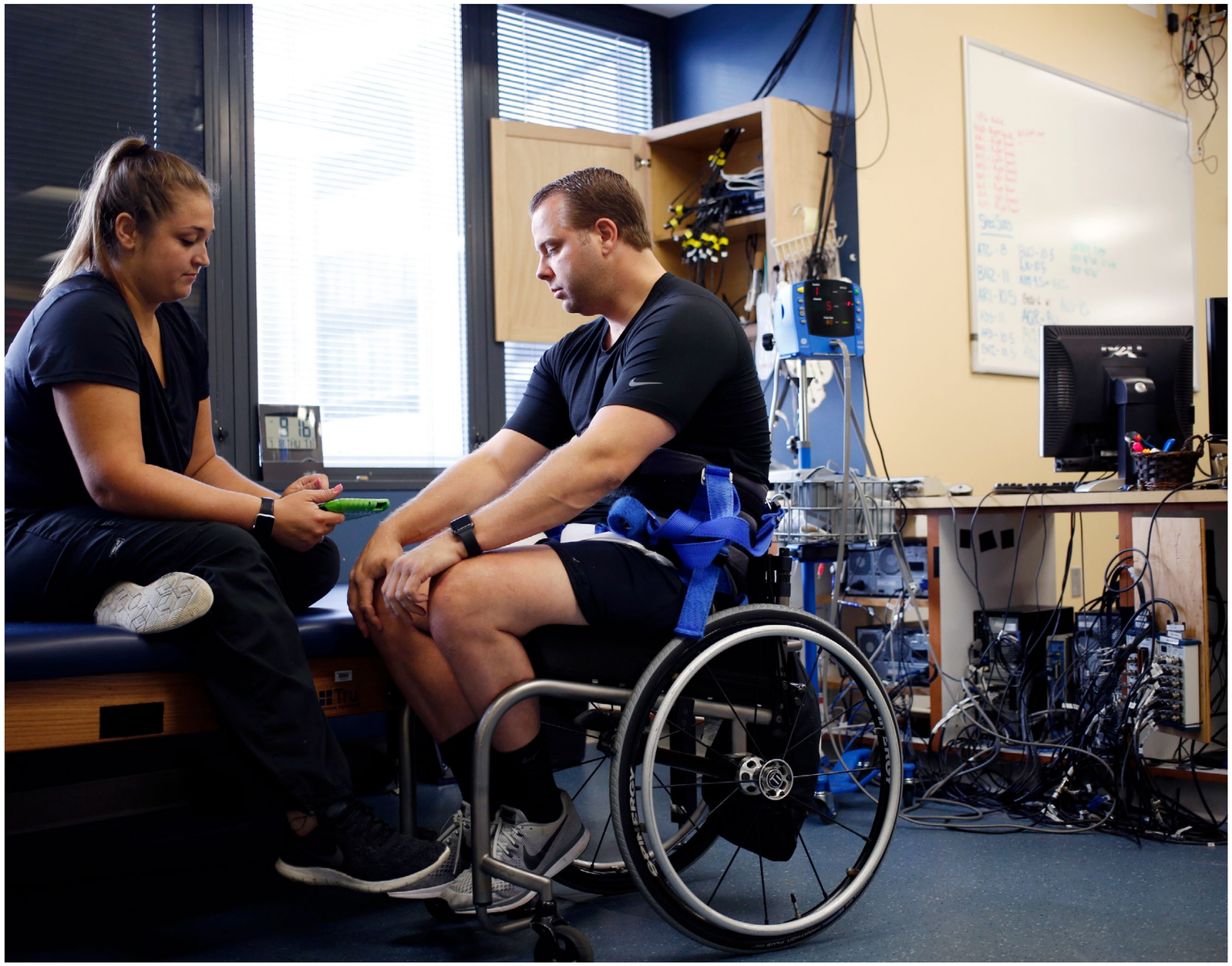
But the devices also seem to offer broader benefits. Some study participants saw improvements in blood pressure, bowel and bladder control and sexual function—abilities that people with spinal cord injuries often value more than the use of their legs. In some cases, these benefits persisted even after the stimulators were turned off. The results have bolstered hopes for an improved quality of life, even for people who were paralyzed years or decades ago, and the findings are upending conventional wisdom about spinal cord injuries. "This is a new ball game," says Reggie Edgerton, a physiologist at the University of California, Los Angeles, who has been closely involved with the work.

The waiting lists to get into stimulation trials are now

thousands of names long. And at least one hospital has begun offering the experimental procedure—at a cost of tens of thousands of dollars—without formal approval or a full reckoning of the risks and benefits involved.

To some, the hype sounds familiar. The quest to cure paralysis has cost hundreds of millions of dollars and has so far resulted in little more than bold predictions and dashed hopes. Actor Christopher Reeve, one of the most recognizable public faces of spinal cord injury, firmly believed he would walk again thanks to the burgeoning field of stem cells. "I know there's a cure coming for the kind of injury that I have," Reeve said in a 2001 interview, three years before he died. But nearly two decades later that long-promised cure has yet to materialize.

The field is at a crucial juncture as it determines how to translate miraculous-sounding results into a workable therapy, says Keith Tansey, a neurologist at the Methodist Rehabilitation Center in Jackson, Miss. Researchers still don't entirely understand how stimulation works. "We've got to learn more about this," he says. "We've got to worry less about whether we looked good on the cover of *Time* magazine and more about whether we're really going to move toward helping patients."



After two years of physical training, Summers had an epidural stimulator implanted in his back.

A PATTERN FOR PROGRESS

The path to Summers's toe wiggle began with cats walking on treadmills.

In the 1970s Edgerton started working with a long-studied model for understanding locomotion. Cats that have had their spinal cord severed can be suspended over a treadmill and trained to walk again by simply guiding their legs in a steplike motion. With practice, the animals will adjust their gaits to match the speed of the treadmill and even switch directions—with no input from the brain required. The spinal circuitry propelling them, called a central pattern generator, controls the movements, and Edgerton was trying to understand how it worked.

In 1993, when Harkema joined Edgerton's lab, she wasn't all that interested in the spine—she says that she chose U.C.L.A. for the weather. But as Harkema began working with the cats, she became fascinated by how the animals regained so much function. Edgerton tasked Harkema with setting up a similar experiment in humans who had spinal cord injuries. Perhaps regimented training designed to awaken a central pattern generator would allow them to walk, too.

It had some success. Step training on the treadmill with bodyweight support helped people with spinal cord injuries, especially less severe injuries, improve their ability to move. But Harkema and Edgerton wanted to see a bigger effect. Epidural stimulators, which deliver

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current to the lower part of the spinal cord, seemed like a good option.

The devices have been used to treat chronic pain since the 1960s. But researchers had seen evidence early on that they could do more. In people with spinal cord injuries, for example, the stimulators seemed to reduce the rate of involuntary spasms. In one study, researchers examined people with spinal cord injuries who had been implanted with stimulators for this reason. When scientists turned up the stimulation, participants began moving their legs rhythmically and automatically. "It was—still is—probably the most direct evidence for a so-called central pattern generator for locomotion in humans," says Karen Minassian, a medical physicist at the Medical University of Vienna. There were even hints from a case study that stimulation could restore the ability to move voluntarily, at least in people with incomplete injuries: those who had retained some sensation and movement in their lower bodies.

In 2002 researchers in Arizona reported suspending a 43-year-old man with a spinal injury over a moving treadmill while stimulating his spine. He also had an incomplete injury. After training and stimulation, he was able to walk with "a near-effortless, coordinated locomotion pattern," according to the authors.

Harkema and Edgerton began discussing the possibility of using the same approach. They just needed a test patient to prove the principle. Summers was determined to be their guy.

Researchers control the electrode array in Summers's spine using a tablet.

STANDING DELIVERED

During the summer of 2006, Rob Summers was living and breathing baseball. A pitcher for the Oregon State University Beavers, he had just missed playing in the College World Series championship because of a hip injury. So he was training hard to secure a starting position for the upcoming season. One night, as he retrieved a gym bag from his car, he heard a vehicle speeding down the street. He caught just a glimpse of the headlights before it struck him and sped off. Summers lay on the ground bleeding until early the next morning, when a neighbor found him.

