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Health & Medicine

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The Satisfaction Diet

FOODS THAT ARE ESPECIALLY SATIATING CAN DECREASE HUNGER, REDUCE BODY FAT AND LOWER BLOOD SUGAR

Plus:

DOES THE PULLOUT METHOD WORK TO PREVENT PREGNANCY?

CANCER RISKS OF SOME ANTIAGING PRODUCTS

ONE STEP CLOSER TO A UNIVERSAL FLU VACCINE

WITH COVERAGE FROM nature

LIZ TORMES

In Search of Satisfaction

In 1944 researchers recognized that millions of people were at risk of famine as a result of the ravages of World War II. To investigate the impact of food deprivation on the human body, 36 healthy men volunteered to endure a six-month semistarvation diet and be observed by scientists and doctors. The result? Hunger made the men obsessed with food. They would dream and fantasize about eating. They reported fatigue, irritability and depression, along with decreased concentration, comprehension and judgment. Interestingly enough, the subjects were allowed about 1,500 calories a day, substantially more than many fad diets endured today. It's no wonder that diets based on restricting food are unsustainable–according to some studies, approximately 95 percent of diets fail over the long term. As Shirin Panahi reports, researchers are now exploring whether a diet that centers on satisfying foods–healthy foods that make the eater happy (imagine that!)--might be the key to maintaining body weight after all (see "Have We Found a Diet That Truly Works?"). What a fulfilling prospect.

Elsewhere in this issue Jen Schwartz takes a compelling look at the science of the withdrawal tactic for preventing pregnancy (see "Can You Prevent Pregnancy with the Pullout Method?"), and Helen Shen covers a wave of research on how boosting the molecule nicotinamide adenine dinucleotide (NAD) might stave off the aging process. The trend is alarming some critics who worry about that molecule's association with cancer (see "Cancer Research Points to Key Unknowns about Popular 'Antiaging' Supplements"). As always, enjoy this issue!

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Health & Medicine

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CHRIS GASH

On the Cover

Foods that are especially satiating can decrease hunger, reduce body fat and lower blood sugar.

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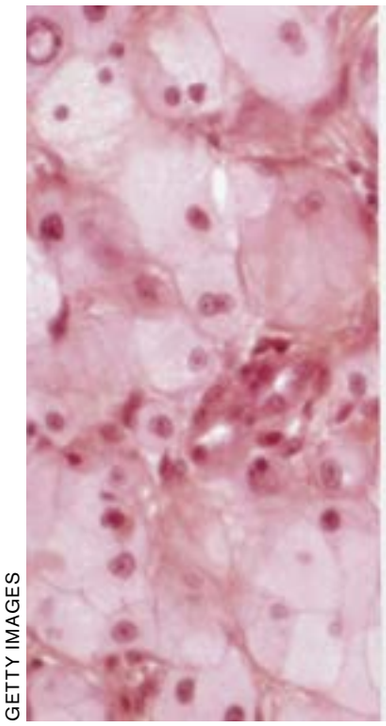

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Brain-Controlled Hearing Aids Could Cut through Crowd Noise

A prototype detects whom you are listening to and amplifies only that speaker's voice—a potential solution to the "cocktail party problem"

AT A CROWDED PARTY or a noisy restaurant, most of us do something that is remarkable. Out of all the voices surrounding us, our brains pick out the one we want to hear and focus on what that person has to say. People with hearing loss are not so fortunate. Noisy situations are especially difficult for them, and hearing aids and cochlear implants do not help much. Such technology generally either amplifies all voices or mushes them together so they are indistinguishable.

The question of how the brain manages the trick of hearing in noise is known as the "cocktail party problem." It is a puzzle that has bedeviled auditory scientists for decades and limited the solutions they have to offer. But researchers have just taken a major step forward toward helping people hear in noise. In a paper published on May 15 in *Science Advances*, engineers from Columbia University's Zuckerman Institute revealed an experimental technology that could lead to a brain-controlled hearing aid. Their proof-of-concept device uses artificial intelligence to separate voices and compare them with a listener's brain waves to identify and amplify the speaker to

whom that listener is paying closest attention.

Nima Mesgarani of Columbia University's Zuckerman Institute, the senior author on the paper, has been working on aspects of the same problem since 2012 when he first discovered it was possible to figure out which voice a listener was focused on by monitoring brain waves.

In 2017, he developed technology that could pull one voice from many, but only if the system was trained to recognize that particular speaker—a severe limitation in real-world communication. Now Mesgarani and his colleagues have achieved a significant step forward by using brain waves to decode whom you are listening to and then separating the interlocutor's voice without the need for training. "To remove that barrier," he says, "is a pretty big breakthrough."

"It's a beautiful piece of work," says auditory neuroscientist Barbara Shinn-Cunningham, director of the Neuroscience Institute at Carnegie-Mellon University, who was not involved in the research. Auditory neuroscientist Andrew Oxenham of the University of Minnesota, who has studied the cocktail party problem for years, says, "This brings the whole field closer to a practical application, but it's not there yet."

What Mesgarani and his colleagues have created is an algorithm, and they have tested it only in epilepsy patients undergoing brain surgery. Such patients provide a rare opportunity for scientists to put electrodes directly into human brains. From a loudspeaker in front of the participants, Mesgarani and his colleagues played two voices (one male, one female) speaking simultaneously. They instructed participants to focus first on one and then the other. The Columbia engineers fed the sound of the voices and the electrical signals from the patients' brains into their algorithm, which sorted the sounds, amplified the attended voice and attenuated the other. "These two inputs go inside this box, and what comes out of it is the modified audio in which the target speaker is louder," Mesgarani says.

Although using brain waves to follow auditory attention is an impressive achievement, the real advance has to do with the algorithm. It uses a sophisticated form of artificial intelligence known as a deep attractor network to separate unknown speakers automatically and in real time. Such neural network models, developed within the last four years, look for statistical regularities in increasingly complex layers of computations to determine which parts of a sound mixture belong together. "Deep learning is the secret sauce that made [this] possible," Mesgarani says.

"We are not trying to simulate the brain. We are just trying to solve the cocktail party problem."
—Nima Mesgarani

It doesn't matter that neuroscientists still haven't fully worked out how the brain hears in noise. "We are not trying to simulate the brain," Mesgarani says. "We are just trying to solve the cocktail party problem." They trained the algorithm with far more examples of human speech than any person would hear in a lifetime. Then they gave it the task of analyzing the detailed, often overlapping information in the spectrograms, or acoustic signatures, created by multiple speakers' voices and separating them into distinct streams of sound. Graphically represented, the paper shows two combined voices as a haze of red and blue dots. Once separated, one voice is a cluster of red dots, the other blue. There is still an element of mystery in how exactly the algorithm does this. "Our guess is that it uses the spectral and temporal information, common onsets and offsets [speech characteristics], and harmonic structures," Mesgarani says. "We tell it that this cloud of red and blue should become separable. It figures out somehow magically this transformation, and suddenly you have two clouds."

Considerable challenges remain before this technology can be used in an actual hearing aid. Mesgarani estimates it will be at least another five years. Of course, a marketable device requires a noninvasive technique for generating EEG recordings of brain waves. Several scientists, including Mesgarani, have shown that in-the-ear or around-the-ear hearing aids with electrodes can work, although they generate a far less precise signal. And while powerful, the algorithm is still not yet successful 100 percent of the time.

In all probability, the first devices to use this technology will help people

with mild to moderate hearing loss. "You probably need some residual hearing," Mesgarani says. "As long as you can track the ups and downs of [one] voice, that would be the kind of signature that this technology would look for."

The talker separation algorithm alone could prove helpful without monitoring brain waves at all, says electrical engineer Mario Svirsky of New York University's Langone Medical Center. "I envision a smartphone app that talks to your hearing aid," he says. "The app shows you icons for different talkers. If you click an icon, then that talker is preferentially amplified and the others attenuated."

As for a true brain-controlled hearing aid, Svirsky fears that the costs may outweigh the benefit and is skeptical one will ever be implemented. But he remains enthusiastic about Mesgarani's work. "The whole idea of having a mind-reading hearing aid is fascinating," Svirsky says. "It's not just science fiction. This research has shown that it is at least a plausible possibility."

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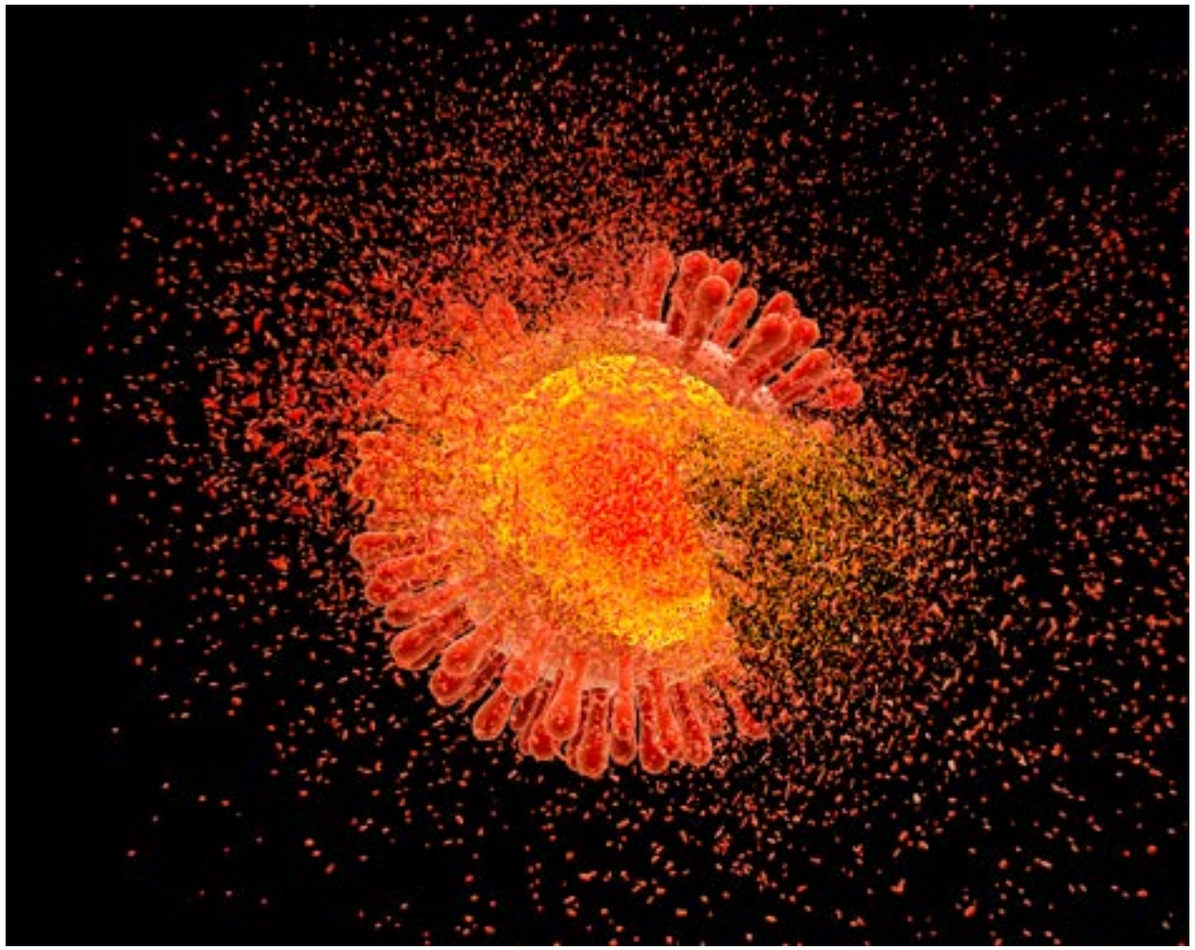
—Lydia Denworth

How to Kill HIV: Target Its "Influencers"

Applying network theory to HIV's structure has revealed the most valuable—and vulnerable—parts of the virus



IN JUST ABOUT ANY system or group, elements with a larger number of connections tend to have more clout than others. Think of Instagram "influencers," for example—or the chief executive officers of companies.

