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Hype or Promise?

The compound is found in everything from coffee to cookies, but the research on its efficacy is scant

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The Straight Dope on CBD

In June 2018 the FDA approved the drug Epidiolex, the first pharmaceutical drug made from cannabidiol (CBD) and intended to treat two very severe forms of epilepsy. The announcement seemed to add to the growing prominence of CBD–although it remains a Schedule I controlled substance in the U.S. In many health food stores and head shops, you can find CBD in everything from body lotion and bath bombs to chocolate and pet treats. A friend recently reported that she spotted CBD-infused condoms while traveling in Amsterdam. CBD is certainly having its moment. It is purported to calm inflammation, anxiety and pain. But the science on the efficacy of CBD is scant. As Amber Dance reports in "CBD: Hype or Promise?" the number of peer-reviewed studies on the compound barely numbers in the dozens. Which is sobering for an industry expected to grow to nearly $15 billion, by some estimates, in the next five years.

In Japan, deregulation of experimental stem cell treatments may prove harmful to many, as David Cyranoski writes in "Stem Cells 2 Go." And so-called vaccine hesitancy–the resistance by small clusters of individuals to get their children vaccinated–is spurring new strategies to track and tackle the spread of deadly diseases, as Lynne Peeples describes in "Rethinking Herd Immunity." As always, enjoy the issue!

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CHRIS GASH

On the Cover

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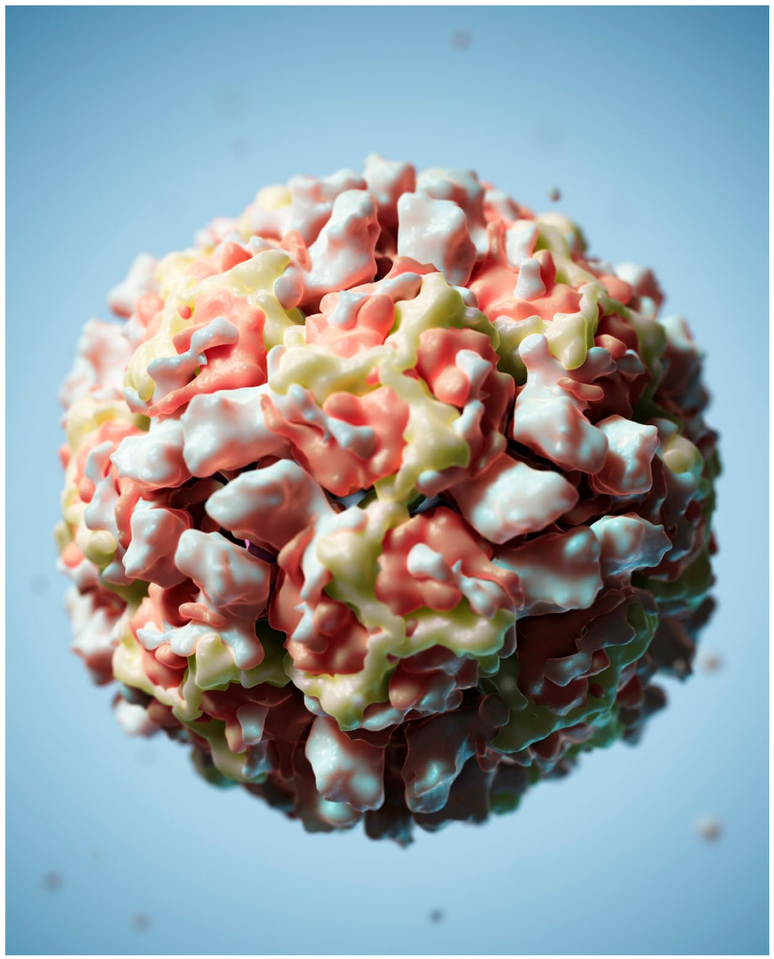

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Can Rabbits Help Unravel the Mystery of Female Orgasm?

A study suggests the phenomenon may have evolved from a mechanism for triggering ovulation

FEMALE ORGASM HAS LONG been a subject of fascination, dating back to Aristotle. Male orgasm is required for ejaculation and transporting sperm for fertilization—but sexual climax is not necessary for a woman to become pregnant. In addition, many women do not reliably experience an orgasm during intercourse. So how did such an elaborate neurochemical process evolve?

Many hypotheses have attempted to explain the origin of female orgasm. One suggests it helps bond women to their partners, increasing the chances of reproduction. Another idea, the so-called upsuck theory, suggests that the contractions caused by orgasm help to draw sperm deeper into the reproductive tract and thus increase the chances of conception. The few studies that have tested this idea do not mimic the conditions of actual sex, however. Others believe female orgasm may simply have evolved as a by-product of male orgasm because male and female sexual anatomy share a common developmental root.

In any case, there must be a reason. "This neuroendocrine reflex is too complex to be an evolutionary

accident," researchers write in a new study published in September in the *Proceedings of the National Academy of Sciences USA*.

The authors recently proposed an alternative hypothesis: the phenomenon evolved from a mechanism for stimulating ovulation. Humans and great apes are known as spontaneous ovulators—they are fertile at certain times during their menstrual cycle, regardless of whether or not they have sex. But for some animals, such as rabbits, cats and camels, ovulation is triggered by sex itself—a process known as copulation-induced ovulation. Could female orgasm have developed from a similar mechanism?

To test the idea, Mihaela Pavlicev, a professor of pediatrics at the University of Cincinnati College of Medicine, and her colleagues conducted a series of experiments in female rabbits. For two weeks, they gave the animals daily doses of the antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI). SSRIs have been found to cause sexual dysfunction in both men and women, so Pavlicev and her team wanted to see if the drug would impact ovulation in the rabbits. A set of control rabbits did not receive fluoxetine. The researchers then had the female rabbits mate with a single male—named Frank—and measured the number of times the females ovulated. They found that the rabbits who received the drug had about 30 percent fewer ovulations after mating than the control animals.

But Pavlicev and her colleagues wanted to confirm fluoxetine was reducing ovulation by way of the central nervous system rather than somehow affecting the ovaries directly. So in a second experiment, they gave some rabbits the drug—but instead of having those rabbits mate with Frank, they injected the animals with human chorionic gonadotropin, a hormone that stimulates ovulation. This time the fluoxetine-treated rabbits experienced roughly the same number of ovulations as the untreated ones, suggesting the drug indeed acts on the central nervous system and not the ovaries. At high doses, fluoxetine is known to cause weight loss—which could, in theory, affect ovulation. But the researchers did not find any relation between the rabbits' body weight and the number of ovulations caused by copulation.

Fluoxetine works by preventing the reabsorption of serotonin in the synapses of brain cells, as well as other tissues. The team conducted a final set of experiments in which it treated rabbit ovaries with fluoxetine in a lab dish and showed that serotonin does not collect in the ovaries—further supporting the notion that it acts at the brain level.

Julie Bakker, a neuroendocrinologist at the University of Liège in Belgium, who studies ovulation in ferrets, was skeptical of the findings, however. A "30 percent reduction in the number of ovulations is very marginal. It would have been much more convincing if there was no ovulation at all," says Bakker, who was not involved in the work. "It would have been nice if the authors had actually measured serotonin in the brain of their rabbits to determine whether their treatment protocol with fluoxetine" raised levels of the neurotransmitter.

Studying orgasm in animal models in tricky. "There's no such thing as orgasm in rabbits," Bakker says—it is more like a light switch, in which male stimulation triggers the brain, which triggers ovulation. In addition to ferrets, she has studied ovulation in mice and rats, and the only kind of orgasmic behavior she has seen is in female rats: It is, she says, "kind of a thrashing behavior—stretching their legs in certain way that might have been uterine contractions." The rabbit experiment is an interesting idea, she adds, but she would like to see more convincing evidence. "It's a door opener," she says.

Raúl Paredes, director of the Juriquilla unit at the National Autonomous University of Mexico's National School of Higher Education, agrees the study is interesting, but he says it is "very reductionist [to assume] that female orgasm consists of a copulation-induced reflex." The bigger issue is how one defines orgasm, he adds. "This is a human construct because, aside from the physiological changes that can occur during sex, the definition involves feelings of pleasure," he says. "This certainly can't be measured in animals."

—Tanya Lewis

Editor's Note *(10/01/19): This story was updated after publication to include comments from Raúl Paredes, director of the Juriquilla unit at the National Autonomous University of Mexico's National School of Higher Education.*

Why U.S. Officials Investigating Mysterious Vaping Deaths Are Focusing on Flavorings

As lung injuries among e-cigarette users mount amid a youth vaping epidemic, the impact of new restrictions remains unclear

AN OUTBREAK OF DEADLY lung injuries in vapers in the U.S.—many of them adolescents—shows no signs of stopping. So far 805 e-cigarettes users have fallen ill, 12 of whom have died. The illnesses are fueling a push among lawmakers and regulators to rein in the sale of e-cigarettes, in particular those with flavors that could be contributing to a worrying surge in youth vaping.

It's illegal for vendors in the U.S. to sell e-cigarettes to those younger than 18; in some states and cities, the age limit is 21. Yet more than a third of the sick vapers are younger than 21, according to the U.S. Centers for Disease Control and Prevention.

Public health officials have yet to find a definitive cause for the lung injuries, according to the CDC. And they worry that some of the affected adolescents might never fully recover. But it's unclear what impact, if any, the new restrictions on e-cigarette sales will have on the health crisis or the problem of youth vaping.

Nature takes a look at the issues.

WHAT EXACTLY ARE U.S. REGULATORS AND LAWMAKERS DOING?

In response to the recent spate of lung injuries, the U.S. Food and Drug Administration—which regulates tobacco products, including e-cigarettes—announced on September 11 that it plans to remove flavored devices from the market, at least temporarily.

The decision came as the agency was already seeking to regulate e-cigarettes after years of lax enforcement. Under FDA regulations, e-cigarette manufacturers must apply for agency approval to market their products. So far none of the companies has submitted an application, but the FDA has nonetheless allowed their devices to stay on the market. The agency has given manufacturers until May 2020 to submit applications to continue selling their products.

Some states aren't waiting for the federal government to act. In response to the recent surge in lung injuries and deaths, New York, Michigan and Rhode Island banned sales of flavored e-cigarettes in September. And on September 24, Massachusetts declared a four-month halt on the sale of all e-cigarettes.

WHY THE FOCUS ON FLAVOR?

Public health officials have long suspected that e-cigarettes with flavors based on fruit or sweet snacks such as "cupcake," "bubble gum" and "apple crack" are designed in particular to appeal to young people. Most adolescents report that flavored e-cigarettes were a key reason they took up vaping, said Anne Schuchat, deputy director of the CDC during testimony before the U.S. House of Representatives on September 24 and 25. "We're extremely concerned about flavors and the role that they play in hooking young people to a life of nicotine."

Data from a national survey

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published in the *New England Journal of Medicine* on September 18 showed that adolescent vaping in the U.S. more than doubled from 2017 to 2019. More than one quarter of U.S. high school seniors, typically 17 to18 years old, reported vaping at least once in the previous 30 days.

DOES ANYONE THINK FLAVORED VAPES SHOULD STAY ON THE MARKET?

Some tobacco-control researchers worry that banning flavors could deter adults from using e-cigarettes in attempts to quit smoking. Seventy to 80 percent of adults say that using flavored vapes was crucial to their smoking-cessation efforts, says David Abrams, a behavioral scientist at New York University. "You don't want something that reminds you of your old cigarette taste or smell," he says.

But the CDC says that adult vapers are more influenced by the nicotine content of an e-cigarette than by its flavor. And despite the fact that many people use e-cigarettes to help them quit smoking, there's little evidence that they are more effective than other tools, said Schuchat at the congressional hearing.

COULD THE FLAVORS THEMSELVES THEMSELVES BE DANGEROUS?

It's unclear. Some chemicals used to flavor e-cigarettes might be toxic, and it's possible that they can damage the lungs, says Albert Rizzo, chief medical officer of the American Lung Association in Chicago. One 2016 study of 51 e-cigarette flavors found that 39 of them contained diacetyl, an additive linked to lung damage.

Another study, published in February, found that some vaping liquids were up to 34 percent cinnamaldehyde, a chemical that can kill lung cells. "When you get to levels like that of a compound like cinnamaldehyde, having some lung difficulties isn't very surprising," says study co-author James Pankow, a chemist at Portland State University in Oregon.