Summers doesn't recall much about the month he spent in hospital, but he does remember that the doctors waited until he was surrounded by family to tell him he was paralyzed. They didn't mince words: "You're never going to walk. You're never going to feel anything." Summers refused to believe it. The doctors didn't know how stubborn he was, how hard he could work. "I'm going to beat this," he told his parents.

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After a year of intense rehab, Summers had regained some sensation in his limbs, but he still couldn't move his lower body; his injury was considered motor complete. Yet Summers was convinced he just needed the right therapy. So he and his parents sent out more than 200 e-mails to research facilities around the world—"Israel, Europe, Russia, Cuba, Japan, China, South America, you name it," Summers says.

The letter-writing campaign led him to a rehabilitation training workshop in Texas, where he met Harkema. By then, she had launched her own lab at the University of Louisville. In September 2007 Summers flew there with his dad to tour the facility. When Harkema mentioned that her team had plans to look at epidural stimulation, Summers was stoked. He was supposed to fly back to Portland the next day, but instead he rented an apartment and called Harkema. "I'm in," he said. "I'll see you tomorrow at 8 A.M."

In Louisville, Summers underwent more than two years of intensive rehab to assess whether he had any capacity for recovery without stimulation. Then, in December 2009, Harkema's team fitted him with an epidural stimulator. They placed a 16-electrode array in the space between his vertebrae and his spinal cord. A wire connected the array to the stimulator, a rechargeable device about half the size of a deck of cards, which sits just above his buttocks. Doctors controlled the stimulator remotely.

When the researchers turned the stimulator on, Summers immediately felt a tingling sensation. Three days later the team tried to get him to stand. Initially a harness supported all of his weight. The team gradually began to reduce that assistance until Summers was standing independently. He looked at his leg muscles contracting in the mirror. "That can't be real," he thought. Then he looked around the room. His mother was in tears. "People were crying and yelling and asking me 'How is this happening?'" Harkema says. "It was a little pandemonium."

"We really try to activate the spinal cord as the brain is trained to do."
—Grégoire Courtine

Still, that was nothing compared with the commotion that erupted six months later, when electrical stimulation allowed Summers to wiggle his toes. Harkema's team hoped to kick-start the circuitry required for standing and stepping in the spine and legs, but they weren't expecting to get any help from the brain. Harkema called Edgerton at his lab in Los Angeles to tell him about Summers's toes. "Oh, God, this can't be true," Edgerton remembers thinking. "Everybody's going to think we're quacks."

STEPS TAKEN

When Harkema and her colleagues published the details of Summers's case in 2011, many scientists were skeptical. "I did not believe it," says Kendall Lee, a neurosurgeon at Mayo Clinic in Rochester, Minn. Everything Lee had been taught told him that once connections to the brain are lost, they don't come back.

But gradually, the evidence began to mount. Harkema and her team published another study in 2014 involving Summers and three more people, including two who had had no movement or sensation in their lower bodies. All regained some voluntary movement. Soon others were trying the approach in humans and looking to see whether it could allow trial participants to take steps off the treadmill.

Grégoire Courtine, a neuroscientist at the Swiss Federal Institute of Technology in Lausanne (EPFL), had also studied with Edgerton, starting at U.C.L.A. a couple of years before Harkema left for Louisville. He moved to Europe in 2008 to study epidural stimulation in rodents and eventually in rhesus macaques.

By 2015 Courtine felt ready to test the technology in humans. His team used the same off-the-shelf pain stimulator Harkema had used but tweaked the software so that the device could deliver patterns of stimulation timed to coincide with the act of walking. "We really try to activate the spinal cord as the brain is trained to do," Courtine says. And there was another major difference from Harkema's studies: Courtine's team recruited people with incomplete injuries, hoping that it might be easier to show recovery in this group than in people with complete injuries.

Meanwhile Edgerton helped a third group, at the Mayo Clinic, get another trial under way. In 2016 Lee, rehabilitation scientist Kristin Zhao and their colleagues set out to replicate Harkema's results. They recruited two participants who did nearly six months of physical therapy before being implanted with the stimulator and then another 10 months with the stimulator turned on. The aim was to show that stimulation and training could improve their ability to stand and move their lower bodies voluntarily. But the first participant achieved those goals so quickly that the researchers decided to add walking to the protocol.

In autumn 2018 the three teams published results on the first eight trial participants. All told, six managed some form of walking across the ground with assistance such as harnesses, crutches or parallel bars. The other two experienced benefits, too: with stimulation, they managed to sit and stand independently, and one could take some steps on a treadmill with support.

"It was really just this past year that the critical mass

built up," says Chet Moritz, a rehabilitation medicine researcher at the University of Washington. "That's really where it started to feel like a breakthrough."

HOPES AWAKEN

The field has seen "breakthroughs" before, though. Reeve argued passionately and convincingly to fund stem cell research in the hope of repairing nerve damage. Videos have shown paralyzed rats whose spines had been injected with cells miraculously regaining the ability to walk or use their paws. A cure has often seemed close at hand.

Replicating those results in people has proved difficult, however. Although there are ongoing human trials with stem cells, some of which show promising results, excitement for the approach—from funders, patients and researchers—has dwindled, Tansey says. Other high-tech approaches to reversing paralysis, such as brain-machine interfaces, are still being developed. Powered exoskeletons are already on the market, but they're expensive. And they don't address the underlying problem of restoring neural connections. "We've all heard 'five years down the road there's going to be a magic pill' or whatever," says Peter Grahn, a neuroscientist at Mayo Clinic, who was a joint first author on the stimulation study and who has a spinal cord injury himself. "That's what you hear all the time because five years is long enough that everyone forgets."

But to a lot of interested onlookers, stimulation shows promise that goes beyond the hype. In particular, it already has a long history in treating chronic pain, says Matthew Rodreick, executive director of Unite 2 Fight Paralysis, an advocacy group for spinal cord injuries based in Hood River, Ore. "This is a device that's on the market and has been implanted in hundreds of thousands of people," he says. That doesn't mean the strategy will succeed, but at least the path to approval has been cleared, he says.

The walking that Summers and others have achieved requires support and close monitoring. But it is only one of the benefits they report experiencing.

There are still major questions as to how stimulation works and why some benefits seem to persist after the stimulators are turned off. It is becoming clearer that for many individuals with injuries considered complete, some neural pathways for motor control from the brain do survive. They're just dormant and cannot elicit a response in the neurons below the site of the injury. Epidural stimulation seems to make neurons more excitable—more likely to fire when confronted with signals from the brain telling them to move a toe or to start walking. Electric current can force neurons to fire and muscles to contract, but that's not what's happening for those

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who have begun to walk. “The person doesn’t have to step,” Moritz says. “It’s not robotic.”

As for why some benefits persist in some participants, there are a couple of possible explanations. Stimulation might allow the individuals to participate more fully in rehabilitation, strengthening muscle and nerve connections through exercise. Or it might promote plasticity, which helps to rewire the circuits around the injury. That’s a particularly tantalizing possibility because it could mean that there is potential for improvement over time.

Still, researchers have yet to work out who might benefit most from the procedure. Harkema says that all 20 people who have been implanted in Louisville have regained some voluntary movement. But to Tansey, it seems clear that not everyone with a spinal cord injury will improve. He wants to see a way to screen individuals—because implanting a medical device inside the spine is no trivial matter. There are risks.

Although the stimulators are approved by the U.S. Food and Drug Administration to treat chronic pain, they do occasionally cause unwanted, even dangerous, side effects. Recipients report that they have been shocked, been burned or suffered nerve damage that led to muscle weakness or even paralysis. A 2018 investigation by the Associated Press found that stimulators have garnered almost 80,000 injury reports since 2008—more than for any other medical device, apart from insulin pumps and metal hip replacements.

And there might be risks that are specific to individuals with spinal cord injuries, who are more susceptible to infections and who often have low bone density. One participant in the latest study from Harkema’s team broke a hip, which required multiple surgeries that led to an infection.