Even within a virus, some structural components—in this case, parts of proteins—have more links to one another than others do. And coaching the immune system to recognize and destroy such influencers is an efficient way to kill HIV, suggests a new study published in May in *Science*.

There has been a lot of excitement in the HIV field following the news in March that a second person, often called the "London patient," was cured after a bone marrow transplant. The donor carried a mutation that makes people naturally resistant to HIV; in effect, the procedure replaced the patient's immune system with a new, resistant one. But bone marrow transplants are risky and invasive, and many experts believe a practical cure for the roughly 37 million HIV-infected people worldwide is more likely to come from smart molecular work. Most HIV-cure research has so far focused on buttressing a person's immune system. The new study turns that approach on its head by looking for the most critical parts of the virus itself.

For the new study, the researchers focused on "elite controllers"—people whose bodies control the virus without the aid of any drugs, and who are estimated to number about one in every 300 infected individuals. It

KATERYNA KON *GETTY IMAGES*

made sense that investigating how their immune systems kill HIV might point the way to a cure, says Bruce Walker, senior author of the paper and director of the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology and Harvard University. "There are not two people who are cured of HIV infection, in my view," Walker says. "There are thousands—and a lot of them who control [the virus] on their own. We, as a field, need to pursue this with the highest priority."

Walker and his colleagues found that elite controllers' immune systems target the most influential regions in the virus. The researchers made this discovery by applying network theory, a type of analysis frequently used in mathematics to chart relationships between objects. They employed the theory to map connections between amino acids, the building blocks of proteins, in three-dimensional molecular structures of HIV proteins. (They used the 3-D structures because two amino acids that appear far apart in a protein's linear sequence may be much closer—and connected—in three dimensions.)

The researchers found that some amino acids tend to have numerous branchlike structures that cause them to interact with many other amino acids. These branched amino acids have a high "network score," Walker says, and are thus the most important to HIV's integrity. HIV can mutate in a defensive response to a drug that targets a specific part of its structure. But the amino acids with high network scores are so important that the virus cannot vary them without great cost to itself: if those amino acids change, the connections are lost.

"If you take a highly networked [amino acid] and mutate it, the virus basically falls apart. It dramatically loses fitness."
—Bruce Walker

"If you take a highly networked [amino acid] and mutate it, the virus basically falls apart," Walker says. "It dramatically loses fitness." This finding makes such amino acids attractive targets for therapy, because attacking them puts the virus in a lose-lose situation: it ends up destroyed whether it mutates or not. Walker's team found that elite controllers' immune systems tend to selectively target these influencer amino acids; in most other infected people, immune systems instead mount futile attacks on other, less important parts of the virus.

"This is impressive and important work," says Andrew McMichael, an emeritus professor of molecular medicine at the University of Oxford, who co-wrote a commentary accompanying the paper but was not involved in the new research. "It explores why some [immune responses] are effective and why some are less effective."

The new research may also resolve some previously inconsistent findings about an immune molecule called B*57—which has been suggested as a magic weapon that elite controllers wield against HIV. B*57 is a subtype of molecules called human leukocyte antigens (HLAs), which make up a key part of the immune system. HLAs carry fragments of viruses to an infected cell's surface so that killer immune cells circulating in the blood can recognize the flagged cell as infected, and destroy both that cell and the virus within it. There are thousands of HLA types, some more common than others, and some better at controlling certain infections. Among these, B*57 is thought to be particularly potent against HIV. But scientists have been puzzled by the fact that not everyone with B*57 is an elite controller—nor do all elite controllers carry B*57. The new paper suggests that what is key is not so much B*57 itself, but the influencer amino acids it targets.

B*57 "is the major determinant of progression or nonprogression [of HIV infection], but it's not totally flawless," McMichael says, adding that the new paper "goes some way toward explaining why that may be."

Walker and others have studied elite controllers for decades. One such patient, Loreen Willenberg, now 65 years old, was diagnosed in 1992 and has since donated hundreds of samples for research. Willenberg, who says she has "an amazing immune system," is invulnerable to dozens of pathogens, including HIV. Tests that measure her immune response to HIV still come back positive, but no test can detect the virus itself. "I've never measured a viral load, ever. It's always been undetectable," Willen-

berg says.

Walker has studied Willenberg for about 15 years. But this time, instead of focusing on the aspects of her genetics that protect her from HIV, the team homed in on which parts of HIV her system attacks. "Here, we don't take into account host genetics at all," Walker says. Yet the study still explains what makes her immune system so remarkable: it selectively attacks the amino acids with the highest network scores. "She fit the pattern perfectly," he says.

With this confirmation of the importance of these influential amino acids, Walker says he hopes to develop a "therapeutic vaccine" that can be given to people already infected with HIV. The vaccine would contain about 30 of the viral parts with the highest network scores. The hope is that it would prime an infected person's immune system to recognize and then go after these key targets, and destroy the virus.

"We believe we can redirect the immune response," Walker says. "We don't know whether this will work, but there's a very strong rationale for it to."

—*Apoorva Mandavilli*

JAN ENKELMANN *GETTY IMAGES*

Cannabis Compound Eases Anxiety and Cravings of Heroin Addiction

Cannabidiol reduces levels of stress hormone and blunts urge to use opioids

AS ANYONE WHO'S DEALT with substance addiction can tell you, breaking the physical intimacy with the drug isn't always the most challenging part of treatment. People trying to avoid resurrecting their addiction also must grapple with reminders of it: the sights, sounds and people who were part of their addictive behaviors. These cues can trigger a craving for the drug, creating anxiety that steers them straight back into addiction for relief.

The opioid epidemic in the United States has taken more than 300,000 lives, and support for people working to keep these drugs out of their orbit has become crucial. Methadone and buprenorphine, the current medical treatment options, help break the physical craving for opioids by targeting the same pathways that opioids use. Although these drugs can ease physical need, they don't quiet the anxiety that environmental cues can trigger, leaving open a door to addiction reentry.

The cannabis compound cannabidiol (CBD), a nonpsychoactive component of cannabis, might be the key to keeping that door locked. Researchers report that among people with opioid addiction, CBD dampens cue-triggered cravings and anxiety, along with reducing stress hormone levels and heart rate. The results were published May 21 in the *American Journal of Psychiatry.*

"These findings provide support for an effect of cannabidiol on this process," says Kathryn McHugh, assistant professor in the department of psychiatry at Harvard Medical School's Division of Alcohol and Drug Abuse, who was not involved in the study. However, she cautions, the results are preliminary, and behavioral therapies are also quite effective at dimming the signal from cues.

The anxiety reduction isn't specific to opioid-related cues and could generalize to other situations, says neuroscientist Yasmin Hurd, first author on the study and director of

the Addiction Institute at the Icahn School of Medicine at Mount Sinai. "It's just that this particular anxiety leads someone to take a drug that can cause them death, and anything we can do to decrease that means increasing the precious chance of preventing relapse and saving their lives."

Hurd and her colleagues conducted a randomized, controlled, double-blind trial of 42 drug-abstinent people with a heroin-use disorder. The participants took either 400 or 800 milligrams of CBD or placebo at different intervals so that researchers could assess the immediate and longer-term effects of the compound. Those in the CBD groups exhibited reduced anxiety and craving in response to drug-related cues such as videos showing drug paraphernalia. They also had reduced levels of the stress hormone cortisol in their saliva and lower heart rates. These effects of CBD lasted a week after the last dose, when little to no CBD would be expected to remain in the body.

The antianxiety effects look promising, but whether or not they will generalize is unclear, says Chandni Hindocha, a research fellow in the division of psychiatry at University College London. Pointing to another study showing that a dose of 400 mg of CBD reduced anxiety about public speaking, she says that in both cases, something triggers the anxiety, rather than its being chronic and generalized. "The system on which CBD acts works to bring the body down to a steady state during acute anxiety," Hindocha says, so CBD may have its effects by speeding up that process.

Pinning down the just-right CBD dose may be tricky, says Gustavo González Cuevas, an associate professor and coordinator in the department of psychology at the European University of Madrid School of Biomedical and Health Sciences, who was not involved in the study. "Sometimes lower doses of CBD have been proven to be more effective than higher doses," he says.

Dose-finding is a next step, says Hurd, in addition to figuring out the best route, oral or inhaled, for administering a CBD-based drug. One thing is for sure, says Hurd: using commercially available "edibles" or smoking cannabis won't be the best choice because these options offer little dosage control.

—Emily Willingham

Species related to the naked mole rat (*Heterocephalus glaber*) share some of its pain-resistant abilities.

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Mole Rat Pain Resistance Could Point the Way to New Analgesics

A novel mechanism has been discovered in the bucktoothed rodents' ability to withstand hurt

THE NAKED MOLE RAT became an unlikely media star in 2008 when researchers showed it is highly resistant to certain types of pain. Physiologist Gary Lewin of the Max Delbrück Center for Molecular Medicine in Berlin, biologist Thomas Park of the University of Illinois at Chicago and their colleagues found that the odd-looking creatures are insensitive

to acid and capsaicin, the substance that gives chilies their burn. Lewin's team has now investigated a range of mole rat relatives, revealing that the naked variety is not the only one resistant to pain. The study uncovers a previously unknown trick for shutting down the sensation, which could lead to the development of new pain-relieving drugs.

The naked mole rat is the original mole rat species, from which numerous others evolved in various parts of Africa, Lewin says. This diversity across habitats makes mole rats an ideal group of animals to study. "As they populated Africa, they probably came into contact with all kinds of different environments," Lewin says. "We wanted to know, 'Are these special properties of the naked mole rat something all African mole rats have, or are they something to do with the environment they're confronted with?'"

In a study published online in May in *Science*, the team assessed the responses of eight kinds of mole rats and two other rodent species to three substances that normally elicit pain: acid, capsaicin and allyl isothiocyanate (AITC), the substance that gives wasabi its fiery heat. When researchers injected the substances in one of the animals' paws, those that experienced pain would lick or flick their limb. In addition to the naked mole rat, two other species (the Cape mole rat and East African root rat) were resistant to acid, and one other (the Natal mole rat) was resistant to capsaicin. The Highveld mole rat, named after the eastern South African region where it lives, was the only species impervious to AITC. "It's absolutely remarkable that five of the [species studied] turned out to have evolved distinct sensory deficits," says neurobiologist Jorg Grandl of Duke University, who was not involved in the study.

The researchers conducted a series of experiments in the Highveld mole rat to probe its resistance to AITC. Their findings revealed a previously unknown mechanism for suppressing pain, involving a single gene coding for an ion channel that, when highly active, prevents pain-sensing neurons from firing. This activity gives the animal a very specific resistance, presumably because it is restricted to cells that sense AITC. But researchers could target this channel in general, anywhere they find it, potentially opening up a whole new class of pain relievers. "Our findings could lead to a drug-discovery program to try and make molecules that increase the function of this channel," Lewin says.

The researchers set out to dissect the genetic and molecular mechanisms underlying this striking variation. They took tissue samples from the spinal cords and dorsal root ganglia (bundles of spinal cord neurons that transmit pain information) of all the species and measured the activity of nearly 7,000 genes. The scientists found evidence of a normal complement of neurons for detecting painful stimuli in each species. And specialized proteins called ion channels, activated by capsaicin or AITC, were present at similar levels in all species—suggesting pain resistance is not simply a case of lacking the relevant detectors. There were differences, however. For instance, the three acid-resistant species had altered activity in 41 genes, almost all of which are likely expressed, or turned on, in sensory neurons, and a few of which are known to encode acid-sensing channels.