These analyses focused on the liquids that e-cigarettes heat and turn into a vapor that users breathe in. The liquids come in cartridges that vapers can swap out of their devices. But that heating process changes the chemical composition of the liquid, says Mignonne Guy, a biobehavioral researcher at Virginia Commonwealth University in Richmond. And scientists are still struggling to identify all the chemicals in the vapor. The plethora of devices and user modifications that are available to consumers results in a complex array of heating conditions and liquid concentrations that complicates the researchers' task.

WILL REMOVING FLAVORS FROM THE MARKET REDUCE YOUTH VAPING?

Although numerous studies have shown that young people are attracted to flavored e-cigarettes, there are no data yet on what would happen to the number of teenage vapers if officials removed these devices from the market, says social scientist Jessica Pepper of RTI International, a nonprofit research group in Research Triangle Park, N.C.

Banning flavored e-cigarettes could also drive demand to the black market, Guy says. She supports the move to pull the devices from the market. But Guy says that as long as refillable e-cigarette cartridges exist, vapers will be able to mix their own liquid and include flavoring chemicals.

WHAT OTHER APPROACHES COULD REDUCE YOUTH VAPING?

Lawmakers have proposed eliminating online sales of e-cigarettes to make it more difficult for adolescents to buy the products. And the FDA has launched an educational program to inform young people about the risks of vaping.

But some lawmakers are pushing for more drastic measures. These include a ban on all e-cigarettes until manufacturers demonstrate that the benefits of using the devices—such as help for people who want to quit smoking cigarettes—outweigh the risks.

"How many children are we going to allow to die before this is considered the emergency it is and we just say no?" asked Jan Schakowsky, Democratic representative from Illinois, at the congressional hearing on September 25. "We should be saying 'no' right now."

—Heidi Ledford

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Could Immunotherapy Treat Diseases Besides Cancer?

Approaches for boosting the body's immune system are being tried for autoimmune and heart conditions, but it is too early to know how well they will work in people

IMMUNOTHERAPY HAS transformed cancer care. Now the tools and new knowledge created by this strategy for treating disease by stimulating the body's immune system are beginning to be employed for everything from fighting autoimmune illnesses to preventing tissue rejection in organ transplants.

Though still mostly confined to scientific labs, the use of this approach outside of cancer has tremendous potential, researchers say, because the immune system is fundamentally involved in every organ and in many health conditions. "The opportunity exists to move what we call the immunorevolution beyond cancer," says Jonathan Epstein, a cardiologist and chief scientific officer for the University of Pennsylvania Health System (Penn Medicine).

In one type of cancer immunotherapy, immune cells called T cells are removed from the body and engineered to target cells that are found only in cancers. The engineered cells, called chimeric antigen receptor T cells (CAR-Ts), have proved exceedingly effective against some types of blood cancers, particularly acute lymphocytic leukemia. Scientists have now started engineering T cells to attack other disease-related cells.

Cancer was a logical first step for immunotherapies, says Marcela Maus, director of cellular immunotherapy at the Massachusetts General Hospital's Cancer Center and an assistant professor at Harvard Medical School. The need for life-extending therapies in cancer is indisputable. There is a willingness to take risks to fight tumors that might otherwise be fatal, she says. Doctors are likely to be more cautious in fighting autoimmune diseases, which can be terrible but also have some existing—if imperfect—treatments. Now that the immunotherapy work has proved so successful in cancer, it makes sense to push it into other illnesses, Maus says.

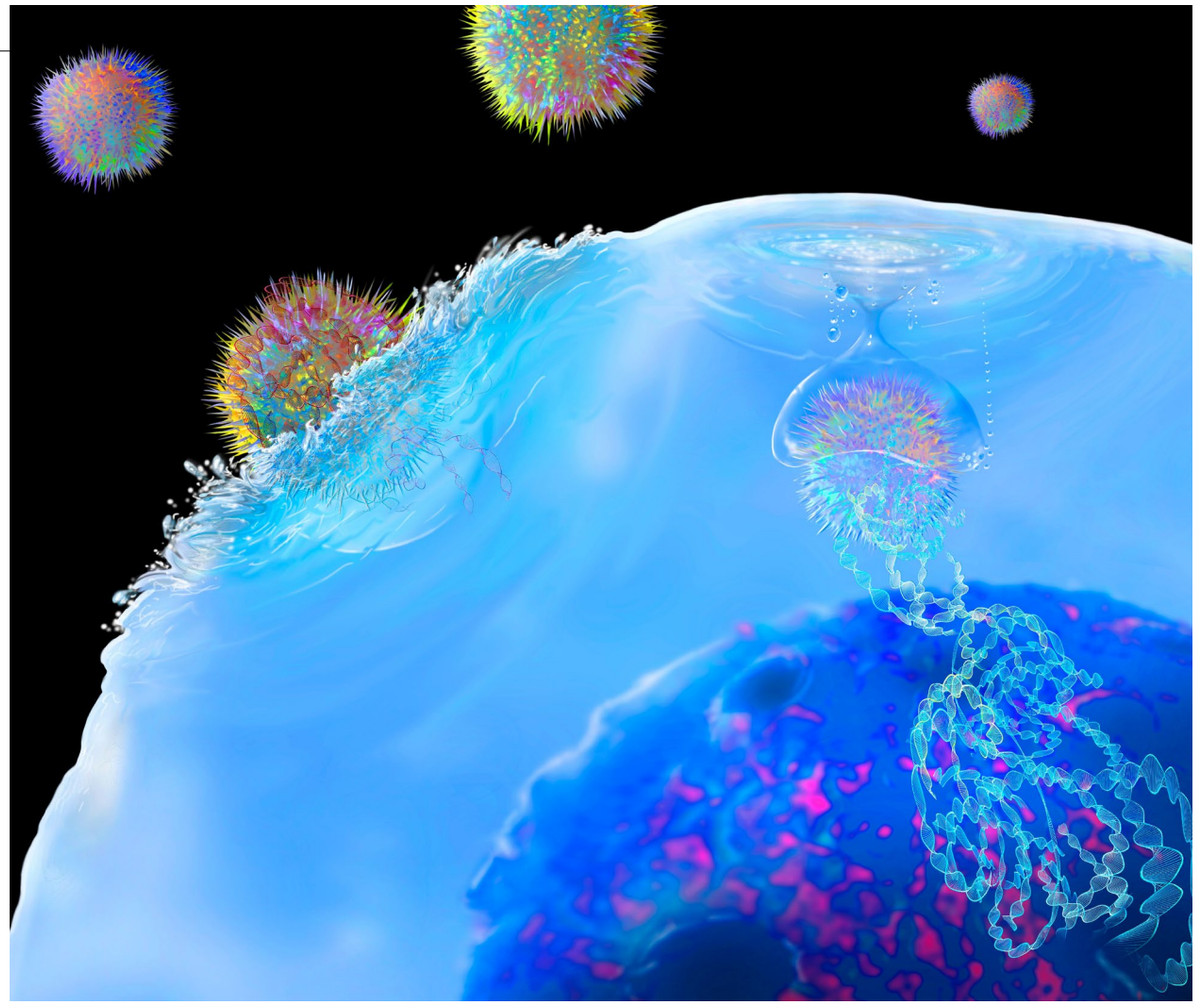


Illustration of chimeric antigen receptor T cell (CAR-T) immunotherapy.

KEITH CHAMBERS *GETTY IMAGES*

A group led by Aimee Payne, a dermatologist at Penn Medicine, is currently preparing for human trials using reengineered T cells to treat an autoimmune-triggered skin disease called pemphigus. In one subform of the affliction that affects about 4,000 Americans, the immune system produces antibodies against proteins that hold the skin together, resulting in painful, debilitating blisters. Payne and her colleagues direct engineered T cells to destroy the immune cells that make these antibodies, and their work has shown promise in animals. Payne says she got the idea for this approach from all the attention successful CAR-Ts were receiving at Penn Medicine. It seemed so simple in retrospect: "You're like, 'Why didn't we think of this earlier?'" she adds. Others had tried to target the antibodies that

cause this skin disease before, without success. Payne says she is more optimistic about the engineered T cells she is using, which she calls CAAR-T cells (with an extra "A"), for chimeric autoantibody receptor T cells because they can make more copies of themselves, so their effects could be long-lasting.

Even decades-old immunotherapies are inspiring present-day work. In Paris, David Klatzmann, an immunologist at Sorbonne University, is experimenting with treating autoimmune disorders with low levels of interleukin-2 (IL-2), an immune-signaling molecule first used to treat cancer in the mid-1980s. Back then, high doses of IL-2 proved effective in a small fraction of metastatic tumors—mainly kidney cancer and melanoma—but caused terrible side effects. Klatzmann's research suggests low doses may be able to treat a wide range of autoimmune conditions by boosting levels of a type of cell called a regulatory T cell, or Treg, which naturally muzzles the immune response. He uses immunotherapy to suppress the immune system—the opposite of what cancer researchers do.

Klatzmann's university and two other French institutions hold a patent on low-dose IL-2, and he is hosting a meeting in November with other researchers and pharmaceutical companies who are exploring its potential for a wide range of diseases. He says IL-2 is the only molecule that preferentially activates Tregs, and "there is Treg insufficiency in almost every autoimmune disease and also inflammatory disease," including atherosclerosis, or the hardening of the arteries. He is now testing his approach in phase II clinical trials for autoimmune illnesses, including lupus, type 1 diabetes and multiple sclerosis.

Jerome Ritz, who runs a cell-manufacturing lab at the Dana-Farber Cancer Institute, says CAR-Ts made with engineered Tregs could also be used against inflammation or in transplant patients to prevent rejection. Stem cell transplants can cure some blood cancers but can also lead to life-threatening graft versus host disease, in which immune cells from the donor attack the recipient. It should be possible to engineer so-called CAR-Tregs to induce tolerance to recipient cells—or even to an entire transplanted organ to prevent rejection, says Ritz, who is also a professor at Harvard Medical School.

"It's interesting science, but it's a long way off from having implications for people with heart disease."
—Eric Topol

Penn Medicine's Epstein recently engineered T cells in mice to attack cells that produce scar tissue after the heart suffers damage. Known as fibrosis, this scarring initially keeps the heart from rupturing, but it can also impair the organ's ability to fill with blood and pump efficiently. Epstein's approach worked in mice, reducing the amount of scar tissue, a study recently published in *Nature* shows. He hopes to test the method in larger animals.

But some experts remain skeptical. Eric Topol, a cardiologist and executive vice president of the Scripps Research Institute, says he doubts Epstein's approach will work in humans. "It's interesting science, but it's a long way off from having implications for people with heart disease," Topol says. Many treatments that work in mice do not translate well in people, he notes. And although fibrosis is clearly a problem in heart failure, it is not as clear that targeting fibrotic tissue will help patients. He also worries about the safety of any intervention that might affect the beating of the heart. "If you muck around with it, you could actually engender serious heart-rhythm problems," he says, "which can be deadly."

Even if this specific work never pans out, Epstein and others say the larger approach is still valid: learning how to manipulate the immune system to fight cancer has taught researchers information they can now use to fight diseases ranging from infections to arthritis.

Maus agrees: "I think we are definitely in a moment where this kind of science, this kind of potential product—engineered T cells—is transformational. They can be applied in so many different settings and diseases," she says. But "I think it's still a little bit early to know whether it's going to be a commercial product for patients."