There have also been some reported problems that are difficult to explain. In 2015 Xander Mozejewski, who has a spinal cord injury, joined one of Edgerton’s trials to test the effect of noninvasive “transcutaneous” stimulation, in which electrodes are placed on the surface of the skin. He later began experiencing spasms and pain in his lower body that grew steadily worse. In 2016 doctors implanted an epidural stimulator to try to control the spasms, but the device seemed to make things worse, and Mozejewski eventually had it removed. In 2018 he filed a medical malpractice suit against U.C.L.A., Edgerton, NeuroRecovery Technologies—the company in San Juan Capistrano, Calif., that Edgerton co-founded—and others. The case is ongoing, but in a statement to *Nature,* Nick Terrafranca, chief executive of NeuroRecovery Technologies, said: “The stimulator has been used with over 60 study participants with no adverse event reported that was directly related to use of the device developed and provided by the company.” Terrafranca adds that side effects the company recorded, including muscle spasms, “were transient in nature.”

Harkema’s research has also garnered some criticism. In 2015 one of her colleagues sent letters to the University of Louisville’s Institutional Review Board, its Human Subjects Protection Program and the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR), which funded some of her work, expressing concern over four of Harkema’s studies. An internal investigation revealed that the scientists had failed to track and monitor adverse events, had deviated from study protocols and had misplaced records. As a result, the NIDILRR defunded one of the studies, a $914,000 investigation into the effects of a muscle relaxer and treadmill training on people with spinal cord injuries. The U.S. Office for Human Research Protections also conducted an investigation but did not impose sanctions on Harkema. The agency also said that corrective actions taken by Harkema’s team had adequately addressed the noncompliance.

Harkema acknowledges that her team wasn’t keeping records perfectly, but she denies all allegations of serious wrongdoing, especially the accusation that her team put patients at risk. “Anyone who visits our research program is actually astonished by all of the things that we put in place in order to protect our research participants,” she says.

Her research has continued apace. The Christopher & Dana Reeve Foundation in Short Hills, N.J., is supporting work to test epidural stimulation in 36 more individuals at the lab in Louisville. As of July, 11 people had been implanted with stimulators.

BEYOND THE FIRST STEPS

In societies built for people without disabilities, walking has taken on an outsized importance. “Walking and standing is sexy,” says Jennifer French, co-founder of the Neurotech Network, a nonprofit organization in St. Petersburg, Fla., that is dedicated to helping people with impairments access neurotechnology devices. “It gets people excited.”

But walking isn’t everything, says Kim Anderson, a researcher at Case Western Reserve University, and president of the North American Spinal Cord Injury Consortium. In 2004 she conducted a survey of nearly 700 people with spinal cord injuries. Regaining arm and hand function was by far the highest priority for people with quadriplegia, followed by regaining sexual function. For people with paraplegia, the most desired improvement was in sexual function, followed by bowel and bladder control and reducing the risk of autonomic dysreflexia, a life-threatening condition characterized by a spike in blood pressure and a drop in heart rate.

After Stefanie Putnam broke her neck in a swimming pool, walking was the least of her concerns. The injury left her immobilized from the neck down, and she couldn’t breathe on her own. “I wasn’t thinking, ‘Let’s stand, let’s walk,’” she says. “I was like, ‘Let’s live.’”

Even after she regained the ability to breathe, she still had problems, particularly with maintaining normal blood pressure. Medication and three sets of corsets couldn't keep it high enough to stop her from fainting. She would pass out six or seven times a day. She couldn't drive a vehicle. She couldn't be alone. And when she started taking university classes, her parents had to tape a sign to the back of her wheelchair advising bystanders to tilt Putnam back if they found her unconscious. "I was so sick of doctors just telling me again and again, 'This is the way it's going to be,'" she says.

In 2017 Putnam moved to Louisville to join another of Harkema's studies—focused not on walking but on the cardiovascular system. For Putnam, the effects of stimulation were immediate and profound. She hasn't passed out in months. She no longer needs round-the-clock care, and she can drive again. The other three participants in the study also showed significant improvements in their blood pressure.

David Darrow, a sixth-year neurosurgery resident at the University of Minnesota Medical School in Minneapolis, has seen countless injuries like those sustained by Putnam and Summers. "It was kind of the worst part of my job," he says. He would repair the structure of the spine knowing that there was nothing he could do to restore its function. So when he heard Edgerton talk about the promise of epidural stimulation at a conference in 2015, "I was just blown away," he says. "I just couldn't figure out why there weren't like two dozen centers working on this."

In between therapy sessions, Summers gets support from Bear, his service dog.

Darrow suspected the findings might be bogus, but he wanted to find out for himself. So he set out to design an entirely new kind of study. Other groups have tested epidural stimulation in combination with intensive rehab before and after the implant. Darrow wanted to know what effect stimulation would have on its own.

The study differs from the other trials in another important way: the experiments are not solely focused on standing or walking. His group is looking instead at voluntary movement and improvements in cardiovascular function, bladder and bowel function, and sexual function.

Darrow and his team have implanted 10 people with stimulators, and in March they published results on the first two participants. Both regained some voluntary movements, such as wiggling their toes and lifting their lower legs. They also saw improvements in bowel and bladder function. Stimulation also helped to regulate blood pressure in one person and restored her ability to have an orgasm during sex. Darrow plans to implant 10 more people and to launch the next studies with the goal

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of getting the therapy to patients as quickly as possible. Epidural stimulation isn't a panacea, but that doesn't matter, he says. "I don't really believe in cure as part of my practice. I am all about making people's lives better incrementally."

FORWARD FOCUS

The demand for new therapies has given birth to a medical tourism industry for spinal cord injuries. In Bangkok, the World Medical Center Hospital offers epidural stimulation—with or without stem cells—to anyone who meets its criteria and can afford the more than U.S.$70,000 price tag. As of July, the hospital, which is affiliated with a company called Unique Access Medical (UAM), had performed 70 implants, says Henning Kalwa, head of patient services. "While other colleagues in the field of neurology are still spinning their wheels with studies, trials and FDA bureaucracy in the pursuit of a cure for paraplegia and quadriplegia, UAM is successfully treating patients," wrote Kalwa in a public post on LinkedIn.

Courtine cautions people with spinal cord injuries against pursuing epidural stimulation outside clinical trials. He has seen stimulators implanted at the wrong spot, and he points out that even the leading scientists don't yet agree on how to configure the stimulation and do the training. "It's way too early," he says. Tansey fears that rushing to treatment could send epidural stimulation the way of stem cells—clinics could pop up offering unsupported therapies that might not work, and serious research could fall by the wayside.

For the scientists, the focus is still on conducting research. Each group seems to have its own ideas about how to move the science forward.

Harkema's team continues to recruit participants for the Reeve-funded study. She has also begun a project looking at the effect of stimulation and training on bowel and bladder function.

"I'm just getting fatigued and frustrated."

—Rob Summers

Courtine, meanwhile, has co-founded a company called GTX medical in Eindhoven in the Netherlands to develop a custom-made stimulator for people with spinal cord injuries. He hopes the technology will be ready in a couple of years. His team is also launching a study to test epidural stimulation in 20 individuals who are less than a month into their recovery. In those people, "there's real potential to see a neurologic recovery," he says, and possibly even growth of new nerve fibers.

The Mayo team has just launched a study comparing transcutaneous stimulation with epidural stimulation. And Darrow is still recruiting participants for his study. "If it does work, even somewhat, we have a responsibility to scientifically and rigorously explore it and also deliver it in a timely fashion," he says.

Summers, meanwhile, is focused on putting one foot in front of the other. After the initial study ended, he left Kentucky and moved around the U.S. Then, in 2018, he moved back to Louisville to participate in another study focused on standing, stepping and voluntary movement. He's now on his second stimulator, and the difference has been profound. The pulses are "crisper and cleaner," Summers says, and each day it feels like he hits a new milestone. On a Tuesday morning in April, he turns the stimulator on, straps into a harness suspended from a metal frame on casters, and begins taking halting steps down the long hallway on the 12th floor of the Frazier Rehabilitation Institute in Louisville.

His girlfriend, Julie Grauert, wears a Team Reeve T-shirt and rolls along behind in Summers's wheelchair, blasting Disney tunes from her phone. "You got it, babe," she says. Their service-dog-in-training, a golden retriever named Bear, follows them.

Some steps look easy. Summers's gray Nikes swing confidently forward and land true. But the workout takes a toll. His legs shake, and occasionally his left foot lands at odd angles. For a moment, Summers's legs buckle, and the harness catches him. "I'm just getting fatigued and frustrated," he says.