The team then focused on Highveld mole rats' unique resistance. "This is the only animal that's ever been found that doesn't avoid AITC," Lewin says. The channel activated by AITC is called TRPA1, and when the researchers examined the *Trpa1* gene in Highveld mole rats, they found a mutation that reduces the channel's sensitivity to the spicy chemical. But they also saw this mutation in three other species that do not have the Highveld mole rat's immunity. Also, these rodents are not just resistant, they seem utterly impervious: increasing the concentration of AITC from 0.75 to 100 percent still failed to trouble the critters, which is difficult to explain purely in terms of reduced sensitivity. "In four different species, the channel had the same insensitivity, but only one species was completely behaviorally insensitive," Lewin says. "So there had to be something else."

The one gene whose activity was significantly different in Highveld mole rats codes for a channel called NALCN, which was more than six times as active as in other species. The team investigated NALCN's function in laboratory-grown cells and found that it acts as a kind of "short circuit" that leaks current, preventing neurons from firing even when sensing the chemical that

normally activates them. The researchers then injected Highveld mole rats with a drug that blocks NALCN, making them sensitive to AITC. The effect disappeared as the drug wore off, strongly supporting NALCN's role in the species' particular superpower. "The researchers used an impressive range of techniques, in multiple species, to look beyond variation in the genetic code and instead identify changes in levels of gene activity that appear critical for one species' pain resistance," says evolutionary biologist Kalina Davies of Queen Mary University of London, who was not involved in the study.

The researchers think these pain resistances are evolutionary adaptations. AITC and other irritants are present in roots, one of mole rats' main food sources, so reduced sensitivity would be generally beneficial. Zoologist and team member Daniel Hart of the University of Pretoria in South Africa discovered that Highveld mole rats often share their burrows with an aggressive, venomous ant species, the Natal droptail. Experiments using venom from the ants showed that these mole rats were the only species resistant to it and that blocking NALCN abolished the resistance. "This is a fascinating dissection of the molecular machinery that senses noxious substances and how it evolved," Grandl says.

The findings show that nature harbors more pain-perception mechanisms than previously appreciated. "The study suggests the response to noxious substances and the molecular basis controlling these are not as conserved as previously thought," Davies says. "The results could have implications for our understanding of controlling pain." Humans also possess the *Nalcn* gene so the implications for developing novel analgesics are fairly straightforward. "It's the same gene we have, except it's massively more expressed in the sensory neurons [of Highveld mole rats] than in any other species," Lewin says. "It's a standard procedure in the pharmaceutical industry to make a channel opener: a small molecule that would open the channel. And we'd predict that could have very powerful analgesic properties, because it would shut down pain receptors," he explains. "With modern methods, we can really discover how evolution solved a problem."

—*Simon Makin*

JUSTIN SULLIVAN *GETTY IMAGES*

New Finding Advances the Search for a Universal Flu Vaccine

Antibodies to a portion of the influenza virus that varies relatively little from strain to strain may provide flu protection in humans

THE QUEST FOR A universal flu vaccine, one that provides long-lasting protection from multiple types of influenza, even those that might cause a pandemic, has moved a step closer.

For the first time, scientists have shown that targeting a specific portion of the flu virus that varies relatively little from strain to strain offers protection in humans. The study was published in the June 3 issue of *Nature Medicine*.

"If you have a universal flu vaccine you would take off the table the need to have to vaccinate persons every single year, and change the vaccine every year," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID). Each year in the U.S., seasonal influenza, or flu, kills more than 36,000 people and hospitalizes 200,000 more. Worldwide, influenza causes 650,000 deaths annually.

Your yearly flu vaccine targets

hemagglutinin, one of the two types of proteins that cover the influenza virus. The protein resembles a mushroom, made up of a cap (head) and a stem (stalk).

Current flu vaccines induce the production of antibodies that recognize the hemagglutinin head and inhibit its ability to mediate viral entry into a cell. However, this portion of the protein undergoes rapid mutation to escape the antibodies, making it necessary to develop a new flu vaccine every year.

In contrast, the hemagglutinin stalk is far more resistant to mutations, providing a target for antibodies that block its activity—the reason it may be a candidate for a universal flu vaccine. Several studies have shown that antibodies against the hemagglutinin stem confer protection in animals, but their role in human infections were unknown until now. "We have shown that stalk antibodies correlate with protection in humans," says Aubree Gordon, a professor of epidemiology at University of Michigan's School of Public Health and co-author of the study. "We've seen an association between having higher levels of stalk antibodies and being protected from both influenza infection and disease."

Gordon and her team have been tracking household flu transmission in a cohort in Managua, Nicaragua, since 2007. For this specific research, they focused on the 2013 and 2015 flu seasons. "We wanted to do two seasons to make sure that whatever we were seeing wasn't specific to one season," she says.

In collaboration with the local health center, the scientists were alerted when someone tested positive for influenza. They took that case and enrolled in the study the afflicted individual's entire household, getting blood samples and following them for three to five weeks. The study tracked a total of 300 household members who lived with the 88 individuals with confirmed influenza. "You're basically getting a population of people who are going to naturally be exposed to influenza," Gordon explains, "and you see who gets sick, and then you can compare the antibody levels of those who got the flu and those who didn't get the flu to see if specific antibodies or antibody groups are correlating with protection."

To measure those antibodies, the blood samples were sent to the lab of Florian Krammer, a study co-author who is a professor in the department of microbiology at the Icahn School of Medicine at Mount Sinai in New York. Krammer used a novel assay to measure the hemagglutinin stalk antibodies. It was built from a molecule containing the stalk of the H1N1 virus—the influenza strain that was the subject of this research—and the head of an avian influenza virus (H6N1) that is not present in humans.

"If you have a universal flu vaccine you would take off the table the need to have to vaccinate persons every single year, and change the vaccine every year."
—Anthony Fauci

"This construct allows us to measure antibodies for the stalk only," Krammer explains, adding: "We developed it here, and we have used it for the last two or three years to measure immune response in animals." However, they didn't have a study that could allow them to test it in humans. "It was with Aubree Gordon's cohorts in Nicaragua that this was possible," he says. The tests showed that a rise of four times in the stalk antibody levels correlated with a 42 percent reduction in influenza infection, and about a 50 percent reduction in symptomatic influenza.

The study, Fauci says, "provides a proof of concept that if we can induce [hemagglutinin] stem antibodies we may be able to have what we call an important step toward a universal flu vaccine. The people pursuing this line of research will be much more energized about doing it."

Work has already begun on vaccine development. At NIAID's Vaccine Research Center, Barney Graham and his team have already started an early-stage (phase I) trial of a vaccine that aims to induce hemagglutinin stem antibodies. "His approach is to take the stem part of the hemagglutinin and put it onto a nanoparticle that

induces a very good immune response," Fauci says, adding: "Peter Palese at the Icahn School of Medicine at Mount Sinai is looking at what happens when you shave off the head of the hemagglutinin molecule and only present the stalk to the body, can you get good antibodies? Those are two laboratories that are looking at the approach of selectively making antibodies against the stalk."

Krammer points out a few caveats for the Nicaraguan study. Influenza A viruses can be categorized into two phylogenetic groups (group 1 and group 2). H1N1, the virus that was studied, belongs to group 1. The research, already underway in Nicaragua, must now be replicated with group 2 viruses to determine if hemagglutinin stalk antibodies also offer protection.

Also, what was measured in the initial study provided protection induced by natural infection. "We don't know if induced antibodies through vaccination are as good. We need to look into that," he says. The next few years should reveal whether this promising finding will turn into a genuine prospect for a long-sought universal flu vaccine.

—Debbie Ponchner

The Human Body Is a Mosaic of Different Genomes

Survey finds that "normal" human tissues are riddled with mutations

THE HUMAN BODY IS a complex mosaic made up of clusters of cells with different genomes—and many of these clusters bear mutations that could contribute to cancer, according to a sweeping survey of 29 different types of tissue.

It is the largest such study to date, and compiles data from thousands of samples collected from about 500 people. The results, published in June in *Science*, could help scientists to better understand how cancer starts, and how to detect it earlier.

"We now appreciate that we are mosaics, and that a substantial number of cells in our body already carry cancer mutations," says Iñigo Martincorena, a geneticist at the Wellcome Sanger Institute in Hinxton, U.K. "These are the seeds of cancer."

Tissue mosaics arise as cells accumulate mutations—from DNA errors that creep in during cell division, or because of exposure to environmental factors such as ultraviolet light or cigarette smoke. When a skin cell with a given mutation divides, it can create a patch of skin that is genetically different from its neighbors.

Skin has a high level of mosaicism compared to other tissues in the body.

GETTY IMAGES

Previous studies have found high levels of mosaicism in the skin, esophagus and blood. Those results were typically gleaned from sequencing specific genes in microscopic tissue samples.

COMPLEX PATTERNS

These studies caught the eye of Gad Getz, a computational biologist at Massachusetts General Hospital in Boston. Getz and his team decided to take a different tack: rather than

sequencing DNA from minute samples, they would mine a database of RNA-sequence data from the Genotype-Tissue Expression (GTEx) project. Because the body uses DNA as a template for making RNA sequences, mutations in DNA are sometimes reflected in RNA.

The decision to study RNA gave Getz and his colleagues quick access to data from 6,700 samples taken from 29 tissues in about 500 people. But their approach has its drawbacks. Not all DNA codes for RNA, so not every DNA mutation will be evident in RNA sequences. And because the samples used for the GTEx project are relatively large, the DNA signature from small clusters of cells with unique genomes might be drowned out by the far larger numbers of other cells.

Overall, the study found fewer examples of mosaicism in some types of tissue than would be expected on the basis of previous research. But the key, says Martincorena, is that the latest analysis demonstrated that mosaicism is present across a wide array of tissues.

Tissues with a high rate of cell division, such as those that make up the skin and esophagus, tended to have more mosaicism than tissues with lower rates of cell division. Mosaicism also increased with age, and was particularly prevalent in the lungs and skin—tissues that are exposed to environmental factors that can damage DNA.

SUBTLE SIGNALS

A gene called *TP53*—which helps to repair DNA damage and is known as the guardian of the genome—was one of the most common mutation sites. Certain changes in *TP53* are associated with cancer, but it might take additional mutations in other genes before cells give rise to tumors.

"What we're seeing are some of the earliest precancerous changes that are then going to accumulate more mutations," says Erin Pleasance, who studies cancer genomics at the British Columbia Cancer Agency in Vancouver, Canada. "Eventually a small proportion of these may become cancer."

Researchers now need to find ways to sort out which of those cells will become tumors and which are "normal," says Cristian Tomasetti, an applied mathematician at Johns Hopkins Medicine in Baltimore, Maryland. That could be crucial for improving efforts to detect cancers early.

Tomasetti has developed methods for detecting tumor DNA circulating in the blood, which researchers hope could one day be used to find early signs of cancer. But he says that his team was initially surprised to find that some of the mutations in their results—which are associated with cancer, and so could have indicated the presence of a tumor—were from a group of normal blood cells.

"This messy situation is the new normal," Tomasetti says. "The challenge is now to figure out up to what point we call something normal."

—Heidi Ledford

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Have We Found a Diet That Truly Works?

The so-called satiating diet seems to help people manage weight and good health without going to extremes

By Shirin Panahi

CHRIS GASH

Shirin Panahi is a postdoctoral researcher in the departments of physical education and kinesiology at Université Laval in Quebec City, Canada. Her goal is to design programs and interventions that promote healthy eating and lifestyle strategies that support health.