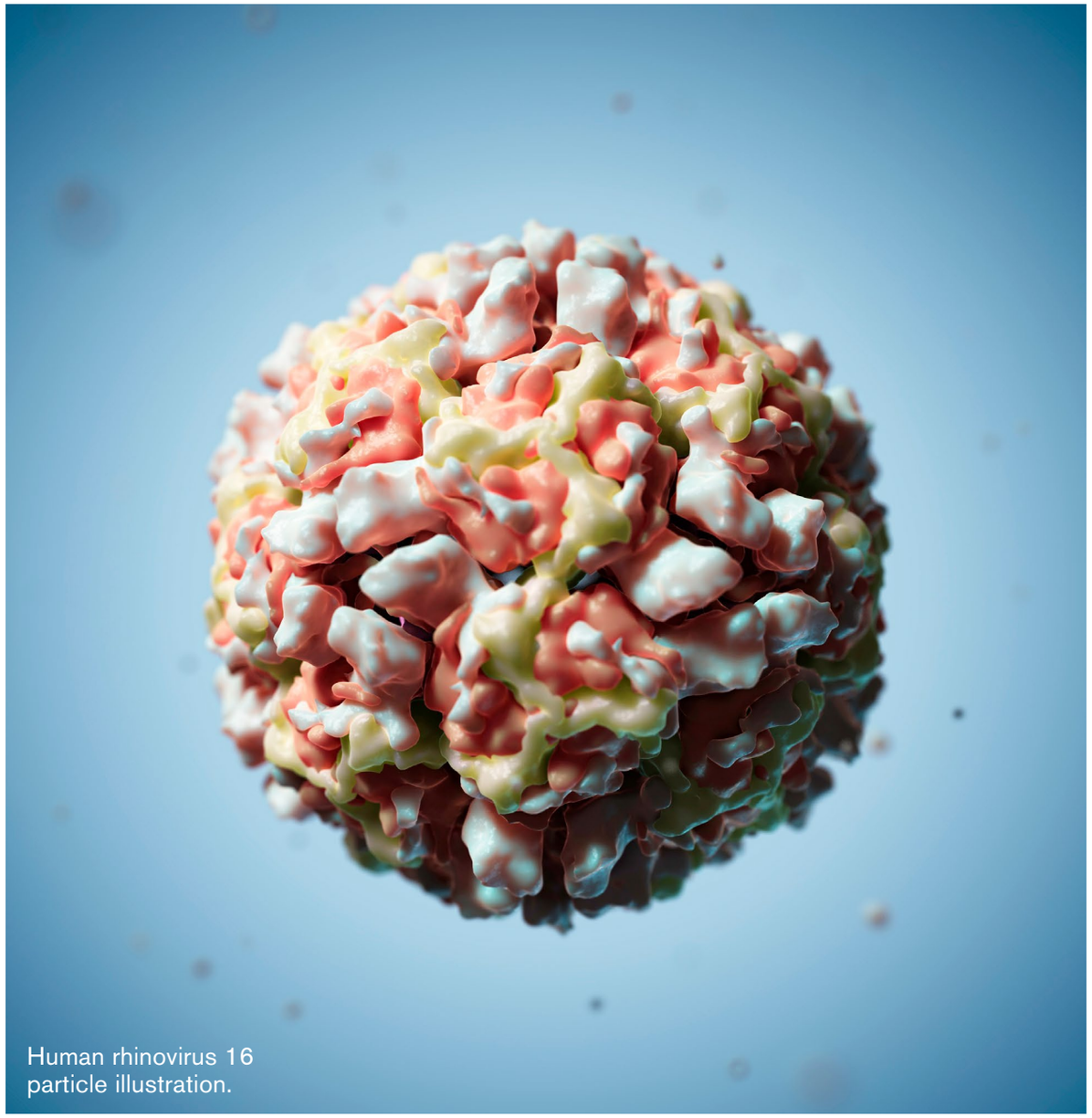
—Karen Weintraub

A Newly Identified Protein May Be the Key to Vanquishing the Common Cold

Inactivating this protein in human cells and mice provided immunity to a range of viruses, but an effective treatment is still a long way off

DEFENDING AGAINST VIRUSES IS one of the thorniest problems in medicine. Vaccines have been a major success story but can still only fend off a fraction of known viruses. They work by "teaching" our immune system to recognize a specific virus so it can mount an effective immune response if it spots that invader in future. Another approach is the use of antivirals, which prevent viruses from replicating and can be used to treat a current infection if administered quickly. Developing safe antivirals is difficult, however, because viruses hijack the host's own cellular machinery to replicate, so interfering can also harm host cells.

A problem for both approaches is the huge diversity of viral pathogens. For instance, the viral group responsible for at least half of all cases of the common cold—rhinovirus—has at least 160 different types. Developing more than 100 vaccines to cure one illness is obviously not practical, and in any case, other viruses also cause colds. Complicating matters further, many viruses can mutate in ways that make them resistant to drugs or capable of overcoming immunity. All of which is why an important goal in virology is the development of "broad spectrum" antivirals that are effective against many viruses simultaneously.



Human rhinovirus 16 particle illustration.

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In a study published in September in *Nature Microbiology*, microbiologist Jan Carette of Stanford University and his colleagues report they have found a human gene that produces a protein essential to the function of numerous enteroviruses, a genus that includes rhinoviruses. Experiments in human cells and mice showed a range of enteroviruses cannot replicate without this host protein. The work could pave the way for antivirals effective against multiple illnesses—including most cases of the common cold—and sheds new light on how viruses exploit their host's own cellular material. Carette and his colleagues have "done a tour de force here, to find this gene and characterize it," says Ann Palmenberg, a virologist at the University of Wisconsin–Madison, who provided some advice and materials for the study but was not directly involved in it. "It's a beautiful piece of work."

Enteroviruses also include poliovirus, coxsackievirus (which causes myocarditis, or heart inflammation)

and EV-D68, a virus that has been linked to acute flaccid myelitis. To search for commonalities between these viruses, the researchers used cutting-edge gene-editing technology to inactivate single genes from human cells grown in a lab dish. First they created a bank of cells that each lacked a different gene, spanning the whole human genome. Then they infected these cells with two enteroviruses: EV-D68 and a "type C" rhinovirus called RV-C15. The latter is a fairly newly discovered rhinovirus type that can seriously exacerbate asthma symptoms and increase the risk of infected infants developing asthma and chronic obstructive pulmonary disease. Although they are both enteroviruses, EV-D68 and RV-C15 are relatively distant relations that mostly make use of different host-cell proteins. The team then looked at which genes were missing in cells that continued to flourish after infection, focusing on the few whose absence thwarted both viruses. In addition to two genes that produce proteins known to be needed by enteroviruses, one little-known one stood out: *SETD3,* which makes a protein of the same name.

Carette and his colleagues next investigated how widely enteroviruses, in general, depend on the protein SETD3. They created cells lacking *SETD3* and infected them with seven viruses representative of the different species of human enteroviruses: one of each of the three types of rhinovirus (A, B and C), poliovirus, two types of coxsackievirus and EV-D68. None of these could flourish in SETD3-deficient cells—their replication rate was reduced 1,000-fold as compared with control cells that possessed the gene. "We could barely detect any virus being replicated in the knockout cells," Carette says, referring to cells engineered not to have the gene. The findings suggest that targeting SETD3 could produce a broadly effective therapeutic. "We really tried to maximize the diversity of enteroviruses we screened for, and [SETD3] was important for all of them; that was quite striking," Carette says. "I'd be surprised if there are enteroviruses that don't require this host factor." This process was done in a widely used cancer cell line, but the team repeated some tests in a cell type that resides in the entrance to the lungs and got similarly impressive results. "For the respiratory viruses, like rhinovirus and EV-D68, the important part is the bronchial epithelial cells because those are where the virus actually replicates," Carette says.

"For the respiratory viruses, like rhinovirus and EV-D68, the important part is the bronchial epithelial cells because those are where the virus actually replicates."
—Jan Carette

Finally, Carette and his team genetically engineered mice that lacked the *SETD3* gene. "To our great surprise, if you make mice that lack this SETD3 enzyme, they're viable and apparently healthy," he says. They did find one defect: the mice had difficulty giving birth. In a recent study, biologist Or Gozani, also at Stanford and co-senior author of the new study, and his colleagues found that in a process called methylation, the SETD3 protein modifies actin, a protein important in cell shape and division and muscle contraction. "It seems actin methylation is important for smooth muscle contraction during childbirth," Carette says. He and his colleagues injected these mice with two enteroviruses—a coxsackievirus and EV-A71, both of which cause fatal neurological disease involving paralysis and brain inflammation. Mice missing *SETD3* appeared immune to both viruses.

The researchers next tried to identify why the viruses need the SETD3 protein. They ruled out its normal function (the actin-modifying role), raising hopes that it could be targeted in ways that do not interfere with this function. Beyond that, they only narrowed it down to *something* to do with replication. Viruses use a combination of their own components and parts they pillage from the cell to build a "replication complex" that acts like a copy machine. "The virus gets in, but it can't start making photocopies of itself," Carette says. "It requires this SETD3 as an essential part of this photocopier."

There are two possibilities: either the viruses use SETD3 in a unique

way, or they co-opt an as yet unknown function of SETD3. The latter possibility means drugs targeting SETD3 could have unforeseen side effects. "There's a long way to go before we'll know if we can develop an antiviral that targets this protein; we're talking many years of work," says microbiologist Vincent Racaniello of Columbia University, who was not involved in the new study. "Just because you can take it out in mice doesn't mean you could take it out in people." The only way to know for certain whether a drug targeting SETD3 was toxic to humans would be to test it in a small human trial. "And if it is, that's the end of the story," Racaniello says. "That really tempers my enthusiasm."

Knowing what the viruses use SETD3 for will largely determine the likelihood of this new target leading to effective therapeutics, Palmenberg says. It will answer questions such as what proportion of SETD3 needs to be blocked to stop viruses replicating and whether that amount applies across many enteroviruses uniformly. This information will determine what a therapeutic would look like, how it would be delivered and whether it will even be feasible. "We simply don't know, because we don't know why the [virus] binds that protein in the first place," Palmenberg says.

In addition to tackling such questions, Carette's team plans to search for drug candidates by screening for chemicals that either stop enteroviruses interacting with SETD3 or degrade the protein. "We have the target but not yet the drug," he says. "We're now focusing on that part." Ultimately he and his colleagues hope to circumvent the problem of viruses developing drug resistance.

Traditional antivirals target viral proteins, making them easy for viruses to thwart. "We do it in a slightly more circumspect way, where you target a host protein, so tha the virus cannot simply mutate away the drug-binding site," Carette says. The approach is known as host-directed therapy because the treatment alters something in the host that the virus needs to function. "It has the potential to be broad spectrum, and there's less chance of developing antiviral resistance," Carette says. "There's real enthusiasm for this kind of approach."

—*Simon Makin*

KITTI BOONNITROD *GETTY IMAGES*

Discovery of Molecular Switch for How Cells Use Oxygen Wins 2019 Nobel Prize in Medicine

Research by William Kaelin, Jr., Peter Ratcliffe and Gregg Semenza led the way for applications in treating anemia, cancer and other diseases

THIS YEAR'S NOBEL PRIZE in Physiology or Medicine was awarded to three researchers who helped reveal the mechanism by which cells in the body sense and adapt to oxygen availability. William Kaelin, Jr., Peter Ratcliffe and Gregg Semenza shared the prize for their work, which has played a critical role in understanding—and ultimately treating—diseases such as anemia and cancer. The scientists will share the prize, worth nine million Swedish kronor ($907,695).

"Oxygen is essential for life and is

used by virtually all animal cells in order to convert food to usable energy," said Randall Johnson of the Karolinska Institute, a member of the Nobel Committee, at a press conference in Sweden announcing the award. "This prize is for three physician scientists who found the molecular switch that regulates how our cells adapt when oxygen levels drop."

Oxygen levels can fall throughout the body—for example, at high altitudes or during exercise—or in a local area, such as at a wound site. Low oxygen levels, or hypoxia, lead to new blood vessel formation, blood cell formation, or glycolysis (anaerobic fermentation). Hypoxia was known to trigger a rise in the hormone erythropoietin (EPO), which is involved in producing red blood cells, but the prizewinning scientists revealed the mechanism for how this process works.

The hypoxia response affects many aspects of physiology, including conditions such as anemia, cancer, stroke, infection and heart attack. Cancer cells, for instance, need a blood supply to grow, and they can hijack this oxygen-sensing system to create more blood vessels. The research is already leading to the development of new treatments.

Semenza, who is at Johns Hopkins University, showed that hypoxia triggers expression of the *EPO* gene. Using genetically modified mice, he revealed that certain DNA segments next to this gene regulate its response to low oxygen levels. Semenza discovered a protein complex called hypoxia-inducible factor (HIF), which is composed of two transcription factors—proteins that control the transcription of DNA into RNA—called HIF-1α and ARNT. When oxygen levels are high, HIF-1α is constantly degraded. But when oxygen is low, HIF-1α increases, binding to the *EPO* gene and other genes and triggering red blood cell formation. Ratcliffe, who is at the University of Oxford and the Francis Crick Institute in England, also studied how oxygen regulates the *EPO* gene. Both his team and Semenza's demonstrated this mechanism was present in all cells.