Summers's version of walking represents astonishing progress, and he continues to improve. But it is still an ongoing experiment. He can't yet take a walk in the park or even amble around his apartment.

A perpetual optimist, Summers views stimulation as nothing short of a cure. For him, the biggest benefits have been the least visible—improvements in blood pressure, bladder and bowel control, sexual function and temperature regulation. And there are the more trivial sensations, such as a deep appreciation for brand-new socks. "I can feel the softness," he says. "It's crazy the little things that I find joy in."

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John Carlisle works in a hospital in Torquay, England. In his spare time, he finds statistical errors in medical research trials.

EMLI BENDIXEN *NATURE*

The Data Detective

Anesthetist John Carlisle has spotted problems in hundreds of research papers—and spurred a leading medical journal to change its practice

By David Adam

If John Carlisle had a cat flap, scientific fraudsters might rest easier at night.

David Adam works for *Nature* magazine.

Carlisle routinely rises at 4.30 A.M. to let out Wizard, the family pet. Then, unable to sleep, he reaches for his laptop and starts typing up data from published papers on clinical trials. Before his wife's alarm clock sounds 90 minutes later, he has usually managed to fill a spreadsheet with the ages, weights and heights of hundreds of people—some of whom, he suspects, never actually existed.

By day, Carlisle is an anesthetist working for England's National Health Service in the seaside town of Torquay. But in his spare time, he roots around the scientific record for suspect data in clinical research. Over the past decade his sleuthing has included trials used to investigate a wide range of health issues, from the benefits of specific diets to guidelines for hospital treatment. It has led to hundreds of papers being retracted and corrected because of both misconduct and mistakes. And it has helped end the careers of some large-scale fakers: of the six scientists worldwide with the most retractions, three were brought down using variants of Carlisle's data analyses.

"His technique has been shown to be incredibly useful," says Paul Myles, director of anesthesia and perioperative medicine at the Alfred Hospital in Melbourne, Australia, who has worked with Carlisle to examine research papers containing dodgy statistics. "He's used it to demonstrate some major examples of fraud."

Carlisle's statistical sideline is not popular with everyone. Critics argue that it has sometimes led to the questioning of papers that aren't obviously flawed, resulting in unjustified suspicion.

But Carlisle believes that he is helping to protect patients, which is why he spends his spare time poring over others' studies. "I do it because my curiosity motivates me to do so," he says, not because of an overwhelming zeal to uncover wrongdoing: "It's important not to become a crusader against misconduct."

Together with the work of other researchers who doggedly check academic papers, his efforts suggest that the gatekeepers of science—journals and institutions—could be doing much more to spot mistakes. In medical trials, the kind that Carlisle focuses on, that can be a matter of life and death.

ANESTHETISTS BEHAVING BADLY

Torquay looks like any other traditional provincial English town, with pretty floral displays on the roundabouts and just enough pastel-colored cottages to catch the eye. Carlisle has lived in the area for 18 years and works at the town's general hospital. In an empty operating theater, after a patient has just been stitched up and wheeled away, he explains how he began to look for faked data in medical research.

More than 10 years ago Carlisle and other anesthesiologists began chattering about results published by a Japanese researcher, Yoshitaka Fujii. In a series of randomized controlled trials (RCTs), Fujii, who then worked at Toho University in Tokyo, claimed to have examined the impact of various medicines on preventing vomiting and nausea in patients after surgery. But the data looked too clean to be true. Carlisle, one among many concerned, decided to check the figures, using statistical tests to pick up unlikely patterns in the data. He showed in 2012 that, in many cases, the likelihood of the patterns having arisen by chance was "infinitesimally small." Prompted in part by this analysis, journal editors asked Fujii's present

and former universities to investigate; Fujii was fired from Toho University in 2012 and had 183 of his papers retracted, an all-time record. Four years later Carlisle co-published an analysis of results from another Japanese anesthesiologist, Yuhji Saitoh—a frequent co-author of Fujii's—and demonstrated that his data were extremely suspicious, too. Saitoh currently has 53 retractions.

Other researchers soon cited Carlisle's work in their own analyses, which used variants of his approach. In 2016 researchers in New Zealand and the U.K., for example, reported problems in papers by Yoshihiro Sato, a bone researcher at a hospital in southern Japan. That ultimately led to 27 retractions, and 66 Sato-authored papers have been retracted in total.

Anesthesia had been rocked by several fraud scandals before Fujii's and Saitoh's cases—including that of German anesthetist Joachim Boldt, who has had more than 90 papers retracted. But Carlisle began to wonder whether only his own field was at fault. So he picked eight leading journals and, working in his spare moments, checked through thousands of randomized trials they had published.

In 2017 he published an analysis in the journal *Anesthesia* stating that he had found suspect data in 90 of more than 5,000 trials published over 16 years. At least 10 of these papers have since been retracted and six corrected, including a high-profile study published in the *New England Journal of Medicine* (*NEJM*) on the health benefits of the Mediterranean diet. In that case, however, there was no suggestion of fraud: the authors had made a mistake in how they randomized participants. After the authors removed erroneous data, the paper was republished with similar conclusions.

Carlisle has kept going. This year he warned about dozens of anesthesia studies by an Italian surgeon, Mario Schietroma of the University of L'Aquila in central Italy, saying that they were not a reliable basis for clinical practice. Myles, who worked on the report with Carlisle, had raised the alarm last year after spotting suspicious similarities in the raw data for control and patient groups in five of Schietroma's papers.

Bottled oxygen, used by anesthetists during surgery.

MARK THOMAS *ALAMY*

The challenges to Schietroma's claims have had an impact in hospitals around the globe. The World Health Organization cited Schietroma's work when, in 2016, it issued a recommendation that anesthetists should routinely boost the oxygen levels they deliver to patients during and after surgery, to help reduce infection. That was a controversial call: anesthetists know that in some procedures, too much oxygen can be associated with an increased risk of complications—and the recommendations would have meant hospitals in poorer countries spending more of their budgets on expensive bottled oxygen, Myles says.

The five papers Myles warned about were quickly retracted, and the WHO revised its recommendation from "strong" to "conditional," meaning that clinicians have more freedom to make different choices for various patients. Schietroma says that his calculations were assessed by an independent statistician and through peer review and that he purposely selected similar groups of patients, so it's not surprising if the data closely match. He also says he lost raw data and documents related to the trials when L'Aquila was struck by an earthquake in 2009. A spokesperson for the university says it has left inquiries to "the competent investigating bodies" but did not explain which bodies those were or whether any investigations were underway.

SPOTTING UNNATURAL DATA

The essence of Carlisle's approach is nothing new, he says: it's simply that real-life data have natural patterns that artificial data struggle to replicate. Such phenomena were spotted in the 1880s, were popularized by U.S. electrical engineer and physicist Frank Benford in 1938,

and have since been used by many statistical checkers. Political scientists, for example, have long used a similar approach to analyze survey data—a technique they call Stouffer's method after sociologist Samuel Stouffer, who popularized it in the 1950s.

In the case of RCTs, Carlisle looks at the baseline measurements that describe the characteristics of the groups of volunteers in the trial, typically the control group and the intervention group. These include height, weight and relevant physiological characteristics—usually described in the first table of a paper.

In a genuine RCT, volunteers are randomly allocated to the control or (one or more) intervention groups. As a result, the mean and the standard deviation for each characteristic should be about the same—but not too identical. That would be suspiciously perfect.

Carlisle first constructs a *p* value for each pairing: a statistical measurement of how likely the reported baseline data points are if one assumes that volunteers were, in fact, randomly allocated to each group. He then pools all these *p* values to get a sense of how random the measurements are overall. A combined *p* value that looks too high suggests that the data are suspiciously well-balanced; too low, and it could show that the patients have been randomized incorrectly.

The method isn't foolproof. The statistical checks demand that the variables in the table are truly independent—whereas in reality, they often aren't. (Height and weight are linked, for example.) In practice, this means that some papers that are flagged as incorrect actually aren't—and for that reason, some statisticians have criticized Carlisle's work.

But Carlisle says that applying his method is a good first step and one that can highlight studies that might deserve a closer look, such as requesting the individual patient data behind the paper.

"It can put up a red flag. Or an amber flag or five or 10 red flags to say this is highly unlikely to be real data," Myles says.