"EAT LESS AND MOVE MORE."

Oh, such simple advice, but is maintaining a healthy weight really that simple? We live in an era of nutritional misinformation and opinions galore. These days, it seems that everyone feels qualified to offer expert advice on diet, exercise and weight loss. With rising obesity rates all around the world, we are constantly searching for approaches to better manage our weight and our health.

For decades, the main strategy for losing weight has been to cut back on calories: what nutritionists call an "energy-restricted diet." Although this often works in the short term, it rarely produces long-term success. It backfires because it can lead to greater feelings of hunger after the weight is lost, more obsessive thoughts about food and eating, and a greater risk of overeating due to negative emotions and stress. These complicate the bodily mechanisms that control appetite and partly explain why most people regain the weight in the long term.

Other types of restrictive diets, such as the popular high-fat, no-carbohydrate ketogenic regimen, have some of the same problems. Like low-calorie diets, they are difficult to follow over a long period of time, which can lead to feelings of frustration and failure. The challenge for researchers has been to find a strategy that is not restrictive and that can reduce feelings of hunger and improve eating habits and overall health without causing some of these negative side effects.

The answer, it turns out, may be a diet constructed from healthy foods that are especially satiating; that is, foods that create feelings of fullness and satisfaction. Nutrition researchers have discovered many such foods, which improve appetite control and decrease food intake, conditions necessary for sustained weight loss. A satiating diet includes foods that are high in protein (such as fish), high in fiber (whole grains, for example) and high in fruits and vegetables. It contains healthy fats, such as the polyunsaturated fats found in avocados, and includes dairy products such as yogurt. Perhaps surprisingly, it might also include capsaicin, the substance that makes jalapenos and other peppers so hot.

What's so special about these foods is that each of them possesses specific characteristics that benefit our health either by decreasing hunger, reducing body fat, lowering blood sugar, improving blood pressure or increasing metabolism. For instance, yogurt contains protein, calcium and lactic acid bacteria, which are the live and active bacteria that help with the growth of good bacteria in the gut. A healthy gut microbiome has been found to help control body weight and improve other aspects of health. In some specific populations, such as people with obesity or type 2 diabetes, these food components have been found to help control appetite and positively impact overall health.

But what if we took all of these key components and combined them into one diet as an approach to manage weight? That's exactly what our team did at Université Laval in Quebec City, Canada. As a nutritional researcher there, I have spent years trying to understand how what we eat affects appetite, body weight and metabolic health over the life span. We took foods containing most of these components and created what we called a "highly satiating diet."

In a 2017 study, 34 obese men were placed on this regimen, which was 20 to 25 percent protein, for 16 weeks. Another 35 obese men followed a standard diet: 10 to 15 percent protein, and based on Canadian national guidelines for healthy eating. The men who followed the highly satiating diet significantly reduced their weight and body fat and had greater feelings of fullness compared to men who followed the standard diet. They were also better able to stick to the highly satiating diet: only 8.6 percent quit the diet, compared to 44.1 percent of the men following the standard diet.

These are very promising findings, but is it possible to maintain the weight lost over the long term with this strategy? What about metabolic and mental health; can it prevent cravings and negative emotions? What about the role of other lifestyle factors on body weight such as sleep, physical activity and prolonged sitting? We don't have the answers yet, but we are planning further studies that we hope will address these questions. If the highly satiating diet proves to have the benefits we saw in our study and if it proves to be sustainable, it could be a realistic and potentially powerful dietary solution to the problem of weight control.

Can You Prevent Pregnancy with the Pullout Method?

An investigation into one of the biggest misconceptions in male fertility

By Jen Schwartz

CHRISTOPH BURGSTEDT *GETTY IMAGES*

Jen Schwartz is a senior editor at *Scientific American* who writes about the intersection of science, technology and society.

It starts with an age-old question: If a man pulls out before ejaculating, can a woman still get pregnant?

In bedrooms, basements and the backs of cars worldwide, millions of sexually active humans make choices (or regret them) based on what should be foundational fertility knowledge. Most trusted sources say the answer is yes—it is unlikely but possible that pregnancy will occur, so don't risk it.

Dig deeper, though, and it quickly becomes unclear exactly where the risk is coming from. Instead of evidence-based education, you'll encounter some of the most durable misconceptions in sexual and reproductive health. When researchers analyzed a year's worth of questions that were submitted to an emergency contraception Web site, they found that almost half of the questions that involved sexual acts "express fear about the pregnancy risk posed by pre-ejaculatory fluid."

Preejaculate—which pretty much everyone calls precum—is the lubricative secretion that is emitted, involuntarily, from the Cowper's gland in the penis during sexual arousal. Its job is to create a hospitable ride for sperm that ultimately pass through the urethra during ejaculation. But whether you query the Internet or an andrology expert about the fertilizing power of that egg-white goo, you're likely to get an answer to a different question—that is, a declaration that pulling out is a terrible form of birth control.

"When we're talking about what's in preejaculate, that's not really the point," said Michael Eisenberg, director of male reproductive medicine and surgery at Stanford University School of Medicine, after I'd asked him the fertilizing-power question in various ways. "We know that pulling out is not effective at preventing pregnancy."

The pullout method—alternatively known as "withdrawing" or "pull and pray" and formally christened in Latin as "coitus interruptus"—is an ancient form of contraception. The Talmud refers to it as "threshing inside and winnowing outside." Globally, it is still one of the most commonly used forms of birth control, particularly in regions without access to modern methods. When performed perfectly every time, it actually has a failure rate that isn't much higher than that of condoms: 4 percent versus 2 percent, respectively. That means about four out of 100 women who rely on the pullout method exclusively will become pregnant during one year of use.

But real life is rarely perfect. Some males cannot reliably perceive the imminence of ejaculation and withdraw too late. Others might emit semen intermittently or over a long period of time instead of as a single event, according to a 1970 family-planning manual. A lot of men don't realize that the highest concentration of sperm occurs in the first spurt of semen—which can be especially problematic if getting drunk slows down their reaction time. Still others don't pull out in time because their pleasure takes precedence over a woman's health and well-being. For reasons such as these, the "typical use" failure rate of coitus interruptus jumps to between 20 and 30 percent.

People in the reproductive-health field largely dismiss the pullout method because they don't believe men have the ability and willpower to withdraw at the correct time, every time. Meanwhile there is a shocking lack of research on whether or not viable sperm are actually present in preejaculate.

The best way to synthesize the answers I collected from physicians, peer-reviewed journals and educational institutions is this: Preejaculate itself does not contain sperm—or maybe it does occasionally, but perhaps it gets contaminated with sperm that has "leaked" from elsewhere. Plus, there's leftover sperm from previous ejaculation. And anyway, Eisenberg says, we should assume that preejaculate "usually has some sperm, which can lead to [contraception] failure."

It is obvious to blame inadequate sex education for our collective confusion. But ironically, write the authors of a

2009 *Contraception* paper, "the notion that pre-ejaculatory fluid can cause pregnancy ... seems to have been introduced by the medical profession itself."

DISPELLING A MYTH?

Where did the fertile prowess of preejaculate originate? Perhaps it was in 1931, when Abraham Stone—a physician and colleague of Planned Parenthood founder Margaret Sanger—wondered how it was even possible for the withdrawal method to fail: Sperm are made in the testicles and don't route through the Cowper's gland on their way out. Stone asked some buddies with microscopes to examine their preejaculate for sperm. Among the 24 samples from 18 men, only four contained many or a few sperm. In a 1938 book, *Practical Birth-Control Methods*, Stone wrote that these figures were insignificant. Regardless, a "myth" that a handful of sperm in preejaculate makes coitus interruptus unreliable took off, and it was "copied uncritically from one textbook another," according to the 1994 edition of the book *Fertility Control.*

This myth was popularized by the classic 1966 textbook *Human Sexual Response*, by William H. Masters and Virginia E. Johnson, according to the *Contraception* paper. These pioneering sex researchers "warned of the possibility of pregnancy from withdrawal due to the presence of sperm in secretions of the Cowper's gland"—a statement that "was apparently not evidence-based but subsequently repeated," the authors write.

The *Contraception* paper's authors also speculate on why sperm seem to have "extraordinary potency" in the eyes of the public. In textbooks and the media, sperm are "often anthropomorphized as masculine, forceful, competitive, and single-mindedly determined to fertilize the egg against all obstacles," they write. Indeed, the memorable 1989 educational film *The Making of Me* features cartoon sperm "men" in a literal race for a sexualized egg "woman," set to a soundtrack that includes Richard Wagner's "Ride of the Valkyries." Additionally, girls often learn to be terrified of sperm yet aren't taught how their own body works: A recent survey of 1,000 American women of reproductive age found that 80 percent of them were not able to correctly answer how many days of each cycle they are fertile.

In textbooks and the media, sperm are "often anthropomorphized as masculine, forceful, competitive, and single-mindedly determined to fertilize the egg against all obstacles."

Since Stone's experiment, there has been little incentive to research coitus interruptus at all, partly because unlike condoms or intrauterine devices (IUDs), there's no contraceptive product to sell. While the pregnancy risk of preejaculate has only been investigated a handful of times, the results challenge popular assumptions and raise new questions.

Here's what the literature tells us: In the early 1990s, a study examined the preejaculate of HIV-positive men to determine if the virus was present. (It was.) An ancillary but "more significant" finding described in *Contraceptive Technology Update* was that "most pre ejaculate samples did not contain any sperm and those that did had only small clumps of a very small amount of sperm which seemed to be immobile." If a larger study confirmed the results, the article said, it "may dispel the myth that pre ejaculate fluid contains sperm."

Only tiny studies have taken place since. In a 2003 experiment with 12 Israeli men who gave at least two samples of preejaculate each, scientists examined the secretions under a microscope and found that none of them contained sperm. Another small study also found no sperm.

Several years ago, researchers in England and the U.S. set out to more rigorously investigate the fertilizing potential of preejaculate, noting that "no study has found motile sperm in the pre-ejaculate." Their paper, published in *Human Fertility* in 2011, analyzed 40 samples of preejaculate from 27 volunteers. Ten of the volunteers (37 percent) produced samples that included "a reasonable proportion" of motile sperm.

Because some of the men gave samples on multiple separate occasions, an intriguing pattern emerged: sperm was present in either all of an individual's samples or in none of them. "It would appear from our study," the authors wrote, "that some men repeatedly leak sperm in their pre-ejaculatory fluid while others do not."

They therefore concluded, "it is tempting to speculate that the use of withdrawal as a means of contraception might be more successful in some men because they are less likely to release sperm with their pre-ejaculate."

Then, in 2016, a larger study of 42 healthy Thai men reported that "actively mobile sperm" were found in only 16.7 percent of the subjects. Unfortunately, the researchers did not collect preejaculate samples on multiple occasions.

To make sense of these conflicting data, I called John Amory, a physician and professor at the University of Washington, who is known for his research on male infertility and novel forms of contraception. I asked him about the plausibility of this "two groups" concept: the idea that men might either always have sperm in their preejaculate or never have it.