Meanwhile Kaelin, who is at the Dana-Farber Cancer Institute in Boston, was studying an inherited syndrome called von Hippel-Lindau (VHL) disease, which greatly increases the risk of certain cancers in some families. He showed that the *VHL* gene encodes a protein that prevents cancer from developing and that cancer cells lacking this gene also had high levels of activity in genes regulated by hypoxia. When the *VHL* gene is introduced to these cells, it restores the activity levels of the genes to normal. But scientists still did not know how oxygen levels regulated this molecular switch. In 2001 Kaelin and Ratcliffe simultaneously demonstrated that when there is enough oxygen present, hydroxyl groups are added to HIF-1α, allowing *VHL* to bind to it and leading to its degradation.

"When I was young, my father's favorite activity was fishing; part of the secret is knowing where to fish. One thing I got right was understanding that von Hippel-Lindau disease was the right place to go fishing."
—William Kaelin, Jr.

The research is already leading to clinical applications. Lowering the expression of the *HIF-1α* gene could limit a tumor's ability to grow a new blood supply. In contrast, increasing its expression could help treat people with anemia.

"It's a good day for [Johns] Hopkins," Semenza said in a livestreamed press conference at the university. The message he had for every scientist training today was: "I was once where you are now, and someday you will be where I am now. We're very lucky to have this career where we get to follow our interests and dreams wherever they lead."

"I'm honored and delighted at the news," Ratcliffe said in a statement. "It's a tribute to the lab, to those who helped me set it up and worked with me on the project over the years, to many others in the field, and not least to my family for their forbearance of all the up and downs."

"I will confess, like most scientists, I did allow myself to dream that maybe one day this would happen," Kaelin said in a livestreamed press conference at Dana-Farber. "When I was young, my father's favorite activity was fishing; part of the secret is knowing

where to fish. One thing I got right was understanding that von Hippel-Lindau disease was the right place to go fishing."

Kaelin's colleagues praised the work. The discoveries "fundamentally defined how cells in the body sense oxygen and how the cells respond to an abundance of oxygen or an absence of oxygen," said Betsy Nabel, president of Brigham Health, where Kaelin is a senior physician, at the Dana-Farber press conference. At the same event, George Daley, dean of Harvard Medical School, added that the work "is a powerful reminder of how critical discoveries and transformative therapies flow from [the] deepest understanding of basic mechanisms."

The awardees were, in some ways, a surprise. There had been speculation that this year's prize would honor the discovery of the gene-editing tool CRISPR, of receptors for immune cells called T cells, or of optogenetics—a technique for using light to control living cells.

Last year's prize was awarded to immunologists James P. Allison and Tasuku Honjo for their work showing how the immune system can be harnessed to fight cancer

—Tanya Lewis

Editor's Note *(10/7/19): This story was updated after publishing to include quotes from Gregg Semenza of Johns Hopkins University, William Kaelin, Jr., of the Dana-Farber Cancer Institute, Peter Ratcliffe of the Francis Crick Institute, Betsy Nabel of Brigham Health and George Daley of Harvard Medical School.*

CBD

Hype or Promise?

The compound is found in everything from coffee to cookies, but the research on its efficacy is scant

By Amber Dance

CHRIS GASH

Science writer **Amber Dance** lives in the Los Angeles area.

IN NOVEMBER 2017 SCIENTISTS AT a subsidiary of Artelo Biosciences in Manchester, U.K., tasked an intern with compiling any scientific study published on the body's absorption, distribution and metabolism of cannabidiol. The company hoped to treat stroke with the compound, which is derived from the cannabis plant and commonly known as CBD, and this background research was crucial.

When the intern returned with all the literature she could find, it was a short stack: only a couple of dozen papers. The scientists were stunned. They'd expected more from a molecule receiving so much attention from the biomedical world and consumers. As they surveyed the scant literature, they wondered: Is this all there is?

The desire for more information about how CBD acts in the body is growing as various companies pursue it in drug development. It's only in the past decade that the first CBD drugs have been approved: Sativex for multiple sclerosis symptoms, in multiple countries; and Epidiolex for certain kinds of epilepsy in children, in the U.S. GW Pharmaceuticals, the maker of both medications, expects European Union approval for Epidiolex soon. Beyond that, there are dozens of ongoing clinical trials for conditions ranging from schizophrenia to Crohn's disease to graft-versus-host disease—not to mention the appearance of CBD in consumer products ranging from oils to coffee to tampons.

"CBD is exploding in popularity," says Nick Jikomes, a neuroscientist and principal research scientist at the cannabis information site Leafly in Seattle. "It seems that every corner store you walk into is selling a CBD something or other." In the U.S. alone, a recent Gallup poll found 14 percent of Americans use CBD products, and the CBD market is projected to top $20 billion per year by 2024, according to one analysis.

CBD could, potentially, treat such a wide variety of conditions because it binds to various receptors in the body, particularly in the endocannabinoid system, which is involved in pain, mood, metabolism, reproduction, and more. These receptors are found in the nervous system, as well as many other tissues, including heart, liver and immune cells. CBD can cause side effects such as nausea, fatigue and irritability but doesn't make people feel high.

Considering that people have used cannabis for millennia, scientists still know surprisingly little about how CBD, often the second most prevalent active compound in the plant, is absorbed and metabolized by the body. "Unfortunately," Jikomes adds, "we don't have the information we would like to have about dosing."

The U.S. National Academies of Sciences, Engineering and Medicine bemoaned the lack of information to help consumers make smart choices about cannabis products in a 2017 report. The authors recommended more research on the biological actions and transportation within the body of cannabis compounds, as well as the effectiveness of different delivery avenues and dose-response curves in diverse populations. Both CBD's complex biochemistry and government regulations that restrict cannabis studies, mostly in the U.S., have conspired to slow a detailed understanding of its metabolism.

The fact that cannabis and CBD are readily available in many parts of the world, sometimes legally and sometimes not, and with or without a prescription, has created a unique medical, commercial and legal conundrum, says Arno Hazekamp, a cannabis researcher and consultant in Leiden, the Netherlands. CBD is being tested in uncontrolled home-based experiments even as scientists strive to match defined doses to medical conditions in official trials.

In fact, GW Pharmaceuticals' early CBD research helped give families of children with epilepsy the idea to try it, with success, well before it was an approved medication. Justin Gover, CEO of the company in Carlsbad, Calif., says of those families, "They inspired and motivated us."

DEARTH OF DATA

By early 2018 Artelo had decided not to pursue CBD for stroke, but the researchers wanted to share what they'd managed to dig up on the compound. In a review of the literature on CBD processing, collaborators at Artelo and the University of Nottingham, U.K., discussed 24 papers, mostly studies of healthy adults.

According to their literature survey, CBD's half-life ranged from one hour to five days, depending on the route of administration: delivering the compound by a

mouth spray meant it lasted just hours, for example. In contrast, injected and smoked CBD persisted for about a day. One study reported that 31 percent of smoked CBD reached the bloodstream. The fraction that reaches the bloodstream from pills or mouth sprays is thought to be much lower, says Sophie Millar, the intern who had been tasked with the literature search at Artelo two years ago and who is now completing a Ph.D. in the endocannabinoid system at the University of Nottingham.

The team went further in a second article, analyzing the doses used in 35 clinical studies. The papers were a "mixed bag," notes study co-author Andrew Yates, a consultant at Artelo. The conditions under study included anxiety, diabetes, chronic pain, and more. Doses ranged from less than one to 50 milligrams per kilogram body weight per day, but no study reported CBD plasma concentrations. About two thirds of the studies reported CBD to be associated with improved outcomes.

"The more successful trials tended to use a higher dose," Yates says. Lower doses seemed to work for anxiety, though. "More research needs to be done, and it needs to be done in a controlled, pharma-like way," Yates says.

That's what companies like Artelo and GW are doing. Since Millar and her colleagues completed their literature searches in August 2018, GW has published more on CBD metabolism in healthy subjects, under various dosing regimens with up to 6,000 milligrams at a time. CBD reached the blood quickly after a single oral dose, hitting its maximum plasma concentration within four or five hours. With twice-daily dosing, the compound reached fairly steady blood levels after two days, although bloodstream CBD did continue to rise over a week. The company concluded that twice-daily treatment provided a steady supply of CBD, with minimal side effects, including nausea, headache and sleepiness.

But that does not mean that other CBD oils would work similarly. "Those data are specific to Epidiolex and the formulation," Gover asserts. "One can't just read through from Epidiolex data into other CBD formulations."

The lack of reliable data on dosing means that some clinical trials might fail not because CBD doesn't help but because they didn't use the right amount. Other trials may land on a dose that's okay but doesn't maximize benefit while minimizing side effects.

Many patients aren't waiting around for more information on dosing. They are eager to try CBD products for many different ailments and going to their physicians for guidance. But in a recent review, physicians noted that many clinicians don't know how much CBD to prescribe, especially if they venture beyond well-understood indications such as epilepsy and psychosis.

It would help if doctors had formulas to predict a starting dose for a given individual with a particular condition, says Jennifer Martin, a pharmacologist and physician at the University of Newcastle in Australia. For many other medications, such as antibiotics, doctors and pharmacists can enter a patient's characteristics—such as age, sex or kidney function—into such equations to receive a suggested dosage. This can be particularly helpful if trials haven't offered up dosing data for every possible patient group, such as people of certain races, Martin says. She is working on such formulas for CBD and THC, another prominent cannabis compound that is responsible for marijuana's high but also has medical benefits.

When Martin searched the literature for CBD dose-guidance equations for a recent review, she, like Millar, came up short. She couldn't find even one paper that met her criteria: intravenous dosing and reporting of individual patient bloodstream concentrations. In contrast, 12 studies were available for THC, which has a longer clinical history.

Martin and her colleagues are now collecting the necessary CBD data: they need correlations between plasma concentration and effects, starting with healthy volunteers, as well as those with liver or kidney problems that might alter drug processing. Data from people who use CBD to treat specific conditions would be useful, too.

"It's a bit scary, really, isn't it?" Martin says. "There's not really much evidence to tell us how much better [CBD] is than other therapies that we've currently got, how much better it is than placebo, and also what dose we should use."

"There's not really much evidence to tell us how much better [CBD] is than other therapies that we've currently got, how much better it is than placebo, and also what dose we should use."

—Jennifer Martin

DOSING DIFFICULTIES

CBD's behavior makes it tricky to understand. It may bind to different cell receptors in the endocannabinoid system and beyond—including receptors in the serotonin, opioid and dopamine systems. And where it binds depends on the dose, Jikomes says. At different concentrations, "it can essentially behave as a different drug," he says. So, more isn't necessarily better. In fact, in one study, antianxiety effects peaked after a 300-milligram dose; 900 milligrams proved less effective.

Another complication: CBD is oil-soluble. The amount of drug absorbed into the bloodstream increases if it's taken with food or infused into oils. GW reported in its 2018 study that plasma concentrations more than quadrupled when the liquid medicine was taken with a high-fat meal, including fried eggs and bacon, compared with the medicine alone. CBD can also be absorbed by the body's fat stores and released later.

All of this means that the ideal prescription will vary by many factors, including but not limited to sex, weight and medical conditions. In the case of the Sativex mouth spray, new users start with one spritz in the evening and slowly work up to an effective dose, with a maximum of 12 sprays daily. Sativex also contains THC, so patients can feel when they've had too much. With Epidiolex, kids start at five milligrams per kilogram body weight per day but can go as high as 20 milligrams if needed to reduce seizures.

Whatever the indication, the best approach is to start with a low dose and raise it slowly over up to two weeks, says Ethan Russo of Vashon, Wash., director of research and development for the International Cannabis and Cannabinoids Institute in Prague.

Another issue is that CBD is a botanical, from a plant that makes more than 100 compounds that come only from cannabis, called cannabinoids, plus other potentially bioactive molecules such as terpenoids. Cannabis extracts available over the counter contain varying amounts of CBD itself, along with other compounds. Indeed, some over-the-counter products, on testing, turn out to have no CBD at all. Even if some CBD is present, it's probably not enough to have an effect, Hazekamp says. "People are massively underdosing themselves."