"I do it because my curiosity motivates me to do so. It's important not to become a crusader against misconduct."

—John Carlisle

MISTAKES VS. MISCREANTS

Carlisle says that he is careful not to attribute any cause to the possible problems he identifies. In 2017, however, when Carlisle's analysis of 5,000 trials appeared in *Anesthesia*—of which he is an editor—an accompanying editorial by anesthetists John Loadsman and Tim McCulloch of the University of Sydney in Australia took a more provocative line.

It talked of "dishonest authors" and "miscreants" and suggested that "more authors of already published RCTs will eventually be getting their tap on the shoulder." It also said: "A strong argument could be made that every journal in the world now needs to apply Carlisle's method to all the RCTs they've ever published."

This provoked a strongly worded response from editors at one journal, *Anesthesiology*, which had published 12 of the papers Carlisle highlighted as problematic. "The Carlisle article is ethically questionable and a disservice to the authors of the previously published articles 'called out' therein," wrote the journal's editor in chief, Evan Kharasch, an anesthesiologist at Duke University. His editorial, co-written with anesthesiologist Timothy Houle of Massachusetts General Hospital, who is the statistical consultant for *Anesthesiology*, highlighted problems such as the fact that the method could flag false positives. "A valid method to detect fabrication and falsification (akin to plagiarism-checking software) would be welcome. The Carlisle method is not such," they wrote in a correspondence to *Anesthesia*.

In May, *Anesthesiology* did correct one of the papers Carlisle had highlighted, noting that it had reported "systematically incorrect" *p* values in two tables and that the authors had lost the original data and couldn't recalculate the values. Kharasch, however, says he stands by his view in the editorial. Carlisle says Loadsman and McCulloch's editorial was "reasonable" and that the criticisms of his work don't undermine its value. "I'm comfortable thinking the effort worthwhile whilst others might not," he says.

THE DATA CHECKERS

Carlisle's isn't the only method to emerge in the past few years for double-checking published data.

Michèle Nuijten, who studies analytical methods at Tilburg University in the Netherlands, has developed what she calls a "spellcheck for statistics" that can scan journal articles to check whether the statistics described are internally consistent. Called statcheck, it verifies, for example, that data reported in the results section agree with the calculated *p* values. It has been used to flag errors, usually numerical typos, in journal articles going back decades.

And Nick Brown, a graduate student in psychology at the University of Groningen, also in the Netherlands, and James Heathers, who studies scientific methods at North-

eastern University, have used a program called GRIM to double-check the calculation of statistical means, as another way to flag suspect data.

Neither technique would work on papers that describe RCTs, such as the studies Carlisle has assessed. Statcheck runs on the strict data-presentation format used by the American Psychological Association. GRIM works only when data are integers, such as the discrete numbers generated in psychology questionnaires, when a value is scored from one to five.

There is growing interest in these kinds of checks, says John Ioannidis of Stanford University, who studies scientific methods and advocates for the better use of statistics to improve reproducibility in science. "They are wonderful tools and very ingenious." But he cautions about jumping to conclusions over the reason for the problems found. "It's a completely different landscape if we're talking about fraud versus if we're talking about some typo," he says.

Brown, Nuijten and Carlisle all agree that their tools can only highlight problems that need to be investigated. "I really don't want to associate statcheck with fraud," Nuijten says. The true value of such tools, Ioannidis says, will be to screen papers for problematic data before they are published—and so prevent fraud or mistakes reaching the literature in the first place.

Carlisle observes that an increasing number of journal editors have contacted him about using his technique in this way. Currently most of this effort is done unofficially on an ad hoc basis and only when editors are already suspicious.

At least two journals have taken things further and now use the statistical checks as part of the publication process for all papers. Carlisle's own journal, *Anesthesia*, uses it routinely, as do editors at the *NEJM*. "We are looking to prevent a rare, but potentially impactful, negative event," a spokesperson for the *NEJM* says. "It is worth the extra time and expense."

"They think that random chance on this occasion got in the way of the truth, of how they know the universe really works. So they change the result to what they think it should have been."

—John Carlisle

Carlisle says he is very impressed that a journal with the status of the *NEJM* has introduced these checks, which he knows first hand are laborious, time-consuming and not universally popular. But automation would be needed to introduce them on the scale required to check even a fraction of the roughly two million papers published across the world every year, he says. He thinks it could be done. Statcheck works in this way and is being used routinely by several psychology journals to screen submissions, Nuijten says. And text-mining techniques have allowed researchers to assess, for instance, the *p* values in thousands of papers as a way to investigate *p* hacking—in which data are tweaked to produce significant *p* values.

One problem, several researchers in the field say, is that funders, journals and many in the scientific community give a relatively low priority to such checks. "It is not a very rewarding type of work to do," Nuijten says. "It's you trying to find flaws in other people's work, and that is not something that will make you very popular."

Even finding that a study is fraudulent does not always end the matter. In 2012 researchers in South Korea submitted to *Anesthesia & Analgesia* a report of a trial that looked at how facial muscle tone could indicate the best time to insert breathing tubes into the throat. Asked, unofficially, to take a look, Carlisle found discrepancies between patient and summary data, and the paper was rejected.

Remarkably, it was then submitted to Carlisle's own journal with different patient data—but Carlisle recognized the paper. It was rejected again, and editors on both journals contacted the authors and their institutions with their concerns. To Carlisle's astonishment, a few months later the paper—unchanged from the last version—was published in the *European Journal of Anaesthesiology*. After Carlisle shared the paper's dubious history with the journal editor, it was retracted in 2017 because of "irregularities in their data, including misrepresentation of results."

After seeing so many cases of fraud, alongside typos and mistakes, Carlisle has developed his own theory of what drives some researchers to make up their data. "They think that random chance on this occasion got in the way of the truth, of how they know the universe really works," he says. "So they change the result to what they think it should have been."

As Carlisle has shown, it takes a determined data checker to spot the deception.

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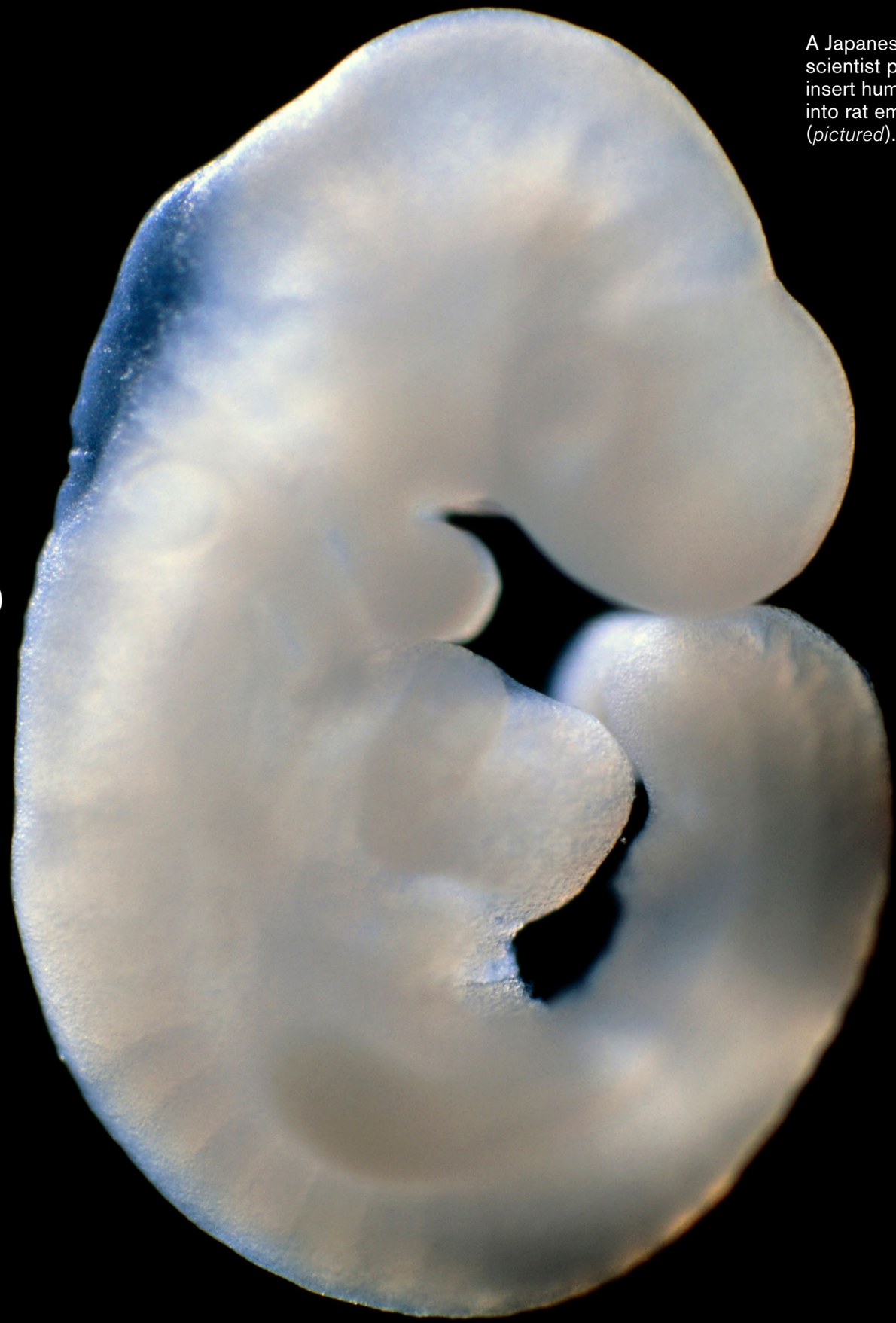
First Human-Animal Embryo Experiments