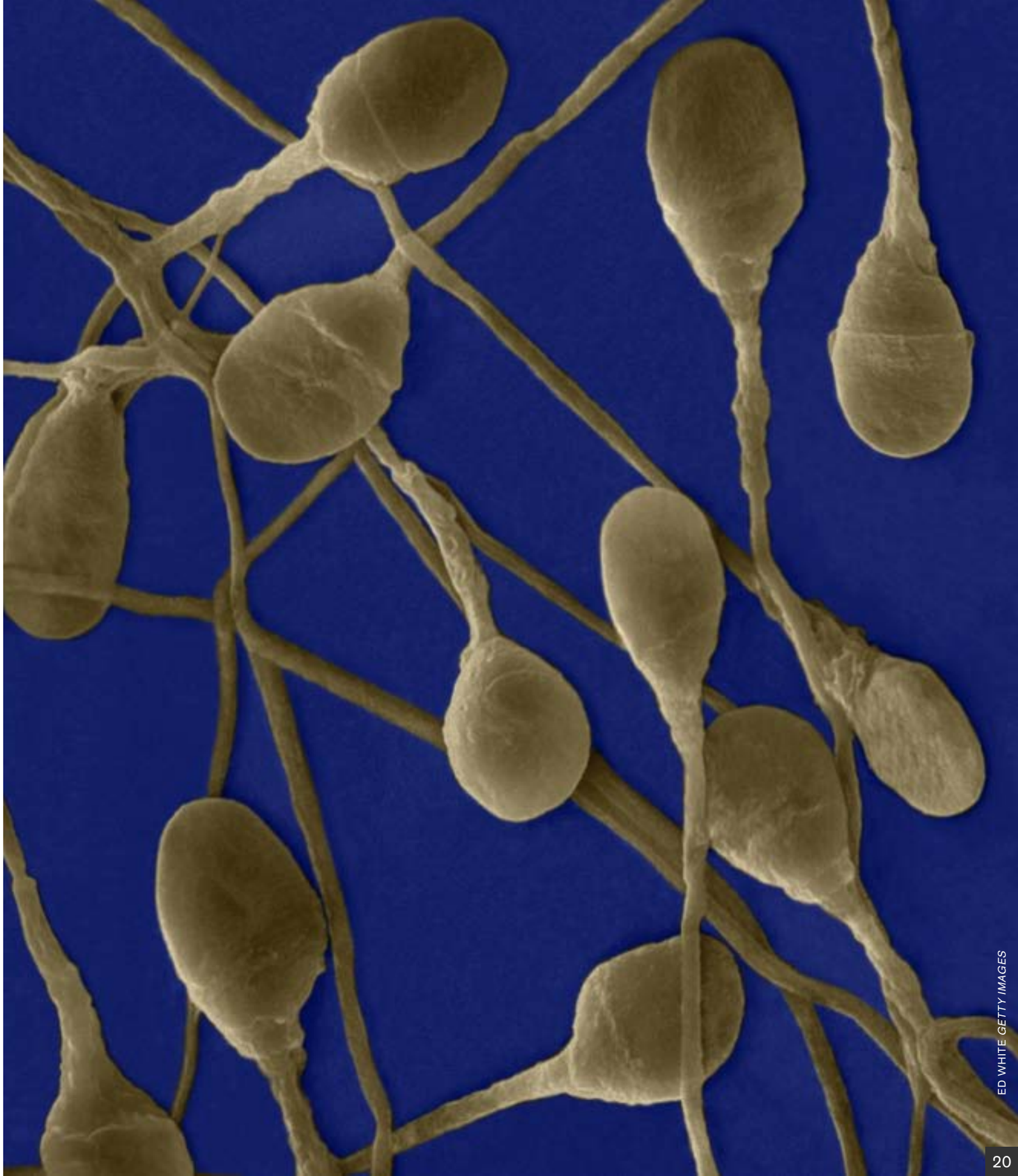
Amory responded with surprise. “See, I didn’t even know that,” he said about the studies. “We were taught [in medical training] that sperm were left over from the last ejaculate.” This is a popular theory. Planned Parenthood similarly says that preejaculate “may pick up sperm from a previous ejaculation as it passes through a man’s urethra.” Wikipedia promotes a familiar fix: just urinate before intercourse, the logic goes, and you’ll flush out lingering sperm.

Though the acidity of urine does harm sperm, I could not find any evidence to prove that this strategy is solid. In fact, researchers in the 2011 *Human Fertility* paper wrote that the volunteers giving samples had, of course, gone to the bathroom several times since their last ejaculation. Therefore, every time the authors observed sperm in preejaculate, the contamination “must have taken place immediately prior to ejaculation.” Clearly, there are consequences to misunderstanding this facet of male fertility.

“FERTILITY IS A TEAM SPORT”

Because we know so little about sperm in preejaculate, the failure rate of pulling out is really more of an “educated guess” and a topic of controversy among experts in the field. The reality is that lots of people in the U.S. use this method to avoid pregnancy. So, do males approach withdrawal as a serious form of contraception and take responsibility for learning how to maximize its efficacy? While plenty of men feel confident discussing the minutia of abortion and female reproductive parts they tend to be quite ignorant of their own fertility.

Greg Sommer discovered just how few males understand their contribution to pregnancy when he launched an at-home sperm-testing kit called Trak. In 2017, he brought his product to the Consumer Electronics Show in Las Vegas. “We had a demo kit at our booth, and I can’t tell you how many guys came up and said, ‘So, what, I pee in the cup?’”Sommer recalls. “And we had to tell them,



ED WHITE *GETTY IMAGES*

'No, there's no sperm in your urine.'"

Sperm awareness got a boost in 2017, when a meta-analysis showed that sperm counts of men from the U.S., Europe, Australia and New Zealand had dropped by more than 50 percent in less than 40 years. "Men are responsible for nearly half of infertility cases but take way too long to get a semen analysis when they are not conceiving naturally," Sommer says. The study was widely framed as a potential crisis in male fertility, sparking some men to consider their sperm functionality more deeply—or just consider it at all.

Whereas women have long shouldered the burden of both preventing pregnancy (with drugs) and causing pregnancy (with assisted-reproduction technologies such as egg freezing), "there is a growing understanding that fertility is a team sport," Eisenberg says. "We need to understand more about the male side."

Recent population surveys have shown that many men *do* want more birth-control options. Without contraception methods beyond condoms, vasectomy and withdrawal, some guys are already doing "all sorts of crazy and potentially dangerous things to make themselves less fertile to avoid pregnancy," Sommer says.

In discussion forums on Trak's infertility education Web site at www.dontcookyourballs.com Sommer found that some men "are biohacking themselves" by using prescription steroid creams to intentionally squash sperm count. Others sit in a hot tub every day. One guy wrote about his "hacked-up underwear heater-type device with a little battery pack," Sommer says. "Don't underestimate men's drive and creativity when it comes to having a better sex life"—meaning men will indeed make efforts and take risks to have sex without condoms.

The Center for Male Contraceptive Research & Development even exploits this incentive to solicit volunteers for clinical drug trials. One image on the center's Instagram account features a boxer with a punching bag.

"We had a demo kit at our booth, and I can't tell you how many guys came up and said, 'So, what, I pee in the cup?' And we had to tell them, 'No, there's no sperm in your urine.' " ***—Greg Sommer***

"Done with condoms? Join the fight for male birth control," it reads, followed by the hashtag #LoveWithoutTheGlove. It seems to be working: A major clinical trial for a hormonal gel began late last year.

It sounds woefully apropos that scientists and entrepreneurs are convincing guys to learn about reproductive responsibility by appealing to their sexual pleasure—particularly at a time when some U.S. lawmakers want to investigate the "criminality" of miscarriages and classify treatment for ectopic pregnancy as an "abortion."

Yet more options and knowledge for preventing pregnancy are good things for everyone. After all, nearly half of all pregnancies in the U.S. are unintended, and the lack of access to birth control and health care providers is not the only problem. Nearly 40 percent of women are not satisfied with the birth-control method they are currently using, according to the Guttmacher Institute. When people dislike their contraception for whatever reason—including health side effects from the pill or the tactile compromises of condoms—they are less likely to use it correctly and consistently.

One day, if the pharmaceutical industry decides to reverse course and fund the development of innovative birth control, we could get genetic tests and other technologies to help people of both sexes figure out what kind of contraception might work best for our individual physiologies and ways of life. In addition to hormones and IUDs, researchers could investigate "proteins, enzymes and genes involved in the reproductive process that could be targeted to prevent pregnancy in both women

PATRICK LLEWELYN-DAVIES *GETTY IMAGES*

and men—and potentially do so in more precise ways," wrote journalist Maya Dusenbery in the May issue of *Scientific American*.

With a personalized-medicine approach, imagine if birth control could be catered to the specific needs and priorities of an individual. In some cases, the task of preventing pregnancy could be truly shared between a couple. "What if the male partner is willing to take on some of the risks and side effects to lower the risks and side effects of his female partner?" Amory says. "No one has really talked about the idea of reframing risk paradigms."

Until this equitable future arrives, understanding the fertilizing potential of an individual's preejaculate could give some men another way to participate in the responsibility of contraception. Let's say that males do fall into two groups, as the Human Fertility study speculates. What if a man—my boyfriend, for instance—could undergo a preejaculate sperm evaluation?

If so, my boyfriend and I might scientifically resolve the final variable in our birth-control efficacy. We use coitus interruptus[1] during my fertile window, the week-long span during which his sperm can potentially fertilize my egg. (An egg is only viable for fertilization for up to 24 hours per menstrual cycle, and sperm can survive in the female body for up to five days.) I determine this window using a technique called the symptothermal method, a means of avoiding pregnancy that involves meticulously tracking changes in cervical fluid and basal-body temperature in order to predict, and then confirm, when ovulation occurs.[2]

We devised this contraception strategy based on our personal risk-benefit analysis and combined physiologies—and it has worked for us so far. But I'd prefer to empirically validate the absence (or problematic presence) of sperm in my boyfriend's preejaculate. Frustrated by the paltry research, I decided to conduct an experiment myself.

"What if the male partner is willing to take on some of the risks and side effects to lower the risks and side effects of his female partner? No one has really talked about the idea of reframing risk paradigms."

—John Amory

FOR SCIENCE!

The Trak test, while approved by the Food and Drug Administration, is not designed for testing preejaculate. Nor is it intended to be used as form of pregnancy prevention. But according to Sommer, it is sensitive enough to pick up on sperm concentration as low as one million per milliliter (M/mL). While that sounds like a lot, "the chance of pregnancy is extremely low," Amory says. "In fertility settings, we take care of a lot of men with those counts who never conceive spontaneously." The World Health Organization has determined that suppressing sperm counts to this threshold appears to decrease the chances of conception to less than 1 percent per year.

I ordered a Trak fertility kit and recruited one study participant: after assuring my boyfriend that his genetic material wouldn't be sent off to a lab and end up in a database (Trak isn't connected to the Internet), he gave me his informed consent.

First, we did a control test to get a sense of his sperm baseline. After 48 hours of abstinence (the minimum length of time for proper semen analysis, according to the WHO), he proffered a five-milliliter ejaculation sample. Per the instructions, we let it sit for 30 minutes to liquefy, gave it a good swirl, then deposited a pipette's worth of fluid into a test prop. That went into the Trak "engine," an adorably sized, battery-powered centrifuge.

My boyfriend stared down the engine until it beeped to signal its finish, recalling the way women glare at pregnancy tests while awaiting the results. A white column in the prop reached above the 55 M/mL mark, signaling that his sperm concentration made it into the "optimal" range for conception. After another 48 hours of abstaining from ejaculation ("for consistent science," I insisted), it was time to test his preejaculate.

"I think accurately testing just precum might be a challenge," Sommer wrote when I informed him of my plans to use his test for off-label endeavors. "Collecting a sample via masturbation might have different discharge dynamics than during intercourse."

The hallowed pages of *Scientific American* are not the place to describe how we collected a full milliliter of unadulterated preejaculate. I will say that our methodology was informed by the science of arousal, a commitment to rigorous research standards and an abundance of humor.

Per the discussions of methodology in the academic studies, we knew it was critical to collect only preejaculate. The authors of the Thai paper wrote that study volunteers might have smeared semen on the collection slides instead of preejaculate, which could mean the number of preejaculate samples that were found to contain sperm was artificially high. In other words, the subjects might have been sloppy, leading to false positives.