Even more standardized products, from pharmaceutical companies or the government, can vary in form and purity. "We're not dealing with a single molecule, in known amounts, as it would be with standard pharmaceutical agents," Russo says. That means that aside from the two government-approved medications, doctors cannot necessarily look to clinical trials to find the right dose to prescribe to a patient, who might get the product from a different source.

There are some in the scientific community who believe that the myriad chemicals in cannabis extracts might be a good thing. The additional compounds can create a sort of synergy known as the entourage effect. In fact, one review found that CBD-rich extracts, compared with purified CBD, worked against epilepsy at lower doses and with fewer side effects. Using such extracts could result in more effective, less expensive medications, Russo suggests. On top of all that, CBD trialists must also consider drug-drug interactions. Like grapefruit juice, CBD can block liver enzymes that break down other drugs.

Despite these myriad challenges, researchers are forging ahead. Some are monitoring people who are already using over-the-counter CBD, from diverse sources and for a variety of ailments, to get a better sense of how much of the compound might work for different conditions. "If you have those data, it doesn't mean you have proof, but then you can narrow down the combinations of products and diseases that really seem to matter," Hazekamp says.

Martin notes that after she published her review on the dearth of data on CBD, she received many calls from scientists eager to collect and share the right information.

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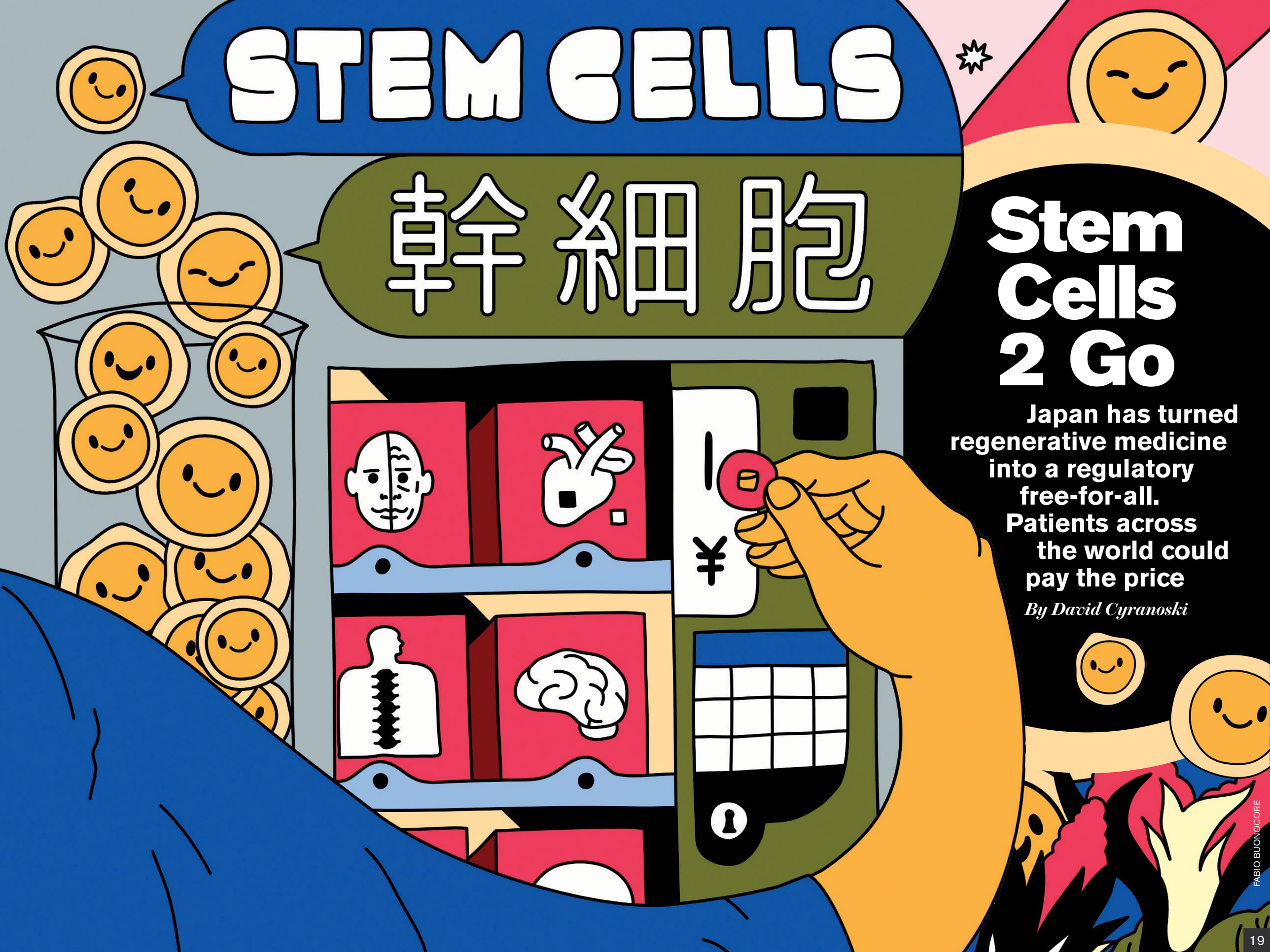

Stem Cells 2 Go

Japan has turned regenerative medicine into a regulatory free-for-all. Patients across the world could pay the price

By David Cyranoski

FABIO BUONOCORE

David Cyranoski works for *Nature* magazine.

TUCKED AWAY IN TOKYO'S TRENDIEST FASHION DISTRICT—TWO FLOORS ABOVE a pricey French patisserie and alongside nail salons and jewelers—the clinicians at Helene Clinic are infusing people with stem cells to treat cardiovascular disease. Smartly dressed female concierges with large bows on their collars shuttle Chinese medical tourists past an aquarium and into the clinic's examination rooms.

During a typical treatment at Helene, clinicians take skin biopsies from behind the ear and extract stem cells from the fat tissue within. Then they multiply the cells, infuse them intravenously and, they claim, let them home in on the damage—in this case, arteries stiffened by atherosclerosis.

Two posters on the wall outline promising results backed by major pharmaceutical companies and published in top scientific journals. They lend an air of legitimacy, but neither presents data on treatments offered at the clinic. When pressed for details by a visitor (who did not identify himself as a journalist), a concierge said that she could not offer evidence that Helene's services are effective at treating the condition, mainly because results vary by patient. She eventually explained that the treatment is more for prevention. "It's for antiaging," she said.

When *Nature* later contacted the company with a list of questions, a representative declined to provide evidence that the treatment works or information on the number of people treated or their outcomes, saying that the company would be announcing the results in future conference presentations. He affirmed that Helene Clinic conducts all the necessary reviews and approvals for the procedures it performs as required by law and that patients have not developed side effects.

Clinics such as this, which sell unproven cell-based therapies, aren't new and aren't unique to Japan. They've become common globally, from Mexico to Ukraine, India and Australia, and regulators are struggling to keep up. In the U.S., authorities have grappled with a surge of clinics selling therapies that are unsupported by evidence and, in some instances, have harmed people. In Japan, however, the proliferation of stem cell clinics is different: it is sanctioned and promoted at the top echelons of government, thanks to a pair of regulatory acts designed to stimulate business and position Japan as a world leader in regenerative medicine.

Five years after Japan adopted these regulations, more than 3,700 treatments, including many based on stem cells, are on offer at hundreds of clinics across the country, and a wave of foreign companies has set up shop there. "Japan has become a focal point for the development of innovative therapies," says Gil Van Bokkelen, chief executive of the biotechnology company Athersys in Cleveland, Ohio, which is pursuing clinical trials of a stem cell–based treatment for stroke and respiratory disease in Japan.

Many companies, however, are taking advantage of the regulatory paths to avoid rigorous testing of their therapies and get them on the market fast. Scientists say that people who use them are probably not getting effective treatments. Most of the therapies approved for serious illnesses are supported by scant evidence, and there have been at least four reports of adverse events, including one death. Even government researchers and academic scientists who support the regulations say that changes are necessary.

Clinics maintain that they are operating within the law. And government officials argue that Japan's system is safer than those in other countries because it keeps tabs on the treatments being offered. But the policies might be giving people false hope about how effective these therapies are.

Meanwhile Japan's bold experiment in deregulation is beginning to influence others. Taiwan and India, for example, have started to follow the country's lead, and regulators elsewhere are feeling pressure from companies, patients and other advocates to speed up the approval process. "If we're left with very different global regulatory standards, it's going to be a really big problem," says Peter Marks, director of the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration.

One of the harshest critics, cardiologist Yoshiki Yui of Kyoto University in Japan, says that the regulation made quick gains in terms of business development but were shortsighted. "They've given no thought to what happens when things go wrong," Yui says.

SAFETY, NOT EFFICACY

Shortly after taking office in December 2012, Japanese Prime Minister Shinzo Abe promised to invest ¥110 billion (U.S.$1 billion) over the next decade into regenerative medicine. The bullish attitude came just months after Shinya Yamanaka of Kyoto University won the Nobel Prize in Physiology or Medicine for his work on induced pluripotent stem cells. Abe boasted that Japan is the world leader in regenerative medicine research but lamented the slow pace of clinical application. He soon announced two measures that he hoped would change that (see "Deregulation in Two Acts").

One of these, the Act on the Safety of Regenerative Medicine (ASRM), adopted in November 2014, allows hospitals and clinics to market cellular therapies without going through the usual kinds of trials to prove that a medicine is effective. To start offering such treatments, hospitals need to show that they have a cell-processing facility that is certified by the Ministry of Health, Labor and Welfare and then pass their proposal by an independent review committee, which must also be certified by the ministry.

Before the legislative change, rogue clinics were springing up and taking advantage of medical tourism. The act was meant to make sure that all clinics are registered so there would be no surprises, says Masayo Takahashi, an ophthalmologist and prominent member of the Japanese Society for Regenerative Medicine, who has been on government regenerative medicine advisory panels. "The strategy is to include everyone, then get gradually stricter" about what deserves to be listed, she says.

But the ASRM's registry can be misleading, critics say. Doug Sipp, who researches regulatory policy at RIKEN in Kobe, says that it has brought "more transparency to the industry." It has forced rogue clinics to meet some basic standards. There is a real risk, however, that patients will view the registry, "as a kind of validation," he says.

For example, Avenue Cell Clinic, a sleek operation in Tokyo that looks more like a spa than a medical center, features the fact that its treatments are listed on the ASRM registry prominently on its Web site. At least 10 patients have had fat-derived stem cells injected into their blood to cure or slow the progression of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS).

An Avenue Cell Clinic customer service representative said on the phone to someone calling for information (who did not identify himself as a journalist) that the symptoms of 50 to 70 percent of patients improved after the therapy, which costs ¥1.5 million yen per dose. Those who benefit are advised to continue infusions every two or three months. "Some people can afford that," the representative said. The clinic has about 1,000 patients per year for other indications.

Five scientists working on regenerative medicine for ALS who were contacted for this

Deregulation in Two Acts

Two laws introduced in Japan in 2014 offer a fast track to the market for stem cell–based treatments and other types of regenerative medicine. The Act on the Safety of Regenerative Medicine (ASRM) allows companies to register a therapy under one of three risk categories.

Fast-Track Categories

Classification	Requirements	Number of therapies registered (by June 2019)
Class III (low risk)	Treatments using cells from a patient and performing a function similar to the one they originally served, such as immune cells activated to fight cancer.	**3,373**
Class II (moderate risk)	Treatments using cells from a patient but performing a different function, such as stem cells derived from fat used to treat atherosclerosis or amyotrophic lateral sclerosis.	**337**
Class I (high risk)	Treatments using cells from a riskier source such as embryonic stem cells, gene-edited cells or cells from another person.	**0**

The Pharmaceutical and Medical Devices Act allows for conditional approval of treatments that have gone through some clinical testing. It gives companies the opportunity to market a treatment nationally and to receive insurance payments, but companies must collect extra data on efficacy over a seven-year period. Only three treatments have received this approval.