The research could eventually lead to new sources of organs for transplant, but ethical and technical hurdles need to be overcome

By David Cyranoski



A Japanese scientist plans to insert human cells into rat embryos (*pictured*).

SINCLAIR STAMMERS *GGETTY IMAGES*

A JAPANESE STEM CELL SCIENTIST IS the first to receive government support to create animal embryos that contain human cells and transplant them into surrogate animals since a ban on the practice was overturned earlier this year.

Hiromitsu Nakauchi, who leads teams at the University of Tokyo and Stanford University, plans to grow human cells in mouse and rat embryos and then transplant those embryos into surrogate animals. Nakauchi's ultimate goal is to pro-duce animals with organs made of human cells that can, eventually, be transplanted into people.

Until March, Japan explicitly forbade the growth of animal embryos containing human cells beyond 14 days or the transplant of such embryos into a surrogate uterus. That month Japan's education and science ministry issued new guidelines allowing the creation of human-animal embryos that can be transplanted into surrogate animals and brought to term.

Human-animal hybrid embryos have been made in countries such as the U.S. but never brought to term. Although the country allows this kind of research, the National Institutes of Health has had a moratorium on funding such work since 2015.

Nakauchi's experiments are the first to be approved under Japan's new rules, by a committee of experts in the science ministry. Final approval from the ministry is expected in October.

Nakauchi says he plans to proceed slowly and will not attempt to bring any hybrid embryos to term for some time. Initially he plans to grow hybrid mouse embryos until 14.5 days, when the animal's organs are mostly formed and it is almost to term. He will do the same experiments in rats, growing the hybrids to near term, about 15.5 days. Later, Nakauchi plans to apply for government approval to grow hybrid embryos in pigs for up to 70 days.

David Cyranoski works for Nature magazine.

"It is good to proceed stepwise with caution, which will make it possible to have a dialogue with the public, which is feeling anxious and has concerns," says science policy researcher Tetsuya Ishii of Hokkaido University in Sapporo, Japan.

ETHICAL CONCERNS

Some bioethicists are concerned about the possibility that human cells might stray beyond development of the targeted organ, travel to the developing animal's brain and potentially affect its cognition.

Nakauchi says these concerns have been taken into consideration in the experiment design. "We are trying to do targeted organ generation, so the cells go only to the pancreas," he says.

The strategy that he and other scientists are exploring is to create an animal embryo that lacks a gene necessary for the production of a certain organ, such as the pancreas, and then to inject human induced pluripotent stem (iPS) cells into the animal embryo. iPS cells are those that have been reprogrammed to an embryonic-like state and can give rise to almost all cell types. As the animal develops, it uses the human iPS cells to make the organ, which it cannot make with its own cells.

In 2017 Nakauchi and his colleagues reported the injection of mouse iPS cells into the embryo of a rat that was unable to produce a pancreas. The rat formed a pancreas made entirely of mouse cells. Nakauchi and his team transplanted that pancreas back into a mouse that had been engineered to have diabetes. The

rat-produced organ was able to control blood sugar levels, effectively curing the mouse of diabetes.

But getting human cells to grow in another species is not easy. Nakauchi and his colleagues announced at the 2018 American Association for the Advancement of Science meeting in Austin, Tex., that they had put human iPS cells into sheep embryos that had been engineered not to produce a pancreas. But the hybrid embryos, grown for 28 days, contained very few human cells and nothing resembling organs. This is probably because of the genetic distance between humans and sheep, Nakauchi says.

It doesn't make sense to bring human-animal hybrid embryos to term using evolutionarily distant species such as pigs and sheep because the human cells will be eliminated from host embryos early on, says Jun Wu, who researches human-animal chimeras at the University of Texas Southwestern Medical Center in Dallas. "Understanding the molecular basis and developing strategies to overcome this barrier will be necessary to move the field forward," Wu says.

Nakauchi says the approval in Japan will allow him to attack this problem. He will be experimenting with iPS cells at subtly different stages and trying some genetically modified iPS cells to try to determine what limits the growth of human cells in animal embryos.

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John Horgan directs the Center for Science Writings at the Stevens Institute of Technology. His books include *The End of Science*, *The End of War* and *Mind-Body Problems*, available for free at mindbodyproblems.com.

MEDICINE

Cancer Medicine Is Failing Us

Our aggressive, expensive approach to cancer is doing more harm than good

I can't quit dwelling on medicine's flaws. I recently reviewed Mind Fixers by historian Anne Harrington and *Medical Nihilism* by philosopher Jacob Stegenga, which critique psychiatry and medicine as a whole, respectively. In this article I'll discuss *The Emperor of All Maladies*, Siddhartha Mukherjee's history of cancer medicine.

In spite of its grim subject, *Emperor* became a bestseller when it was published in 2010 (as well as winning a Pulitzer Prize and inspiring a PBS series)—and with good reason. Mukherjee is a gifted writer, and his status as an insider, a professor of oncology at Columbia University, gives his book a compelling personal dimension. He keeps you riveted with stories about patients, including his own, desperate to be cured, and physicians, including himself, desperate to cure them.

The emotional effect of *Emperor* is thus quite different from that of *Nihilism* and *Fixers*. The overall tone of the latter two books is critical, with an edge of righteous anger toward the medical community. *Emperor*, in contrast, is inspirational. Mukherjee expresses, for the most part, admiration for his fellow oncologists. But the substance of all three books is essentially the same. All tell tales of scientific arrogance, overreaching and failure on a massive scale.

Mammography (*pictured*) and other cancer-screening methods have led to massive overdiagnosis and overtreatment of patients as well as higher costs.

GETTY IMAGES

Medieval doctors, Mukherjee informs us, cut out tumors, burned them and doused them with acid. Modern researchers sought to move past these primitive methods by finding "magic bullets," which attack disease without harming healthy tissue. But

by the 20th century, the major treatments for cancer were surgery, radiation and chemotherapy, which cut, burn and poison the body. Early chemotherapies, Mukherjee notes, were inspired by mustard gas, a chemical weapon, and radiation causes cancer.

Physicians kept making treatments more "radical" in their efforts to eradicate every last vestige of cancer, so that it would not return. Physicians cut more and more tissue from patients' bodies and administered higher and higher doses of chemotherapy and radiation, bringing patients closer and closer to death. Physicians adhered to a bravado that Mukherjee describes as "the Hippocratic oath upside down."

In 1933 surgeons discussing stomach cancer quoted, approvingly, an old Arab saying that "he is no physician who has not slain many patients." Concern for patients' quality of life was castigated as "mistaken kindness." In 1962 a ward where children were administered multiple chemotherapy agents was called a "butcher shop."

Switching to the realm of politics, Mukherjee recounts how cancer researcher Sydney Farber and philanthropist Mary Lasker mastered the arts of marketing and fundraising and turned the struggle against cancer into a crusade. Their efforts culminated in the so-called National Cancer Act, signed into law by President Richard Nixon in 1971, which boosted federal funding for cancer research. Farber assured Congress, "We will in a relatively short period of time make vast inroads on the cancer problem."