(Anecdotally, appealing to male pride created a strong motivation for my volunteer to endure the 30-ish minutes it took to retrieve enough volume of pure preejacu-

late to run the Trak test. "Wow, look at how much you're producing," I cheered about halfway through. By comparison, the academic study subjects were likely masturbating, presumably alone, in a lab, and I humbly hypothesize that they may have gotten bored. The authors of the 2011 *Human Fertility* study even suggested that subjects might have knowingly handed over samples of ejaculate fluid because they were embarrassed they couldn't produce sufficient preejaculate.)

We ran the preejaculate test just as with my boyfriend's ejaculate: a full pipette of well-mixed fluid went into the prop, followed by a six-minute spin in the centrifuge. Then we peered into the measuring strip under bright light and couldn't find even a speck of white. If there was sperm present, the concentration was likely below one million per milliliter, which means my boyfriend's preejaculate sample could be considered infertile by WHO standards.

Though promising, one at-home test doesn't confirm anything. We would need to replicate this experiment several more times. Sperm count in semen changes over time and is affected by health factors, so perhaps the same is true for preejaculate. Because Trak is not intended for such diagnostics, it would be best to compare the results of our experiments with lab tests at a fertility clinic (if they'd even indulge such a request).

Larger questions abound: Even if there are sperm in preejaculate, can they swim? Are all of their parts intact? And if the sperm present in preejaculate aren't simply "left over" from the last ejaculation, then from where might they be "leaking," as the literature suggests?

Filling these knowledge gaps has the potential to fine-tune the math of pregnancy risk. Imagine if males were able to better gauge whether the pullout method is a useful tool in their contraception arsenal or, more critically, whether it is too risky even when the act itself is performed correctly every time.

After all, contraceptive use in the real world is more varied and circumstantial than the behavioral patterns that determine "failure rates." Few people use only one method in the same exact way every time they have sex. Recent surveys suggest that coitus interruptus is actually employed more frequently than previous research suggests and often in conjunction with other methods. If some men do consistently have viable sperm in their preejaculate, it might help explain the 4 percent failure rate of the withdrawal method despite "perfect" use. It would not be the first time the medical field was wrong to blame contraceptive failure on user error instead of physiological variation.

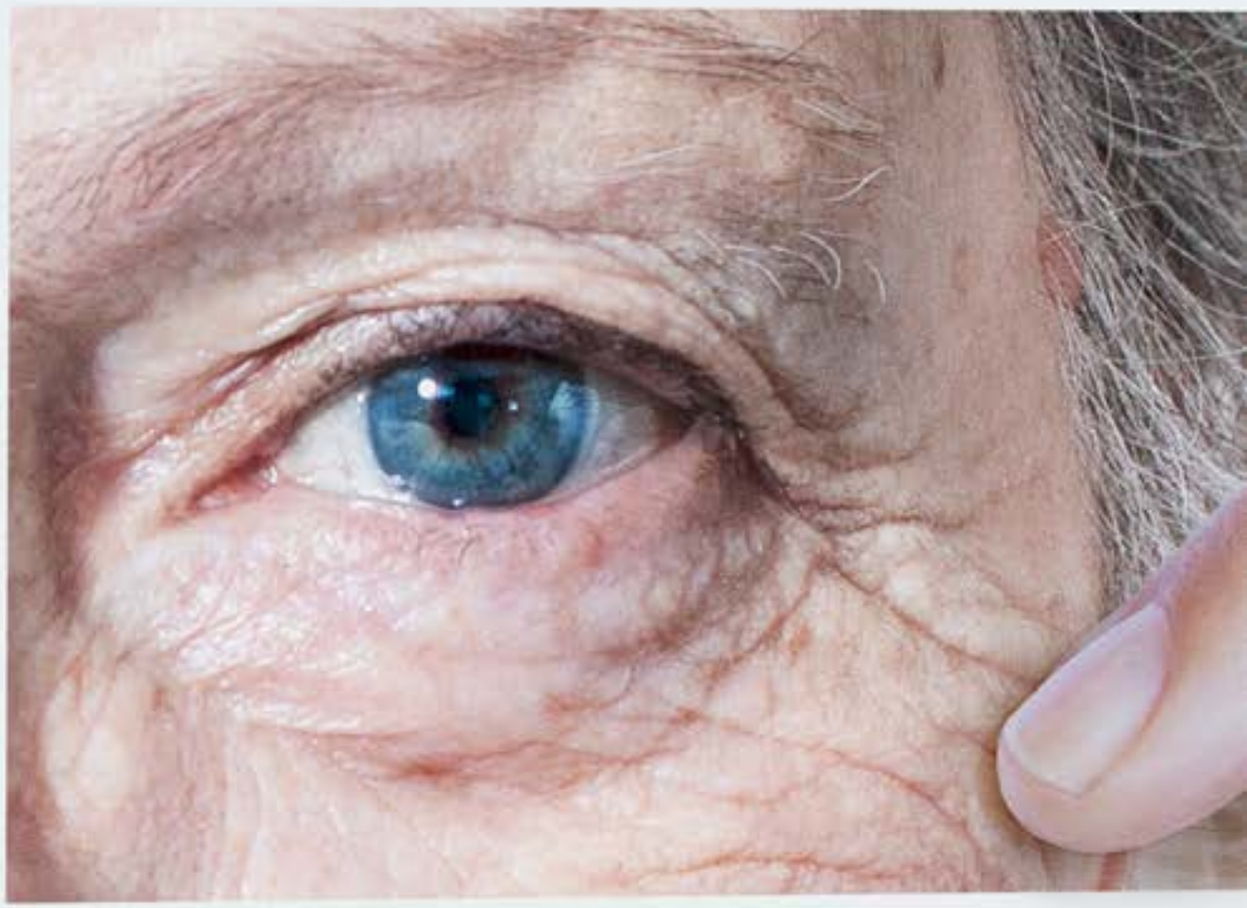
At the least, researching the mechanisms of preejaculate and pregnancy risk could add evidence-based nuance to sex education. As Amory told me after reviewing the studies on preejaculate, "I think this is an example of when you drill down on a 'truth,' one finds it's not based on much."

[1] We could use condoms during my "fertile window," but their failure rate over time is not significantly lower than coitus interruptus. Given the best available science and our personal considerations, we chose to be in control over preventing user error rather than risk the uncertainty of product failure.

[2] The symptothermal method should not be confused with the rhythm method or similar counting techniques. With perfect use, it can be just as effective as the pill at preventing pregnancy. While I chart my data in a cycle-tracking app, I do not consult predictive algorithms to determine when I am fertile. Like all contraceptive methods, the symptothermal method is certainly not right for everyone. It can, however, be used as an excellent educational tool for learning about fertility and reproductive health.

ED WHITE *GETTY IMAGES*

Cancer Research Points to Key Unknowns about Popular "Antiaging" Supplements



The health promises of boosting an important metabolic molecule may be clouded by its possible role in promoting cancer cell growth

By Helen Shen

DMITRI OTIS *GETTY IMAGES*

Helen Shen is a science writer based in Sunnyvale, Calif. She has contributed to *Nature*, *Science* and the *Boston Globe*.

As the world's aging population grows rapidly, so has its appetite for health tips, tricks and products that could help guard against the ravages of time. Among countless dietary supplements—vitamins, minerals and other products—some people have pinned their hopes on a molecule called nicotinamide adenine dinucleotide (NAD), a key player in the cellular production of energy. Often written as NAD^+, the name of its oxidized form, the molecule participates in a host of metabolic pathways and is involved in other important processes, such as DNA repair. NAD^+ levels naturally decline as people and animals age, and this loss has been proposed as contributing to the underlying physiology of aging.

Studies show that boosting NAD^+ levels can extend life span in yeast, worms and mice. Animal research also indicates NAD^+'s promise for improving several aspects of health. Raising levels of the molecule in old mice appears to rejuvenate mitochondria—the cell's energy factories, which falter over time. Other mouse studies have demonstrated benefits such as improved cardiovascular function, enhanced muscle regeneration and better glucose metabolism with NAD^+ supplementation.

Banking on such results, multiple companies currently sell dietary supplements containing NAD^+ precursors such as nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN). NR supplements, in particular, have attracted buzz for the scientific star power associated with two major suppliers, ChromaDex and Elysium Health. The companies' research advisers hail from institutions such as Stanford, Harvard and Columbia University. Elysium's scientific advisory board currently boasts eight Nobel laureates.

But the NR business and some scientists involved have attracted their share of criticism as well. Unlike drugs, dietary supplements are lightly regulated by U.S. authorities, allowing them to be sold before research confirms their safety and effectiveness in humans. Recent clinical trials funded by ChromaDex and Elysium show that adults taking NR-containing supplements for six to eight weeks experience increased levels of NAD^+ in their blood without serious side effects. But researchers are still working to prove that NR can actually improve human health—a sticking point for critics and an issue acknowledged by the companies themselves.

"Not everything that works in mice works in humans, which is why it's critical to do the rigorous human trials," says Leonard Guarente, a co-founder of Elysium and its chief scientist. The company is studying the effectiveness of its NR-containing supplement for a number of conditions in people, including kidney injury and fatty liver. Early this year, Elysium published a small trial showing that its product could potentially slow the neurodegenerative disease amyotrophic lateral sclerosis. ChromaDex's NR supplement is also the subject of many clinical trials, with the company recently sponsoring a study of its effects on cognitive function, mood and sleep in people older than 55.

For very different reasons, NAD^+ has also attracted a wave of attention from cancer researchers. Recent studies suggest that cancer cells of many types depend on NAD^+ to sustain their rapid growth and that cutting off the NAD^+ supply could be an effective strategy for killing certain cancers. The data from these studies paint a more complicated picture of NAD^+ and raise new questions about the diverse ways taking an NAD^+-boosting supplement might influence health. "It might still slow down the aging part, but it might fuel the cancer part," says Versha Banerji, a clinician-scientist at the University of Manitoba. "We just need to figure out more about the biology of both of those processes, to figure out how we can make people age well and also not get cancer."

In a *Nature Cell Biology* study in February scientists reported a newly discovered role for NAD^+ metabolism at the intersection of cellular aging and cancer—specifically, in a process called cellular senescence. Senescence occurs when aging, damaged cells stop dividing. The process can help suppress cancer, but it leads cells to produce inflammatory molecules that can also promote cancer growth under certain conditions. In the *Nature Cell Biology* study, Rugang Zhang of the Wistar Institute and his colleagues found that in cells entering senescence, rising levels of NAMPT (a major NAD^+-producing enzyme in mammals) encourage the release of inflammatory and potentially

protumor molecules. Consistent with those findings, mice genetically predisposed toward pancreatic cancer developed more precancerous and cancerous growths when they consumed the NAD^+ precursor NMN. Zhang says more research is needed to fully understand the role of NAD^+ in cancer, but he adds that "we should be cautious and bear in mind the potential downside of NAD^+ supplementation as a dietary approach for antiaging."

Zhang's work is part of a growing body of research that has drawn attention to NAD^+ metabolism in cancer, particularly involving NAMPT. Compared with healthy tissues, elevated NAMPT levels have been reported in several human cancers, including; colorectal, ovarian, breast and prostate cancers. In studies in animals and cells, drugs that inhibit NAMPT have shown promise in killing cancer cells or enhancing the effectiveness of other cancer therapies.

In 2016 researchers at Washington University School of Medicine in St. Louis found that among people with glioblastoma—an aggressive form of brain cancer—tumors with higher NAMPT levels correlated with shorter survival times. When human glioblastoma cells were implanted in mice, the cells proliferated and established new tumors. But when researchers suppressed NAMPT in these cells before implantation, they later saw reduced brain-tumor formation and increased survival in the mice—suggesting that glioblastoma cells depend on NAMPT and NAD^+ to thrive.