Conditional Approvals

Treatment	Purpose
HeartSheet	Cells from skeletal muscle are used to seed a sheet of tissue designed to help heal damaged heart muscle.
Stemirac	Uses stem cells derived from bone marrow to try to treat spinal-cord injury.
CLBS12	Uses blood-forming stem cells to treat critical limb ischemia.

story said that there was no convincing evidence that this kind of stem cell treatment would help people with the disease, and there are several reasons to think that it wouldn't work. Robert Baloh, who studies ALS at the Cedars-Sinai Regenerative Medicine Institute in Los Angeles, put it bluntly: "Quackery and false treatments have been marketed directly to patients for hundreds of years, and this is no different." A representative from Avenue Cell Clinic refused a formal request for an interview from *Nature* but stated in an e-mail that the clinic is acting in accordance with the ASRM. When pushed for a response to the verdict from ALS scientists, the representative said that they were too busy treating patients to respond.

In addition to the questions about evidence and efficacy, there are also concerns about the qualifications and independence of the committees that approve such treatments for inclusion in the registry. The health ministry requires that these committees comprise five to eight people and include specialists in cell biology, regenerative medicine, clinical research and cell culture. It also requires input from lawyers, bioethicists and biostatisticians. But rules about conflicts of interest on the committee have been lax.

Helene Clinic, for example, had an in-house committee that approved some of its therapies, including a treatment for atherosclerosis. A representative for the company says that this therapy was never given to patients, and Helene now uses an independent, third-party committee. The in-house committee was disbanded in March, according to the health ministry. The ALS treatment and several other therapies offered by Avenue Cell Clinic were approved by a committee that includes a staff physician. The clinic did not respond to questions about this.

The ministry instituted policies in April to prevent such conflicts. But even with fully independent committees, clinics can shop around for the answer they want.

Japanese Prime Minister Shinzo Abe (*right*) with stem cell biologist Shinya Yamanaka (*left*) and then RIKEN president Ryoji Noyori (*center*) at a lab visit in 2013.

Yoji Sato, who heads the cellular therapeutics unit of Japan's National Institute of Health Sciences in Kawasaki and who sits on two committees himself, says that "committee surfing" is a big problem.

The government is considering extra fixes, such as requiring training to make the committee system better. "Maybe there is a conflict of interest in the committees, maybe the treatments are not effective, but that's our limit right now," Sato says.

He nonetheless argues that the system is superior to what exists in the U.S., where regulators are continually chasing rogue clinics. Sato cites the case of two people who lost their sight after receiving an unproven and unapproved stem cell treatment in Florida. It took the FDA four years and a tortuous legal battle to stop the company from offering the treatment. In Japan, for those lacking committee approval, "the police can go and arrest people," Sato says.

CONDITIONAL APPROVAL

The other important policy that Abe's government implemented in 2014 is known as the Pharmaceutical and Medical Devices Act. Under it, a company can earn "conditional approval" to sell a treatment nationwide—not just at a single clinic or hospital—and have the costs covered by the insurance system. Unlike with the ASRM, the firm needs to present data that suggest efficacy from a small clinical trial. It can then sell the treatment for up to seven years, as it ostensibly collects better efficacy data. So far only three treatments have earned conditional approval: one for spinal-cord injury, one for heart disease and one for critical limb ischemia, a painful condition characterized by reduced blood flow to the extremities.

But the pared-down clinical trials necessary for conditional approval have stoked concern in the scientific community. A 2016 report from the International Society for Stem Cell Research said that giving marketing approval on the basis of small-scale trials could slow down rigorous evaluations of the treatments and "erode confidence in the scientific standards of the field."

Anecdotally, some people have reported issues. One man with a chronic heart condition, who asked not to be named to protect his privacy, tried an experimental treatment that involves creating a thin sheet of tissue using

GETTY IMAGES

transplanted muscle cells extracted from a patient's thigh and placing it onto the damaged heart during open-chest surgery. A version of the treatment, called HeartSheet, was conditionally approved for treating a condition known as ischemic cardiomyopathy in 2015. The man, who had a different type of cardiomyopathy, met one of the technology's co-creators, Yoshiki Sawa, a surgeon at Osaka University in Japan. Sawa told the man that he would be a good candidate for the experimental treatment.

The patient, who was under the impression he was receiving HeartSheet, was worried because few people with his diagnosis had received the treatment, and he had never had heart surgery before. But he gave it a chance.

The man says that he never felt his condition improve. Nine months later he suddenly started feeling a shortness of breath he had never experienced before. Diagnosed with cardiac failure, he was hospitalized for a month. A month after being released, he was hospitalized again.

A little more than a year after trying the procedure, he was told he needed a heart transplant. "I was told things were getting worse," he says.

Without more information, it is impossible to say whether the experimental treatment contributed to the man's cardiac failure. It is just one case, and other explanations are possible. But the uncertainty illustrates part of the problem. The clinical trial that led to HeartSheet's conditional approval included only seven people. Terumo Corporation, which markets the treatment, is still collecting data on its effectiveness for ischemic cardiomyopathy; it says the patient did not receive HeartSheet as part of his treatment. Little is known about the rate and type of adverse events that people might encounter.

Central to the debate over Japan's policy is the value of randomized, placebo-controlled trials. These are conventionally considered to be the gold standard for clinical research, but Japan's government followed a position floated by the Japanese Society for Regenerative Medicine in 2012, which specifies that trial designs to prove efficacy should not always require control groups receiving a placebo or conventional therapies.

"The law was made for men of good nature, but there are many that are not good. In 10 years, cell therapy will be very good. So we can tolerate criticism now."

—Masayo Takahashi

In clinical trials leading to the approval of HeartSheet, Sawa stated that the natural progression expected for such patients was steady degeneration. Five of the seven people who received HeartSheet didn't get worse, and so the treatment looked like it was helping. But a study of some 3,500 individuals in Japan shows that most people with a similar severity of heart disease to the people in Sawa's trial get better or are stable without drastic intervention. Sawa did not respond to a request for comment.

Japan's health ministry has stuck by its stance on placebo-controlled clinical trials for regenerative medicine. Following the criticism of a treatment for spinal-cord injury called STR01 that went on sale in May, Shinji Miyamoto, a health ministry representative, argued that double-blinded experiments with the therapy were "structurally impossible" and said that a sham procedure or placebo "would raise ethical issues."

Bioethicists have long debated the potential harms caused by sham treatments in clinical trials and whether they are fair to participants. Some are certainly too invasive, says Jonathan Kimmelman, a bioethicist at McGill University, who has advised the Japanese government on clinical-trial policy. But doctors researching stem cell therapies for spinal-cord injury say that a placebo-controlled trial for this condition would be relatively easy.

Osamu Honmou, a neurosurgeon at Sapporo Medical University in Japan, who offers STR01, had previously advocated for double-blinded, placebo-controlled trials to prove the treatment's efficacy in people who have had a stroke. According to a 2016 publication, he expected to be in the middle of carrying out just such a trial by now. But he did not respond to *Nature*'s request for clarification as to what makes such trials appropriate for treating the damage caused by stroke but not for spinal injuries. A health ministry representative says that a sham procedure would be unethical in the latter case because patients need treatment within a certain window of time, after which therapy might prove less effective. Such arguments, however, assume that the procedure is effective.

Several prominent scientists in Japan have told *Nature* that STR01, also known as Stemirac, shouldn't have been approved for spinal-cord injury. "Abe's cabinet needs one or two examples of success in science urgently," says one cardiologist, who did not want to be named. "Abe's cabinet is being too aggressive." The administration did not respond to requests for comment.

GLOBAL AMBITIONS

Despite holes in the system, Japan is trying to get its regenerative medicine policies adopted elsewhere, in part to secure markets for its treatments. According to a five-year

plan released this March by the health ministry's drug-regulating division, the government funds outreach programs aimed at disseminating Japan's model for regulating regenerative medicine products and fostering trust toward Japanese regulatory agencies and getting Japan's regulatory model introduced in other countries."

The efforts seem to be making an impact, Sato says. Taiwan has drafted a conditional-approval law for regenerative medicines based on Japan's legislation, and South Korea approved a system similar to Japan's in August. India mentioned Japan's system in deliberations leading to its first regenerative medicine conditional approval in 2015. And this year mainland China announced a draft policy that would give hospitals free rein to use stem cells as "medical practice." "Several other countries have responded in kind, prioritizing a skewed vision of economic competitiveness over patient welfare," Sipp says.

Some hope to see a similar system in the U.K., and say that the timing—with the country's exit from the European Union looming—is right. In a February 2018 interview with the BBC, Ajan Reginald, co-founder and chief executive of Celixir, a company in Stratford-upon-Avon, that makes a cellular therapy called Heartcel for heart disease, said that Brexit could offer the U.K. a chance to introduce its own accelerated regulatory pathway.

"There is a lot of enthusiasm among certain people in the U.K. to adopt the Japanese model," says Patricia Murray, a stem cell biologist at the University of Liverpool. The kind of deregulation done in Japan, she says, "will enable companies to sell their bogus therapies direct to consumers."

And the rapid pace of development has presented a challenge for regulators elsewhere. The FDA has been under increasing pressure from businesses and patient groups—including the California Institute for Regenerative Medicine and conservative think tank The Heartland Institute—to take an approach more like Japan's.

Marks explains that it is a problem because people point to Japan and say, "'You guys at the FDA, you're just not approving stuff.'" Marks was responding to questions at a medical journalism conference in May in Baltimore and he affirmed that his group wants to see new treatments made available. "We just want to see that they're safe and effective."

Lee Buckler, the chief executive of regenerative medicine company RepliCel in Vancouver, B.C., which licensed its skin-rejuvenation product to the Tokyo-based cosmetics company Shiseido in 2016, sees this pressure as a plus. He says people who desire fast access to medicines see what's happening in Japan and "press for similar access in their country."

Pride over Japan's achievements in stem cell biology and regenerative medicine have played a large part in the efforts to grow the industry. But Yamanaka, who has been one of the most prominent faces of those achievements, has remained relatively quiet on matters of deregulation.

In contrast to the quickly moving currents elsewhere in the country, Yamanaka's institute, which is dedicated to bringing stem cell treatments to the clinic, seems unwilling to rush through a clinical trial. "Double-blinding control should be considered whenever possible," Yamanaka told *Nature*. And although he understands that this can be difficult for some cell therapies, even in those cases, "scientists should do their best to make clinical trials as objective and scientific as possible."

In the absence of objective and scientific measures, it becomes difficult to know what and who to trust, some stem cell researchers say. "There is a problem," Takahashi observes. "The law was made for men of good nature, but there are many that are not good." Still, she takes the long view: "In 10 years, cell therapy will be very good. So we can tolerate criticism now."

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Rethinking Herd Immunity

The global rise of "vaccine hesitancy" is changing the landscape of disease transmission

By Lynne Peeples

ERIC COLLINS

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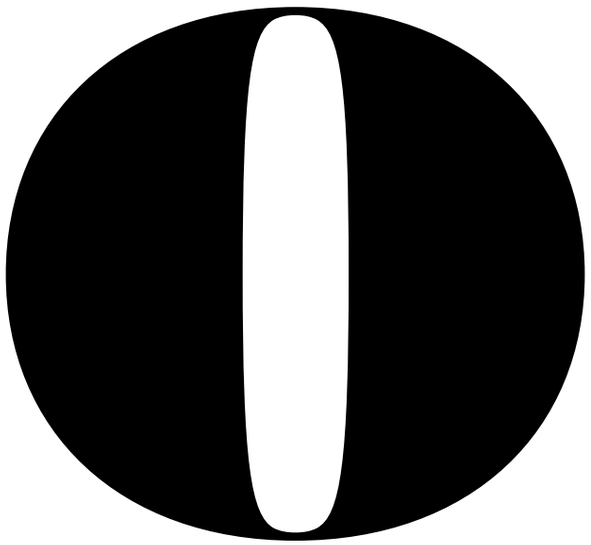

ON JANUARY 13, 2008, AN UNVACCINATED SEVEN-YEAR-old boy returned home to San Diego from a family vacation in Switzerland. He and his family were unaware at the time that he had been infected with measles during their trip. He became sick within a week of arriving home and only received a diagnosis of measles the following week. Public health officials scrambled to assess the situation and ultimately determined that, by unintentionally importing the virus causing measles, he had exposed 839 people in the San Diego area to it, of whom 11 also developed the disease, including a hospitalized infant who was too young to be vaccinated.