Skeptics warned that declarations of imminent victory were grossly premature, and they turned out to be right. In 1986 physician-statistician John Bailar and co-author Elaine Smith reported that between 1962 and 1985 cancer mortality rates rose by 8.7 percent. "We are losing the war on cancer," they announced. The article "shook the world of oncology by its roots," Mukherjee writes. Over the subsequent decade, oncologists insisted they were making progress. But in a 1997 article, "Cancer Undefeated," Bailar and Helen Gornik presented evidence that between 1970 and 1994, as funding for research rose sharply, cancer mortality increased by 6 percent.

Researchers have found virtual cures for certain uncommon types of cancer, such as lymphoblastic leukemia and Hodgkin's lymphoma, especially in children.

More bad news followed. In the 1990s bone marrow transplants—in part because of intense lobbying by patient-advocacy groups—became a popular therapy for breast cancer in spite of their complexity, toxicity and cost. About 40,000 women worldwide were treated for a cost as high as $4 billion. Transplants were "big business," Mukherjee writes, "big medicine, big money, big infrastructure, big risks." A 1999 trial found that transplant therapy conferred "no discernible benefits." The treatment gave some women acute leukemia, which was "far worse than the cancers they had begun with."

There have been genuine victories, which Mukherjee details. Researchers have found virtual cures for certain uncommon types of cancer, such as lymphoblastic leukemia and Hodgkin's lymphoma, especially in children. They have developed medications that extend lives, such as Herceptin and tamoxifen for breast cancer and Gleevec for leukemias and other cancers. And they have unraveled the complex biology of cancer, tracing it to genes, hormones, viruses and retroviruses as well as to carcinogens like those found in cigarettes.

In a section at the end of his book entitled "The Fruits of Long Endeavors," Mukherjee asserts that oncologists' hard work is finally paying off. Between 1990 and 2005, the age-adjusted U.S. cancer mortality rate fell 15 percent, "a decline unprecedented in the history of the disease." Because cancer rates go up with age, mortality rates are adjusted for the aging of the population. Mukherjee attributes the drop to declines in smoking as well as tests such as mammograms and advances in chemotherapy.

He tempers his optimism, suggesting that the more we learn about cancer's hideously complex, shape-shifting etiology, the less likely it seems that we will vanquish it once and for all. Knowledge of cancer's biology "is unlikely to eradicate cancer fully from our lives," Mukherjee writes. No "simple, universal, or definitive cure is in sight—and is never likely to be." We must accept this fact, he says, and

yet keep fighting, avoiding the extremes of delusional hope and defeatism.

This is wise advice, and *Emperor* is a splendid piece of science journalism, but Mukherjee's insider status is a weakness as well as a strength. He doesn't want to offend colleagues, and as a researcher he must believe his efforts will bear fruit. I kept wondering how a more neutral scholar—such as Harrington or Stegenga—would have treated the same material, updated to the present. Such a scholar might have raised the following points:

***Cancer remains undefeated.** The decline that Mukherjee celebrated in 2010 has continued at a pace of about 1percent per year. U.S. mortality rates have fallen 27 percent since 1991, according to the American Cancer Institute. But this decrease came after a long increase that peaked in the early 1990s and followed a rise in smoking. The linkage of cancer to tobacco, which led to declines in smoking (another story well told by Mukherjee), has probably saved more lives than all other cancer-related scientific advances put together.

The current mortality rate for all cancers in the U.S. is roughly what it was in 1930. According to the invaluable Web finissite Our World in Data, mortality from lung cancer, by far the biggest killer, has returned to its 1970 rate. Although the death rates of some cancers, notably of the stomach and breast, have recently declined, death rates of liver, pancreatic and brain cancer have increased. Absolute death tolls from cancer keep climbing, increasing from 278,561 in 1990 to more than 400,000 in 2017.

***Tests do more harm than good.** In *Emperor*, Mukherjee has an excellent discussion of the limits of mammograms and other tests for cancer (which he revisits in a 2017 New Yorker article). He notes that screening cannot catch some fast-growing cancers, and it flags tumors that if left alone would never have caused harm, a trend called overdiagnosis. He nonetheless claims that testing has helped bring down cancer mortality rates.

That claim looks increasingly dubious. To paraphrase Mukherjee, testing represents an inversion—or perversion—of the Hippocratic oath to do no harm. A 2015 review of screening methods for cancer and other diseases found that none extend life, when all causes of mortality are taken into account. Studies have revealed that tests such as mammograms and screening for prostate cancer have led to massive overdiagnosis and overtreatment.

A 2018 study warned that "more harm than benefit is created for most commonly used tests." The following passage deserves emphasis:

"*Screening is big business: more screening means more patients, more clinical revenue to diagnostic and clinical departments, and more survivors in need of care and follow- up. Critics are met with fierce opposition and not much changes. We believe, however, that a major, radical change is urgently needed after more than four decades of enormous investments and failing expectations.*"

***The profit motive corrupts cancer medicine.** The costs of cancer care in the U.S. are expected to reach $175 billion next year, up from $125 billion in 2010. Mukherjee is certainly worried about surging costs. In a recent *New Yorker* article, he expresses concern that new immunotherapies, on which he is working, cost hundreds of thousands of dollars per patient and more than a million if follow-up care is included. He hopes that "continuous, iterative improvements" will make the drugs affordable.

Mukherjee is understandably reluctant to accuse his fellow oncologists of bad faith, that is, greed. But last April the *New York Times* reported that top officials at Memorial Sloan Kettering Cancer Center "repeatedly violated policies on financial conflicts of interest, fostering a culture in which profits appeared to take precedence over research and patient care." Memorial Sloan Kettering and other cancer centers, which compete for patients, spent $173 million in 2015 on what one critic called "misleading" advertisements that exploit "false hopes."

The ferocious competition for grants might also be engendering adverse effects. Since Nixon declared war on cancer in 1971, the budget for the National Cancer Institute has risen from $400 million to $5.74 billion. A 2012 examination of 53 "landmark" cancer studies found that only six could be reproduced. The so-called Reproducibility Project: Cancer Biology has examined more recent highly cited studies. So far only five of 14 have been confirmed without qualification.

***Cancer kills fewer people in countries that spend less on care.** The U.S. spends far more per capita on health care, including cancer care, than any other country, but higher expenditures have not led to longer lives. Quite the contrary. Europe, which spends much less on cancer care than the U.S., has lower cancer mortality rates, according to a 2015 study. So do countries such as Mexico, Italy and Brazil, according to Our World in Data. These data corroborate concerns that the aggressive, expensive American approach to cancer is doing more harm than good.

In their books, Stegenga and Harrington advocate that psychiatry and other branches of medicine be practiced more sparingly, with more humility and caution. Stegenga calls this "gentle medicine." Gentle cancer medicine would mean much less testing and treatment, which should lead to lower costs and better health.

Gentle cancer medicine seems unlikely in our hypercapitalist culture. It can only take root if we consumers demand it and stop insisting on getting dubious tests and treatments. We may never cure cancer, which results from the collision of our complex biology with entropy. But if we can curtail our fear and greed, our cancer care will surely improve.

Matt Lamkin is an associate professor at the University of Tulsa College of Law and served as a fellow at Stanford Law School's Center for Law and the Biosciences. His work has been published in the *New England Journal of Medicine*, *JAMA Psychiatry*, *Bioethics*, the *AMA Journal of Ethics*, the *Journal of Law, Medicine, and Ethics*, and numerous legal journals.

MEDICINE

Psychedelic Medicine Is Coming. The Law Isn't Ready

A surprising resurgence of psychedelic research has produced its first FDA-approved treatment, with more likely on the way

ROBIN OLIMB *GETTY IMAGES*

In March the U.S. Food and Drug Administration approved esketamine, a drug that produces psychedelic effects, to treat depression—the first psychedelic ever to clear that bar. Meanwhile the FDA has granted "breakthrough therapy" status—a designation that enables fast-tracked research—to study MDMA (also called "ecstasy") as a treatment for post-traumatic stress disorder and psilocybin as a treatment for major depression.