What might this result say about NAD^+-boosting supplements? "There's a lot of buzz about taking NAD^+ precursors for their antiaging effects, which is based on a lot of great science," said Albert Kim, senior author of the 2016 study, in a School of Medicine press release "I don't know if taking NAD^+ precursors makes existing tumors grow faster, but one implication of our work is that we don't yet fully understand all of the consequences of enhancing NAD^+ levels."

These emerging questions are not ruffling makers of NR supplements. "I'm not losing sleep over this," says Charles Brenner, chief scientific adviser for ChromaDex. Reports of higher-than-normal NAMPT levels in many cancers do not prove that high NAD^+ levels actually promote cancer growth, he notes. He contends that studies that kill cancer cells by suppressing the NAD^+-producing enzyme also do not properly address the issue. "Whether low NAD^+ would block cancer and whether high NAD^+ would promote cancer are two separate questions," he says.

"There is tremendous interest in the NAD^+ field right now. And I'm pretty sure sooner or later, we will have the evidence to answer this."
—Shashi Gujar

Indeed, Zhang's study is one of the first to directly show that providing supplemental NAD^+, via the precursor NMN, was associated with increased cancerous growths in mice. But Elysium's Guarente is skeptical of the data, arguing that Zhang's study showed a small effect in a small number of animals and that it has yet to be replicated by other groups. "I don't think the evidence is there at all to say that raising NAD^+ levels would favor cancer," Guarente says.

At the moment, the idea that elevating NAD^+ levels could fuel cancer growth remains a hypothesis, but it is one that has attracted considerable attention. Cancer cells have high metabolic needs, including processes requiring NAD^+. And many types of cancer cells boost NAD^+-making enzymes and then die when those enzymes are blocked by drugs. "We know that they like NAD^+, but it's too early to say, if you add NAD^+, whether they will grow really fast," says Shashi Gujar, a cancer immunologist at Dalhousie University. "Many labs are working to figure that out."

The answer may not be a single or straightforward one. NAD^+ is a ubiquitous and fundamental molecule, involved in many biological pathways and cellular operations. Its ingestion could lead to a mix of positive and negative outcomes, the balance of which might depend on context. NAD^+ precursors, consumed orally, may be taken up by some tissues more than others. And different cell types are known to employ distinct metabolic programs, which could lead to tissue-specific responses to NAD^+.

Like the tissues from which they arise, cancers are diverse in their cellular ways—and at least some run counter to the "cancer fuel" hypothesis of NAD^+. A 2014 study, for instance, reported that in a mouse model of liver cancer, inhibiting NAD^+ production was a key step by which an errant gene caused DNA damage and tumor formation. In this case, feeding NR to the mice actually helped protect against these harmful effects.

Together these findings do not necessarily point to ready answers for consumers interested in NR or NMN supplements, so much as they highlight questions for scientists to address in the coming years. "I would say that given that many people are taking these supplements for health benefits, a study of what these do to cancer risk or existing cancer biology is warranted," says Matthew Vander Heiden, a clinician-scientist at the Massachusetts Institute of Technology's Koch Institute for Integrative Cancer Research.

The need for more evidence is a sentiment that is shared by others. "There is tremendous interest in the NAD^+ field right now," Gujar says. "And I'm pretty sure sooner or later, we will have the evidence to answer this."

Rafael Amado is president of research and development at Adaptimmune.

OBSERVATIONS

The Next Wave of Immuno-Oncology

A cutting-edge therapy currently used for blood cancers is now being adapted to fight solid tumors

In 2017, the first immuno-oncology cell therapies, known as chimeric antigen receptor T cells, or CAR T, were approved by the U.S. Food and Drug Administration. Immuno-oncology cell therapy is a field that leverages the immune system by modifying, and thereby enhancing, immune cells to target cancer. It accomplishes this by interdicting pathways that maintain checks and balances on cellular elements of the immune system, thereby disrupting the tolerance of the body to the growth and spread of cancer.

CAR T therapies have had an unprecedented success in blood cancers, such as certain leukemias and lymphomas. They have shown high response rates and redefined the treatment of patients who have exhausted other options. The therapeutic success relies on an antibody fragment that binds to a surface protein on leukemias and lymphomas; the protein is

Illustration of CAR T cell cancer immunotherapy in action.

JUAN GAERTNER *GETTY IMAGES*

known as CD19. The antibody fragment is linked to stimulatory and signaling molecules that fire upon binding of the antibody with the CD19 molecule, thereby activating the T cells and making them destroy the cancer cell.

Patients in dire need of novel treatment options are the driving force behind the impetus of Adaptimmune and many companies in the life sciences industry to continue the quest to eradicate metastatic cancer.

SOLID TUMOR CHALLENGES

CAR T therapies have shown limited success in solid tumors, since they do not typically express a molecule on their surface that is unique to the solid tumor and not to normal tissue. This, coupled with the complex matrix in which cancer cells grow, makes it challenging to develop cellular therapies for solid tumors.

One way to overcome this challenge is to target proteins expressed inside the cell rather than large cell surface proteins. This sort of immune response involves the activation of T cells against a portion of an internal protein that the T cell sees as foreign. These protein fragments, known as peptides, dock with protein structures known as major histocompatibility antigens (MHC) on the cell surface, which is the cellular network that governs the presentation of self versus nonself peptides and lets T cells distinguish friend from foe.

T cells are some of the "surveyors and assassins" of the immune system. They have T cell receptors (TCRs) on their surface, and they circulate through the body, binding foreign peptides on the surface of cells that are infected by foreign organisms such as viruses and bacteria. When a cell is infected, bits of that organism's protein make it to the surface, docking with the right MHC. Surveying T cells can see these proteins through their TCRs and kill them to prevent propagation of the infection.

However, cancer cells have proteins that look similar to the body's own, not like foreign proteins, which creates an ability to evade the immune system. This makes it difficult to effectively target tumors with our body's own naturally occurring TCRs. When cancer cells develop mutations, they may present novel aberrant peptides, but often the malignant cell and other elements of the tumor dampen the T cell response by interfering with the molecular network that regulates how the T cell functions. The unraveling of some of the proteins that regulate T cell function against tumor cells resulted in two scientists sharing the 2018 Nobel Prize in Physiology or Medicine.

THE POTENTIAL OF ENHANCED RECEPTORS

Companies are now exploring how to enhance the body's naturally occurring TCRs to target solid tumors. Engineering TCRs to have optimal affinity to the docking peptide enables the receptors to more easily identify proteins from cancer cells that would have otherwise not be recognized as foreign.

These engineered TCRs can be put into a patient's own T cells and then returned to the patient. These newly enhanced T cells can kill tumors, multiply and attack more cancer cells than a patient's naturally occurring T cells.

At Adaptimmune, we utilize our unique SPEAR (specific peptide enhanced affinity receptor) T cell platform to engineer TCRs so that they can recognize cancer proteins on solid tumors. Adaptimmune's SPEAR T cell therapy targeting a protein called NY-ESO, now transitioned to GlaxoSmithKline, has shown efficacy in two unique sarcoma types—both very difficult-to-treat solid tumors.

FUTURE IMMUNO-ONCOLOGY

There is still more to come from the immuno-oncology cell therapy field with respect to utilizing TCRs, since many solid tumors recur and become incurable. This is why Adaptimmune is conducting clinical trials with multiple engineered TCRs across a broad range of solid tumors. The company is also investigating next-generation TCRs armed with molecules to further improve the engineered T cells' ability to target and destroy solid tumors. These enhanced approaches will likely lead to longer-lasting antitumor responses.

Patients in dire need of novel treatment options are the driving force behind the impetus of Adaptimmune and many companies in the life sciences industry to continue the quest to eradicate metastatic cancer. The field has come a long way, and its potential appears boundless as scientists unravel the intricate interplay between cancer and anticancer immunity.

Related Video

Jon Morgenstern is an internationally recognized expert on the treatment of substance use disorders. He leads addiction research at Wellbridge Addiction Treatment and Research and serves as assistant vice president of addiction services at Northwell Health.

OBSERVATIONS

A New Approach to Addiction Treatment

We need to create learning laboratories where researchers interact directly with patients

GETTY IMAGES

The nation's growing addiction crisis has amplified the urgent and long-standing need for integrating research into the substance abuse treatment and recovery process. While there has been an increase in research activity focused on addiction issues, the challenge is that it often takes a decade or more before important clinical findings can be implemented into real-world care delivery.

How can the industry address this problem and make continuous quality improvement a cornerstone of substance abuse treatment? I believe we need to create addiction treatment learning laboratories that are embedded into, and coexist with, treatment and recovery centers.

The goal of this approach is to accelerate the translation of basic science discoveries into actionable treatment methodologies that can be shared with and help advance the work of addiction professionals nationwide.

WHY NOW

While research has generated evidence of treatment efficacy in highly controlled settings, there is limited understanding of how to apply this knowledge in ongoing care regimens. For example, most programs offer a variety of different treatments, but there is no research on the impact of these multicomponent programs or how to tailor care to the unique problems of individual patients.

Additionally, because there is little knowledge of how best to measure progress in treatment, it can

be very difficult to make critical decisions about when to extend care or introduce a new treatment. As a result, the current standard of substance use disorder (SUD) treatment too often provides a one-size-fits-all set of services, or if treatment is personalized, it is based on clinical intuition without the benefit of research.

Drug addiction has now become the deadliest public health crisis in recent U.S. history. To address this major epidemic, it is imperative to find new and innovative approaches to treatment.

CRITICAL DATA

Compared to other areas of health care, the addiction field lags behind in the use and analysis of data. Certainly, the human element can't be replaced, but collecting and analyzing data in a manner that is actionable will help more patients. The need is for real-time data collection to enable care that is tailored to the individual and how he or she changes over time.

For the most part, current SUD treatment programs do not have this capacity as part of routine operations. Consequently, the industry must now begin to work toward developing state-of-the-art clinical informatic platforms that can collect research quality data on every patient at admission, during treatment and for several years following discharge.

The goal is for researchers to be able to identify treatment outcomes and patterns, and in doing so understand the interventions that work best for individual patients. Once best practices along the continuum are identified, clinicians can then integrate them into everyday clinical care.

Bottom line: Being able to see if outcomes improve as treatment is modified will be a significant advancement in the addiction field.

AFFILIATIONS AND COLLABORATIONS

Establishing strong affiliations with the nation's leading health care providers and building collaborative relationships with major research institutions will play an important role in accelerating the integration of research into the substance abuse treatment and recovery process.

A good example of this is how Northwell Health, the largest health care provider in New York, and Engel Burman, a leading developer of assisted-living facilities, have engaged in a joint venture with Wellbridge Addiction Treatment and Research. This unique venture will approach addiction in a modern way by aligning best practices in a manner similar to how Northwell addresses other illnesses like diabetes and cancer.

A key advantage of this venture will be having access to the necessary resources to explore some of the more promising areas of addiction treatment, including mapping genetic profiles directly to optimize addiction treatment, as well as expanding research on how genetic biomarkers can inform the use of medications.

Other important areas of study might include imaging, neuroscience, precision medicine and comparative effectiveness. There are huge differences in how patients respond to treatment, which is why integrating research into the treatment process creates a tremendous opportunity to identify more precise markers for determining how a specific patient responds to specific treatments.

Affiliations and collaborations can also help create opportunities to study large cohorts of patients, support continuum of care by tracking patients' recovery, and explore new options for staying in touch with patients over extended periods of time.

Key to all of this will be the ability to leverage the intersection of health care and technology (i.e., "connected health") and apply it to addiction treatment. For example, many of the techniques found effective for other chronic diseases can also be used to promote better management of addiction care.