This all happened despite the fact that some 95 percent of children in San Diego County had been vaccinated against the disease. That proportion, according to the concept of herd immunity, should be enough to keep measles at bay and protect those left unvaccinated. So why did the outbreak still occur? That question has become more common as outbreaks of preventable disease increasingly crop up in areas thought to have good population-level protection.

Public health researchers note two critical factors that continue to drive epidemics of measles, polio, whooping cough (pertussis) and other vaccine-preventable diseases—even when broad vaccination rates are high: growing numbers of domestic and international travelers and proliferating pockets of parents who choose not to vaccinate their children.

"The risk of transmission for some of these diseases in a globally connected world is higher," says Orin Levine, director of vaccine delivery at the Bill & Melinda Gates Foundation in Seattle. "Infectious disease threats don't recognize and are not bound by borders; the best line of defense we have is to create virtual walls of immunity by increasing vaccination coverage everywhere in the world so that viruses can't make anybody anywhere sick."

Levine and others talk about a need to consider population immunity at both a global and hyperlocal level. Take the case of the seven-year-old boy who returned to San Diego with measles. His parents had chosen not to vaccinate him or his siblings. And he attended a San Diego charter school in which parents of 17 percent of the students had signed personal beliefs exemption forms to opt their children out of required vaccinations. So while the average vaccination rate may have been high across the county, it varied locally; rates in some neighborhoods like his fell far below the necessary threshold to achieve herd immunity.

In effect, a cluster of unvaccinated children acts as piled-up kindling. When the infected boy returned home, he was the match that lit the pile. And the fuel kept the virus sustained long enough that it could jump to other vulnerable piles. "If you've got disease popping up in a community, that herd immunity in essence goes away," says Seth Berkley, CEO of Gavi, the Vaccine Alliance, a public-private health partnership that aims to increase access to immunizations.

Recent headlines describe similar stories: an unvaccinated five-year-old French boy reintroduced measles to Costa Rica in February, and ongoing measles outbreaks in the U.S. have resulted from infected travelers transporting the virus from undervaccinated areas of Eastern Europe and Israel to close-knit undervaccinated communities in Washington State and New York State. A man traveling in March from the affected ultra-Orthodox Jewish community in New York City unknowingly sparked another outbreak in southeastern Michigan.

In January the World Health Organization listed "vaccine hesitancy," which describes the reluctance or refusal to vaccinate despite the availability of vaccines, among

the top 10 global health threats in 2019. Irrational concerns about vaccine safety, such as the now debunked theory that the vaccine against measles, mumps and rubella causes autism, continue to circulate globally, expedited by the widening availability of mobile phones and the Internet.

"This social contagion is so important and can't be disentangled from the disease itself," says Alessandro Vespignani, a computational epidemiologist at Northeastern University. Hesitancy among parents in Houston or Hong Kong could well put parents in Caracas or Cologne at greater risk of misinformation and all of their children at greater risk of infection. "We live in a globally interconnected world, and there is no way that what we do locally is not having an impact on the global scale."

SUSSING OUT SUSCEPTIBILITY CLUSTERS

Measles is among the most contagious of all infectious diseases. Some nine out of every 10 unvaccinated people who come into contact with the virus will contract it. And someone can be contagious for days before they know they are infected, providing plenty of time for a ride on a plane or train or at least a solid social schedule. Although the virus may not recognize borders, the toll it takes varies widely around the world. Measles fatality rates are below 0.1 percent in developed countries, yet rates exceed 10 percent in some poor countries where people may be undernourished or lack access to care. Between 2000 and 2017 measles vaccination prevented an estimated 21.1 million deaths around the world, according to the WHO.

It was during a mid-2000s measles epidemic in Marcel Salathé's home country of Switzerland—the epidemic that spread to San Diego, as well as to Austria, Norway and other nearby counties—when he began to contemplate the role of beliefs in the spread of vaccine-preventable disease. Word was out that many Swiss parents had deliberately avoided getting their children vaccinated.

Salathé, a digital epidemiologist at the Swiss Federal Institute of Technology Lausanne, had always incorporated the behavior of viruses but not that of humans, in his models of infectious disease dynamics. But soon he began to see that belief systems, too, were a powerful predictor. In a 2008 paper, he described how opinion-generated "susceptibility clusters"—pockets of vaccine-hesitant parents and their children, for example—allow a virus to persist and to jump to other clusters. The phenomenon, he suggested in the paper, "effectively reduces herd immunity."

In a survey after the San Diego outbreak, local parents who chose not to vaccinate their children said they believed that getting these immunizations against vaccine-preventable diseases was unnecessary because of the low risk of catching these diseases. After all, measles was declared eliminated in the U.S. in 2000. In countries like the U.S., "hesitancy exists because of the success of vaccines," Gavi's Berkley says. In contrast, he adds, in many developing countries today, "you see children dying and becoming disabled all around you [from vaccine-preventable disease]. When that happens, of course, parents—at least parents who understand science—want their children to be protected."

"The vast majority of people around the world want access to immunization," says Kate Dodson, vice president for global health strategy with the United Nations Foundation. Yet one in five people who want the measles vaccine, she notes, are not able to get it. Often those one in five people also cluster together as they face common political, economic or cultural challenges. In the Democratic Republic of the Congo, 1.8 million children miss out on a full course of vaccines every year largely because of difficulties in reaching clinics or clinics running out of vaccines. Ongoing conflict in parts of Pakistan and Syria impedes access to vaccines for many people.

The end result of poor access to vaccines parallels that of vaccine hesitancy. Both barriers need to be addressed, according to public health researchers, because either can create a geographical cluster of unvaccinated people that becomes fertile ground for a virus to proliferate. "Are they refusing to be vaccinated or failing to be vaccinated? From the standpoint of the measles virus, it doesn't care why they aren't vaccinated," says Matthew Ferrari, a statistical disease modeler at the Pennsylvania State University. To measles, he adds, a cluster arising from a lack of access "looks just like a kindergarten full of kids whose parents are actively refusing vaccination."

VIRAL SPREAD

Misinformation, Berkley says, "really is spreading at the speed of light." And the implications go beyond measles to other diseases. Berkley refers to measles as the "canary in the coal mine." Because of its high rate of infectiousness, it is usually the first vaccine-preventable disease to show up when overall vaccination rates start slipping. Should trends continue, outbreaks of pertussis, tetanus and other diseases that require lower levels of coverage to achieve herd immunity, could be close behind.

For this reason, measles is "the perfect disease to study," adds Bruce Lee, an international health professor at the Johns Hopkins School of Public Health. Its rise can also raise a warning that further vaccine-preventable diseases such as hepatitis B, for which symptoms tend to be less obvious and more delayed, "may be spreading more quietly and insidiously."

Social media–fueled antivaccination campaigns are thwarting measles vaccination efforts around the world, including in India, Israel, Madagascar, Venezuela and Ukraine, among other countries. In northern Nigeria, work to eradicate polio is being derailed by dangerously false rumors that the vaccine is contaminated with antifertility agents and that vaccine deployment is a ploy to infect children with the monkeypox virus. And it is not only conflict and poverty that stop some parents in Paki-

stan from vaccinating their children. Distrust in vaccination campaigns grew—and reverberated online—after the U.S. conducted a sham hepatitis B vaccination project in its targeting of Osama bin Laden. The Central Intelligence Agency attempted to obtain DNA from Osama's relatives to confirm his whereabouts before storming the Abbottabad compound.

Ulterior motives are at play as well. The Russian Twitter bots responsible for spreading fake news during the 2016 U.S. election have also been pushing antivaccine misinformation to further promote political polarization. Meanwhile some Web sites appear to be cashing in on parents' fears by selling antivaccine books, supplements and online seminars.

All that online vaccine hesitancy chatter may at least have one silver lining: the creation of valuable data. Salathé has found that tracking tweets on Twitter, for example, can help identify local clusters of vaccine hesitancy. Data from Internet search engines and other social media sites, too, offer volumes of useful information.

Combining these behavioral data with streams of information from medical records, flight logs and mobile phones may enable models to more powerfully predict the spread of vaccine-preventable diseases and better target vaccination and education campaigns. According to Vespignani, "This is a way to simulate disease much closer to what we do with the weather forecast."

In addition to long incubation time, another difficulty in modeling a disease like measles is relative scarcity in recent decades. "Now, unfortunately, we have enough cases and outbreaks where modeling can become a kind of good intelligence," Vespignani says.

To account for the geographical variability in vaccine coverage, which has also been a hurdle for modelers, researchers are now rapidly increasing their resolution. In a paper published in April, Jonathan Mosser and his colleagues estimated vaccine coverage at a resolution of five kilometers by five kilometers in 52 African countries. They found that while diphtheria-pertussis-tetanus (DPT) vaccine coverage had increased across Africa, "substantial geographical inequalities" persisted within and across countries. Better localization of clusters of unvaccinated people could improve simulations of disease spread, says Mosser, a clinical fellow at the Institute for Health Metrics and Evaluation at the University of Washington. "All the ingredients are there," adds Salathé, noting the recent availability of big data, computational power and complex algorithms. "The challenge is really to put everything together."

GOOD POLICY

Policy approaches may aid in tackling vaccine hesitancy, too. On May 10, in response to a measles outbreak that had sickened 74 kids, Washington State Governor Jay Inslee signed a bill to remove the ability of parents to exempt their children from measles, mumps and rubella vaccination for personal or philosophical reasons. Every U.S. state allows exemptions when medically necessary. And all but three states allow religious exemptions. Washington had been among the more than a dozen remaining states that also allow exemptions for "personal, moral or other beliefs."

In a 2018 paper, Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine, and his colleagues identified 15 counties in the U.S. with populations at risk for measles and other vaccine-preventable diseases because of high rates of nonmedical exemptions. About half of those counties were reporting outbreaks of measles in 2019.

Even a 2015 state ban on all nonmedical exemptions seems to have fallen short in California, where another bill was proposed that would prevent parents from doctor-shopping for medical exemptions to bypass the law.

Vaccination has always been the province of either local or state governments. In 1905 the U.S. Supreme Court upheld the authority of Cambridge, Mass., to require vaccination against smallpox after a minister refused over safety concerns. But more action is needed at the national and international levels, says Lawrence Gostin, a professor of global health law at Georgetown University. He laid out a detailed three-pronged strategy in a paper published in April.

"The federal government, as a matter of constitutional law, is not permitted to directly tell states what to do," he says. "But it can condition federal dollars based on the states' conformance with federal standards, which, in this case, would be to eliminate or significantly tighten all nonmedical exemptions."

He is also recommending that the feds work with social media companies to "filter out unscientific, unsubstantiated information about vaccines," as well as fund state and local advocacy campaigns to restore faith among the public in the safety and importance of vaccines. "The campaign wouldn't accuse parents of being ill-willed," Gostin says. "It would assume, as I assume, that if most mothers and fathers had access to reliable, trusted sources of scientific information, then they would do right thing and vaccinate their children."

Hotez highlights the same three strategies—and underscores their urgency. He has spent most of his career developing vaccines for globally neglected diseases and says he worries that the spreading vaccine hesitancy will "compound the problem" of introducing new vaccines for malaria, dengue, and the like.

"All countries that are experiencing significant vaccine hesitancy should have a similar kind of plan," Gostin observes. "Vaccines were the greatest public health achievement of the 20th century, and we want it to continue into the 21st century."

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OBSERVATIONS

The False Promise of Fish Oil Supplements

After decades of speculation that they "may work" to reduce cardiovascular disease, the lack of demonstrated benefit leads to the conclusion that consumers are wasting their money

GETTY IMAGES

Every 38 seconds someone in the U.S. dies from cardiovascular disease. Even more worrisome: deaths from cardiovascular disease have been rising dramatically since 2011 following years of decline. Strokes, heart attacks and other cardiovascular events cause great suffering and are an enormous health care burden.

These statistics are particularly troubling because every month, approximately 19 million people in the U.S. take fish oil supplements, many in the hopes of preventing heart disease—despite the absence of reliable evidence that such supplements (also called omega-3 fatty acid supplements) prevent cardiovascular disease and its serious consequences. To the contrary, all studies of fish oil supplements conducted to date have failed to show any significant clinical benefits beyond those of standard-of-care therapy.