While these and other psychedelic drugs show promise as treatments for specific illnesses, FDA approval means doctors could also prescribe them for other, "off-label" purposes—including enhancing the quality of life of people who do not suffer from any disorder. Hence, if MDMA gains approval as a treatment for PTSD, psychiatrists could prescribe the drug for very different purposes. Indeed, before the federal government banned MDMA, therapists reported striking success in using MDMA to improve the quality of intimate relationships. Recent research bolsters these claims, finding that the drug enhances emotional empathy, increases

feelings of closeness, and promotes thoughtfulness and contemplativeness.

Similarly, while psilocybin has shown potential as a treatment for depression and anxiety, physicians could also prescribe the drug to promote the well-being of healthy individuals. When researchers at Johns Hopkins gave psilocybin to healthy participants with no history of hallucinogen use, nearly 80 percent reported that their experiences "increased their current sense of personal well-being or life satisfaction 'moderately' or 'very much'"—effects that persisted for more than a year.

Yet while the FDA generally does not regulate physicians' prescribing practices, a federal law called the Controlled Substances Act bars them from writing prescriptions without a "legitimate medical purpose." Although this prohibition aims to prevent doctors from acting as drug traffickers, the law does not explain which purposes qualify as "legitimate" nor how to distinguish valid prescriptions from those that merely enable patients' illicit drug use.

Would prescribing a psychedelic drug simply to promote empathy or increase "life satisfaction" fall within the scope of legitimate medicine—or would these practices render the physician a drug dealer?

To many, the answer may seem obvious: to qualify as a "medical" use, a drug must be prescribed to treat an illness. But in fact, medical practice has always included interventions aimed at promoting the well-being of healthy individuals. Doctors provide contraceptives and induce abortions regardless of whether their patients' health is threatened by pregnancy. Plastic surgeons first honed their skills treating the traumas of World War I but quickly found themselves reshaping normal bodies and faces simply to enhance appearance.

Today physicians may prescribe stimulants to improve performance at school or minor tranquilizers to help cope with the ordinary stresses of modern life, regardless of whether patients meet the diagnostic criteria of a specific disorder. Indeed, some diagnoses themselves seem little more than thinly veiled excuses to prescribe drugs simply to enhance quality of life—as when the FDA approved flibanserin to treat a condition called "hypoactive sexual desire disorder," which consists of not desiring sex as much as one would prefer.

At a time when "lifestyle drugs" are marketed as consumer products, it is increasingly difficult to draw a bright line that distinguishes legitimate medical practices from their illicit cousins. If prescribing mind-altering drugs to help healthy people achieve desirable mental states falls within the bounds of legitimate medicine, what is left of the concept of recreational use?

These line-drawing challenges argue for moving away from the drug war's simplistic, punitive approach in favor of more sophisticated strategies for minimizing the risks of psychotropic drugs. For example, when the FDA determines that a drug poses special risks, the agency can require risk evaluation and mitigation strategies, or REMS, to promote the safe use of the drug.

Rather than focusing on whether a drug is prescribed for a "legitimate medical purpose," REMS can require physicians to register with the FDA and receive special training to prescribe the drug. Risk management plans can also stipulate that physicians may only dispense the drug in specific health care settings and that a health care professional must monitor each patient using the drug.

Similar strategies could be used to mitigate any unique risks posed by psychedelics, without limiting their use to patients suffering from particular disorders. One can imagine a system in which psychedelic drugs could be lawfully prescribed to a healthy individual but only as part of a guided therapy session led by a specially trained physician. Multiple studies have found that both MDMA and psilocybin can be safely administered in well-supervised clinical settings like these, without harming patients or promoting drug dependence.

The prospect of psychedelic drugs gaining approval as treatments will force a reckoning for our existing system of drug control. While current policies characterize any use of these substances as illicit abuse, acknowledging that these drugs may offer meaningful benefits will require more flexible approaches. Psychedelic medicine may prove to be the thin end of a wedge that moves drug policy away from the elusive goal of eradication in favor of more nuanced strategies that harness the benefits of psychotropic drugs while minimizing their risks.

Adam Myers is chief of population health at Cleveland Clinic and chair of Cleveland Clinic Community Care.

PUBLIC HEALTH

Population Health: How We Can Cure What's Ailing Health Care

Looking at circumstances beyond the clinic is a key to better outcomes

GERD ALTMANN *PIXABAY*

In just a year and a half, the 2020 presidential election will be upon us. And as with every campaign so far this millennium, health care is sure to be a hot topic once again.

Ever rising costs, elusive accessibility and the future of the Affordable Care Act are sure-to-be-debated health care issues. But a too often overlooked problem is a pragmatic one: Why aren't we getting an acceptable bang for our health care buck?

The U.S. spends more on health care than the rest of the top 11 industrial countries, yet we come in at number 11—dead last—in meaningful health outcomes, such as life expectancy. This despite spending more money per capita on health care than any other nation.

And sadly, that result is typical for us; the U.S. has finished 11 out of 11 in meaningful health outcomes every year since 2004.

You might ask how we can we spend so much on health care but still do so poorly. It's a fair—and troubling—question.

I believe part of the answer is that we're not proactive enough in U.S. health care. One way we can correct that is to more uniformly adopt the proactive approach embodied in population health.

SOCIAL DETERMINANTS MATTER

Population health is a model for improving patient care quality and experiences while reducing costs. It focuses on all the determinants of health, including the social determinants, and the need to better address prevention and other external factors. These "determinants" include access to food, financial security, safe housing, transportation, education, access to adequate behavioral health support, and necessary assis-

tance to counter adverse childhood events.

Think about the last time you visited a health care facility. Were any of the determinants mentioned above addressed during your exam, consultation or procedure? Hopefully yes, but we don't uniformly address these as often as would be beneficial. A population health framework is promising because it encourages all stakeholders to look at the conditions into which people are born, grow, live, work and age and determine how changes can be made within vital areas to improve their future health outcomes.

Here's how a population health approach can make a difference:

I once witnessed the care of a patient who suffered from chronic obstructive pulmonary disease, which blocks airflow to lungs and makes it difficult to breathe. Over the course of a particularly hot Texas summer, he was admitted to the hospital time and time again—racking up more than $60,000 in medical expenses. Doctors were treating his breathing problems repeatedly, but they did not understand why the patient continued to have trouble.

One population health–oriented physician dug a bit deeper, holding in-depth conversations about the patient in the hospital—and later, having a team member visit his home. There it was discovered that he lived without an air conditioner. A caring individual purchased and installed a $400 air conditioner for him, and his hospital visits stopped.

In essence, $60,000 in treatment costs could have been avoided almost entirely if the social determinant of his health issue—the lack of air-conditioning—was pursued and discovered earlier.

MORE ATTENTION TO PREVENTION

And therein lies the problem. In the U.S., we treat health issues that arise. But we don't spend much time trying to prevent them.

The U.S. health care system is designed to follow a transactional model that emphasizes excellence in highly complex and interventional care. This means if you're in need of treatment for cancer or a heart transplant, the U.S. health care system is the place for you. Nobody does "hard" cases better.

But when it comes to delivering less complex, "block and tackle" care, which accounts for up to 90 percent of the care in this country, our health care system is not as consistently excellent. And what we are lacking seems, on the surface, to be so simple—such as administering immunizations, promoting good nutrition and physical activity, and supporting active engagement for health outcomes.

With respect to active engagement, our new population health approach at Cleveland Clinic has us striving to move beyond "reactive" care. Rather than just simply addressing individual patients' needs on a visit-by-visit basis, our Community Care program is leveraging a wealth of data and an expanded care team to proactively address the health needs of populations. That means if we haven't heard from a patient in a while, we will—with their preauthorized consent—reach out to them to discuss their current health status and determine appropriate care steps, if any.

Population health principles require health care providers to consider how social circumstances drive patient behaviors and outcomes. We have to think about our patients' lives outside of medical facilities, including their ability to afford medication and access nutritious food and whether they have reliable transportation to and from their medical appointments and pharmacies.

By examining the conditions outside of the hospital or the primary care office, health care stakeholders can more readily tackle all factors that are responsible for negative health outcomes and in turn build a health system that responds to those conditions in a holistic manner.

And that's an approach that should get everyone's vote.

SCIENTIFIC AMERICAN
Health & Medicine

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