Drug addiction has now become the deadliest public health crisis in recent U.S. history. To address this major epidemic, it is imperative to find new and innovative approaches to treatment. While having patients down the hall from researchers is very rare in addiction treatment centers, it is now absolutely necessary to study, properly treat and ultimately overcome this devastating disease.

Rick Hohner is senior integrated care manager at NeuroFlow.

OBSERVATIONS

The Case for Collaborative Care

It produces better patient outcomes. Here's why it works and how it can be effectively deployed

GETTY IMAGES

Several years ago, a patient of mine was suffering from intrusive thoughts and associated rituals stemming from a case of obsessive compulsive disorder (OCD). One day, she took a significant risk and shared her distress with her primary care provider, who realized that she needed a behavioral health clinician (BHC). Fortunately, one was "embedded" at the same health care provider where I work—a concept that is gaining in popularity.

Soon, she eliminated 90 percent of her ritualized behaviors and regained control. If she had not spoken up, and her primary care provider was not equipped to input data and integrate with a BHC, the story might have ended differently.

Every day, patients visit a health care provider or hospital in order to discuss one or more physical symptoms, when in reality what they may really need is to talk about their mental health. In a collaborative care model (also called integrated care or health homes), the opportunity for patients to receive comprehensive care for all of their physical and behavioral health needs is greatly enhanced.

Untreated behavioral health issues can have significant downstream repercussions on physical health, and can occasionally cause an alteration to treatment protocols. Whether it is heart disease or cancer or psoriasis, physical ailments are closely connected to mental health conditions such as depression and anxiety.

When psychological problems lead to or exacerbate physical symptoms in a traditional "compartmentalized care" setting, it is more likely that the patient's overall health (mind and body) will be impacted by disconnected treatment. Cardiologists are not skilled psychiatrists, and vice versa, but by coming together in a collaborative care model, they can each be more confident in knowing that their patient is receiving holistic treatment.

The collaborative care team may include a

primary care physician, a mental health specialist (social workers, psychiatric nurse practitioners, counselors, psychologists, and psychiatrists), and other physical medicine specialists who may be treating the patient. All team members agree to hold each other accountable and to work in sharing their knowledge of the patient with the overall goal of using this information to ensure the best possible outcome.

Each team member is expected to set goals with the patient that are aligned with and supportive of those from other team members. This model implies that team members share ideas, outcomes (positive or otherwise) and recommendations with each other in a respectful and supportive manner. Finally, the team evaluates the outcomes using validated measures and makes adjustments to the collaborative plan accordingly.

GAINING TRACTION

Research around collaborative and integrated care models began in the 1970s, so this is not a new idea, but adoption has been tepid. Fortunately, with more than 80 trials completed, there is greater acceptance of this approach as a well-supported model of care. In true collaborative fashion, many of these trials involved multiple specialties, including OB-GYN, pediatrics and pain management, and studied patients with a range of complex needs. As recently as 2016, the American Psychiatric Association and the Academy of Psychosomatic Medicine (since renamed the Academy of Consultation-Liaison Psychiatry) issued a report and a public statement recommending collaborative care.

One case study, tracking the impact of collaborative care in a hospital system, demonstrated a 57 percent reduction in depression among primary care patients. Results like these can nudge other health care systems and leaders to adopt technologies and software that facilitate the collaborative care approach.

THE ROAD AHEAD

The benefits of patient-centered collaborative care go beyond better physical and mental health. This approach takes into account the patient's values, beliefs and preferences while encouraging him or her to actively participate in an individualized treatment plan. Additionally, the economic benefits of collaborative care must not be overlooked. Depression costs employers an estimated $44 billion annually in lost productivity.

Across all disciplines, we need to find ways to integrate our knowledge and skills so that everyone can engage in such a dynamic and effective mode of care. Despite the positive results from collaborative care models, there is still work to be done to successfully adopt these practices across our health care landscape. I recently joined NeuroFlow, a health care technology company whose goal is to bridge the gap between mental and physical health in all care settings. But currently, fewer than 3 percent of psychiatrists and psychiatric nurse practitioners work with primary care physicians in designing and implementing treatment plans for their shared patients. Increasing that percentage would allow many more patients to reap the benefits.

Abigail Meola is a student at Stevens Institute of Technology in Hoboken, New Jersey. She studies science communications and writes for the school's newspaper *The Stute*.

GETTY IMAGES

OBSERVATIONS

The Polycystic Sisterhood

Infertility is on the rise, but one major cause—polycystic ovarian syndrome—gets too little attention

Ask anyone in a sorority and they will tell you that sisterhood is priceless. I'm not in a sorority, but I am not a stranger to the concept. I have two biological sisters of my own and recently joined another sisterhood inadvertently: the women suffering from polycystic ovarian syndrome (PCOS).

Sure, it's not your typical social club. It is certainly not as much fun. But women with PCOS have a bond as close as you would find in any sorority. We are a scientific cysterhood, you might say.

I first caught a glimpse of my emerging PCOS when I gained close to 40 pounds in six months. I was in my second year of college, and though I was well aware of the "freshman 15," I was doubtful that a "sophomore 60" was another rite of passage. I had low energy and extreme mood swings. I had my thyroid levels checked more times than I can count.

Polycystic ovarian syndrome is a common but complex endocrine disorder affecting a woman's hormones, metabolism and reproductive capabilities. It is the leading cause of infertility among women. Some 5 to 10 percent of women suffer from the disorder worldwide, and the number in the U.S. is as high as 15 percent and climbing. But as common as it is, it is equally confusing.

The name of the disorder suggests multiple cysts in the ovaries, which is only partially true. You do not need to have any cysts to be diagnosed with the syndrome. To add even more ambiguity, the "cysts" associated with the disorder are more accurately categorized as "follicles,"

since they are not lined or fluid-filled, and are significantly smaller than the typical cyst. The National Institutes of Health's PCOS workshop panel even moved to rebrand the syndrome, since the current name "causes confusion and is a barrier to effective education."

Misnomers aside, the syndrome has some characteristic symptoms that wreak havoc on the body. One of the hallmarks of PCOS is hyperandrogenemia, or extremely elevated levels of male hormones (testosterone, DHEA and more). Hormone imbalance by itself can cause many side effects—excess body hair, mood swings, anxiety and depression, insulin resistance, and uncontrolled weight gain, to name a few. In addition, PCOS women usually have irregular ovulation, which can make it hard to get pregnant regardless of whether the mother is otherwise fertile.

On top of the day-to-day challenges, women with PCOS are at much higher risk of life-threatening diseases. According to the advocacy group PCOS Challenge, polycystic ovarian syndrome makes a woman more likely to develop cardiovascular disease or type 2 diabetes. In fact, the NIH predicts that over half of women with PCOS will have diabetes or prediabetes by the age of 40. These women are also two to four times more likely to develop some types of reproductive cancers such as endometrial or breast cancer.

Once I finally learned that I had PCOS, I tried numerous unsuccessful treatments. I started wearing an estrogen patch, which made me so depressed that I was lying in bed for most of the day, bawling my eyes out to Coldplay songs. I took inositol, an alternative to synthetic progesterone. I drank turmeric and cinnamon. And I ended up taking metformin, a diabetes drug and common off-label treatment for PCOS sufferers with insulin resistance.

These are all accepted treatments for PCOS, along with the inevitable recommendations about diet and exercise. None of them are perfect remedies, and thus there is no official cure for the syndrome. Doctors constantly emphasize the importance of lowering weight and body fat, but weight loss is nearly impossible because of the unique hormonal and metabolic challenges of PCOS.

As for the cause of PCOS, the story gets even more convoluted. The syndrome was first described over 80 years ago by the gynecologists Irving Stein and Michael Leventhal, yet researchers today are not much closer to figuring out the root of the problem.

At the Endocrine Society's annual meeting in San Diego this past March, experts brought up plastic as a potential aggravator of PCOS. Microplastics get into the body from food and water. Once there, plastic is a major endocrine disruptor because it mimics hormones in the bloodstream. The Endocrine Society's official scientific statement notes that chemicals found in common household plastics have been linked with PCOS in both rats and humans.

The fact that genes underlying the syndrome continue to be passed on in such high volume is puzzling for scientists because PCOS decreases fertility, thus minimizing reproductive success. Many people have posed explanations for this confusing genetic inheritance, such as the idea from Sabine Eggers and her colleagues that childless women have inclusive fitness because they help raise other women's children. I am unconvinced.

In 2017, another theory started gaining traction when a study led by Paolo Giacobini claimed to identify both the cause and the cure for PCOS. In experiments on mice, Giacobini's team traced elevated levels of two hormones, anti-Mullerian hormone (AMH) and gonadotropin-releasing hormone (GnRH), that when present in the womb caused fetuses to develop PCOS. GnRH is inhibited by various well-known cancer medications, so by treating adult women doctors could, in theory, prevent future generations from developing PCOS. Researchers and patients were temporarily abuzz, but with a big caveat. The potential cure was only viable for PCOS mice without excess body fat, meaning it is not applicable to most cases of the syndrome.

Even with theories like these swirling around the scientific community, there is still no cure, no comprehensive treatment and no definitive cause for PCOS.

Doctors often fail to diagnose people with this condition—so often that 50 percent of women with PCOS do not know they have it. In a survey published in the *Journal of Clinical Endocrinology & Metabolism*, nearly half of women visited three or more doctors and a third of them took more than two years before receiving a PCOS diagnosis.

The general public and scientific community are equally slow on the uptake. Even though more than 10 million American women might suffer from PCOS, the NIH research budget is significantly lower for PCOS than other prominent women's health issues.

Why? For one, PCOS is extremely complicated, possibly without much payoff for big pharmaceutical companies. There have been fewer than 1,000 clinical trials ever conducted on PCOS patients, and only about 10 percent of these were done by industry.

Likewise, polycystic ovarian syndrome involves a complex network of scientists, physicians and patients. The breadth of different disciplines involved makes knowledge sharing difficult. The field is ill defined, and scientists have barely even come to a consensus about what the syndrome is.

PCOS affects women only, yet without the celebrity status of other women's health issues like breast cancer. But if the #MeToo movement or International Women's Day are indicators, today's women are not willing to sit idle. Enter the PCOS sisterhood.

Women from all walks of life are banding together on social media to support each other and learn more about their PCOS. Actress and comedian Lauren Ash, famous for her role in the NBC show *Superstore*, accidentally became an activist for PCOS when she announced her diagnosis on Twitter. "It was one of the best things I ever did," she said in an interview with *Women's Health*. "Within hours I had thousands of replies and messages from other women saying, 'No way! Me too!'" She decided to make an Instagram page (@pcos_sisterhood) where she accepts the stories, advice and questions of other "PCOS warriors."

Support groups have been working tirelessly to gain awareness for the syndrome. The organization PCOS Challenge met on Capitol Hill in March for a PCOS Advocacy Day, with Lauren Ash joining the group to speak to lawmakers. The PCOS Awareness Association recently established September as PCOS Awareness Month.

Although there have yet to be major strides in funding and discovery, patients have been active in making incremental changes and providing support to one another. The countless social media pages dedicated to PCOS have actually been able to contribute to the knowledge base by aggregating data from women with the syndrome. For instance, women have uncovered a high incidence of PCOS-related binge-eating disorders and have helped to reveal the inefficacy of some formerly accepted treatment plans.

PCOS is on the rise worldwide and is especially problematic in the U.S., where there is an existing infertility crisis. We need to prioritize PCOS research. It significantly impacts every woman who endures it. If you suffer from polycystic ovarian syndrome, take this chance to become part of the sisterhood—and know that you are not, so to speak, ovary-acting.

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