Consumers have been told so many times that dietary fish oil supplements promote heart health that it seems to be accepted as factual. But this conventional thinking is not supported by the science. After decades of promises that fish oil "may work," the lack of demonstrated benefit leads me to conclude that consumers are wasting their money on supplements in an effort to reduce cardiovascular risk.

A summary of all the evidence was recently published in the prestigious medical publication *Annals of Internal Medicine*. This review, published July 9, 2019, examined the effectiveness of 24 supplements and diets in preventing cardiovascular disease. The authors evaluated nine systematic reviews and four randomized controlled trials, which encompassed 277 trials and 992,129 participants. Findings indicated that few nutritional supplements or dietary interventions offered any protection

against cardiovascular disease or death and that some may actually cause harm. Omega-3 products, in particular, yielded "low-certainty" evidence that they were associated with reduced risk for myocardial infarction and coronary heart disease.

Because the U.S. Food and Drug Administration classification for dietary supplements such as fish oil is different from that of prescription drugs, these supplements are not manufactured or reviewed by the FDA in as stringent a manner. Most found on the market—unlike prescription medications and certain over-the-counter (OTC) drugs—have not demonstrated effectiveness and safety in placebo-controlled clinical trials. This can be confusing: fish oil supplements, for example, are readily available to patients and often have labels that imply a benefit to cardiovascular health, yet they are not intended to treat any medical condition.

This study is just the latest in a growing body of evidence demonstrating the absence of benefit of fish oil supplements for heart health. Other studies looking into what common fish oil supplements actually contain have found they have lower amounts of omega-3 than specified on the label, variable content and unregulated purity, and potentially significant levels of saturated fat and rancid oils.

It's not just patients who are confused about the tested efficacy and safety of fish oil supplements. A survey conducted by Fairleigh Dickinson University's PublicMind found that among those physicians and pharmacists who had recommended a nonprescription omega-3 product to patients, more than four in five (85 percent) believed incorrectly that they had recommended an FDA-approved OTC product. Thirty percent of pharmacists and 22 percent of physicians stated, incorrectly, that prescription and dietary supplement omega-3 products are similar in strength and content. This is an example of the adage that if something is said often enough, people will believe it to be true.

To help stop the alarming increase in deaths from heart disease, patients at risk for cardiovascular disease, as well as their health care providers, need to have an evidence-based rationale for what they use and recommend for heart health. Fish oil supplements should be treated with the same scrutiny as a prescription medication, particularly if patients or consumers are taking them for the specific purpose of preventing or treating cardiovascular disease.

As Amitabh C. Pandey and Eric J. Topol of Scripps Research Translational Institute, Scripps Research, and Scripps Clinic said in their editorial regarding the review published in the *Annals of Internal Medicine,* "it would be reasonable to hold off on any supplement . . . in all guidelines and recommendations."

Editor's Note *(9/27/2019): Because of an error on the part of Mason's representative, the biography attached to this post failed to disclose his relationship with Amarin Corporation. The company manufactures a triglyceride-lowering drug called Vascepa, which competes in the marketplace with fish oil supplements. Mason has been the author of 12 papers on fish oil, 10 of which were supported by Amarin, and another of which was "critically reviewed" by employees of the company.*

Mary Beth Pfeiffer, a resident of New York State's Hudson Valley, is an investigative journalist and author of *Lyme: The First Epidemic of Climate Change.*

OBSERVATIONS

Getting Serious about Tick-Borne Diseases

The U.S. vanquished malaria and beat back AIDS, but Lyme and other illnesses are raging unchecked

Deer tick (*Ixodes dammini*), carrier of Lyme disease.

GETTY IMAGES

In the 1980s the fight against AIDS was tragically delayed, in part because the virus primarily affected the marginalized populations of drug addicts and gay men.

Today another epidemic rages unchecked: the number of Lyme disease cases has doubled since 2004, for a total of more than 400,000. The victims are mainly residents of suburban and rural enclaves—93 percent white, many middle class, and surely an atypical disenfranchised group.

These people, including many children, are infected by ticks in backyards and on playgrounds, while walking their dog or visiting a park. At least 10 to 20 percent stay sick for a year, with 5 percent still suffering 15 years later—this among patients receiving early treatment, who have the best outcomes. Brain inflammation, nerve damage and "severe" functional impairment have been documented.

Yet when patients blame failed tests and treatments for their persistent symptoms, when they seek additional care for Lyme disease, they are often told they suffer from anxiety or chronic fatigue syndrome. They are derided, called anti-science, denied insurance reimbursement.

They are dismissed in ways comparable to those experienced by their AIDS-afflicted brethren.

We are at a crossroads for Lyme and other serious tick-borne diseases. A controversy over the cause of lingering symptoms—is it ongoing infection or something else?—has so stymied progress that it has let mushroom an army of ticks. There is a solution. When society finally accepted the threat and gravity of AIDS, scientific conferences, fellowships and laboratories were funded. Researchers carried out clinical studies—11,500 are listed to date in the U.S. government's database of clinical trials. Scientists found answers.

We must do the same for Lyme disease, for which, by comparison, only 66 studies have been conducted. We must build an infrastructure to attack the illness.

In the past century the U.S. has faced two major epidemics caused by bugs that bite. The responses were drastically different: In the 1930s the country financed huge public works programs that, by 1951, brought mosquito populations under control and eradicated malaria. But since the 1970s government agencies have battled Lyme disease largely by urging people to use repellent, wear white clothing and do body checks.

The upshot: mosquito-borne diseases are "largely suppressed" while "tick-borne diseases are rampant," scientists reported recently in the journal *BMC Public Health*. For ticks, "proven and scalable control measures do not exist," wrote three officials from the U.S. Centers for Disease Control and Prevention in 2018.

Somehow insects that fly are far scarier than eight-legged arachnids that lie in wait on a bit of shaggy grass, their forelegs waving expectantly, when they sense the breath of a passing human.

In 2017 mosquito-borne West Nile virus, which currently infects about 2,000 people annually in the U.S. received $42 million in support from the U.S. National Institutes of Health. Lyme disease, with 20 times the number of reported cases, got half as much, a figure that has changed little in a decade.

Just months after the mosquito-borne Zika virus emerged in 2016, Congress appropriated $1.1 billion, alarmed over its real potential to cause birth defects. The epidemic quickly petered out, however, with just seven mosquito-acquired Zika cases reported in the U.S. in 2017. That year 42,700 Lyme disease cases were reported, about a tenth of what the CDC suspects the actual toll, because most cases go unreported.

Lyme disease from black-legged ticks is only a part of the problem. Cases of anaplasmosis and ehrlichiosis have soared, increasing sixfold since 2004. Malarialike babesiosis, once limited to coastal islands, has been reported in 27 states; it makes Lyme disease far worse. The lone star tick, common in the South, has migrated to vast tracts of new territory as the climate has warmed, its bite causing a potentially severe meat allergy unheard of a decade ago. In 2017 the Asian longhorned tick became the first new tick species in the U.S. in 80 years. Now in 11 states, the ticks so infested five cows in North Carolina recently that they died of anemia from blood loss. The implications for agriculture could be dire because female longhorned ticks can clone themselves, vastly increasing birth rates.

Too much time has been wasted amid arguments over so-called chronic Lyme disease. We know we have a problem. It demands a "paradigm shift," as the authors of the *BMC* article put it.

We must put aside our entrenched views of Lyme disease, for which research funding has been paltry and static. The ranks of the infected and infirm are growing. Prevention efforts have failed. Do the work on ticks.

Daphna Joel, Ph.D., is a professor in the School of Psychological Sciences and a member of the Sagol School of Neuroscience at Tel Aviv University. She is the author of *Gender Mosaic: Beyond the Myth of the Male and Female Brain.*

OBSERVATIONS

It's Time for a World without Gender

Let's treat people based on who they are rather than on the form of their genitals

The idea of gender is undergoing a revolution, as unconventional gender behaviors gain in acceptance. At the same time, however, virtually every societal move away from the gender binary—such as permitting gender-neutral designations on various documents—triggers a corresponding backlash.

These controversies bring to the fore a centuries-old question: How fundamental are sex categories? Do humans "naturally" belong to one of two groups, female or male, that are distinct not only in the form of their genitals but also in their brains and behavior?

For about 1 percent of humans, answering this question in the affirmative leads to a great deal of physical and emotional pain. These are people born with intersex genitals; for them, being forced to fit into one of two sex categories often means facing ostracism or undergoing medically unnecessary surgeries. But what about all the others? Do humans with female and male genitals belong to two distinct classes?

Studies comparing groups of women and men often find differences between the two. Some of these are small (for example, women's reading comprehension is, on average, slightly better than men's); other differences are large (for example, most women prefer a man as a sex partner, whereas most men prefer a woman). One can argue ad infinitum as to whether these differences stem directly from an individual's sex (for example, a result of exposure to high levels of testosterone in the womb) or from the different ways in which society treats individuals with female and male genitals. But this nature-versus-nurture debate is irrelevant to this question: Do women and men belong to two distinct classes?

If so, then characteristics on which women and men differ should add up consistently within each

individual—just as genital organs do (most humans have genital organs that are either all male or all female; only that 1 percent with intersex genitals have a mixture of the two types). But differences in brain and behavior between men and women don't add up in this manner. Very few individuals have only female-typical or only male-typical characteristics. Most humans are a mixture of both—a unique mosaic of female-typical and male-typical characteristics. Our scores on various neural, psychological and behavioral parameters don't consistently add up in any one person. Rather they mix up. You may very well score high on the ability to visualize geometrical objects, as is more common in men, but at the same time, you may be more interested in people than in things, as is more common in women. You may be a nurturing type and also good at fixing things. The list of potential mosaics goes on and on.

But if humans are mosaics of features, why do men and women sometimes seem to be so distinct? The answer lies in the binary division itself. Even though humans do not belong to two distinct sets in terms of their brain and behavior, the binary division of humans into two social categories is real, and it exerts a profound effect on the way we behave and the way we perceive ourselves and others. The gender binary assigns different roles, status and power to humans with male and female genitals, and different expectations from them in terms of their behavior, preferences and psychological characteristics; it forces a population of human mosaics into a binary straitjacket.

Some of the effects of this role assignment may be relatively benign—discouraging people from baking cookies or mastering other skills they might consider "gender-inappropriate." But many are not: even in gender-aware Western societies, the binary affects women's and men's career choices; exposes women to gender and sexual harassment; and leaves men to die in droves in armed conflicts and in work-related accidents.

It is time to get rid of the gender binary. It is time to start treating people according to their unique mosaics of characteristics rather than according to the form of their genitals. It is time for a world with no gender.

A world with no gender means that the form of one's genitals, whether female, male or intersex, has no social meaning—just as being right- or left-handed has no inherent meaning. (Although it used to: not so long ago left-handed people were considered less capable than those who are right-handed, and parents would force their left-handed children to use the right. It's no coincidence that "right" is another word for "correct."

Scientists, meanwhile, searched for the neural deficits responsible for left-handedness. All these efforts have vanished, even though we are still left- or right-handed, and even though left-handed people are often frustrated that many tools and other objects are designed only for righties.

A world without gender does not mean there would be no differences, on a group level, between humans with female and male genitals. But in a world without gender, we simply wouldn't care. And why should we? If your child excels in math or if you love poetry, does it really matter whether there are more people with female or male genitals among math wizards or poetry buffs?

I've had people tell me that the gender binary is a direct consequence of there being two sex categories. But even if this were true, it would provide an even stronger argument for getting rid of the binary gender system. Because if the effects of sex are unavoidable, then there is surely no need for a complex social system to enforce them.

A world without gender is a world in which humans are encouraged to develop their full human potential. It's a world in which characteristics that are considered desirable for humans, such as empathy and assertiveness, are encouraged in everyone, regardless of the form of their genitals—and regardless of whether they have difficulties in acquiring these characteristics because of their genes, hormones, inadequate parental treatment or socioeconomic conditions. At the same time, children and adults possessing characteristics that are considered undesirable, such as aggressiveness, are helped in overcoming them, regardless of their cause.

A world without gender is a world in which humans are free to fully express their talents in all areas, be it math or poetry—or both; in which humans are treated according to who they are and not according to the form of their genitals; in which even the thought of grouping them by their genitals sounds as bizarre as grouping people according to the color of their eyes.

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