

SCIENTIFIC  
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**Health &**  
Medicine

# Generation Ketamine

THE PARTY DRUG IS  
INSPIRING A NEW ERA OF  
DEPRESSION TREATMENTS.  
BUT IS THERE MORE  
TO THE STORY?

WITH COVERAGE FROM  
**nature**

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*Plus:*

**A SILENT  
DISEASE ON  
THE RISE**

**NEW  
CONNECTIONS  
BETWEEN THE  
GUT AND BRAIN**

**YOUR HEALTH  
INSURANCE  
MAY BE  
PUTTING YOU  
IN DANGER**



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# New Frontiers in Health and Medicine

At the end of last year, Chinese geneticist He Jiankui shocked the world by announcing that he had successfully altered the genes of twin baby girls to prevent them from ever contracting HIV. The research community's response was quick and harsh: he had flouted the ethical guidelines for manipulating the genomes of embryos, it said, and seemed unaware of the Pandora's box he had pried open. While this one rogue scientist's activities (if found to be true) have the potential to bruise public opinion of new, powerful medical technology, the promise of the technique, CRISPR-Cas 9 gene editing, is undeniable: the potential to block diseases with an underlying genetic basis before they begin, literally editing them out of the human genome for generations to come. The science and medical community will have a lot of talking to do in the coming years about how to manage this new technology and what impacts we can expect to see on human health.

And this isn't the only health and medicine issue worth digging into. An unrelenting opioid crisis continues to sweep through the U.S., as do reemerging diseases and surprising epidemics. The medical community has rallied around new technologies—immune-based treatments for cancers, for example, and revolutionary genetic technology, such as CRISPR. Unanswered questions remain about the potential of medical marijuana, the relation between the gut and the brain, and the true scientific value of the latest wellness trends. And that's just scratching the surface.

It seems prime time for *Scientific American* to contribute to the conversation in a more substantial way. Therefore, I am thrilled to introduce our newest subscription product: *Scientific American Health&Medicine*. This bimonthly publication will include articles from *Scientific American* and *Nature* and will explore the cutting-edge science of everything from human health and epidemiology to biotechnology and medicine. It's just what the doctor ordered.

As always we are eager for your feedback! Send us your thoughts at [editors@sciam.com](mailto:editors@sciam.com)

**Andrea Gawrylewski**  
Collections Editor



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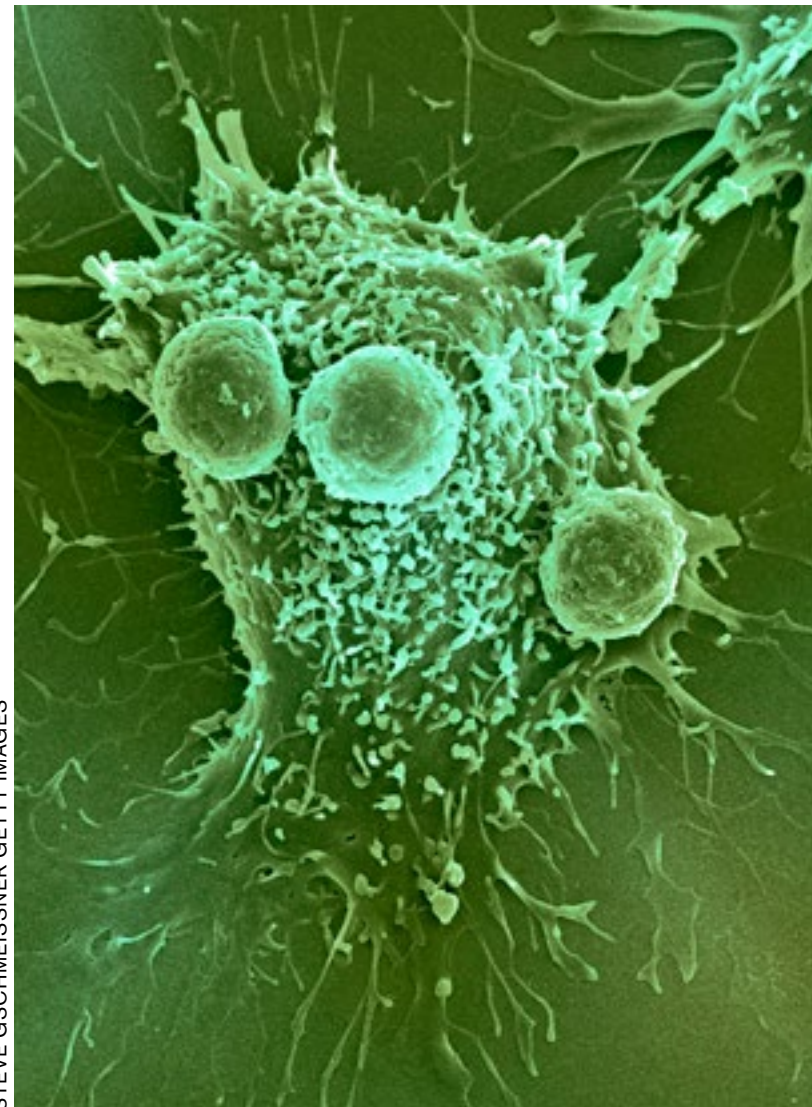
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## How Marijuana Harms a Developing Baby's Brain

Three studies in rodents suggest prenatal exposure to the drug may pose risks for infants

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MARIJUANA HAS BEEN legalized in some capacity in 31 U.S. states, in large part due to a softening stance around the potential harms of the drug and recognition of its medical benefits. As a result, cannabis has become the most commonly used illicit drug during pregnancy.

One recent study revealed that in 2016 7 percent of pregnant women in California used marijuana, with rates as high as 22 percent among teenage mothers. In Colorado 69 percent of dispensaries recommended the drug to pregnant women to help with morning sickness.

Whereas marijuana is not a major health risk for most adults, prenatal drug exposure can be harmful to unborn babies. Previous research has shown infants exposed to

cannabis in the womb are 50 percent more likely to have a lower birth weight. Now three new studies presented last November at the Society for Neuroscience annual meeting in San Diego suggest prenatal cannabis exposure—at least in rodents—could have serious consequences for fetal brain development. “There’s become this relaxation—in part because [marijuana] is becoming legal in many states around the country—that it’s fine,” says Yasmin Hurd, who is director of the Addiction Institute at the Icahn School of Medicine at Mount Sinai and was not involved in the new research. But, she adds, just because a drug is not very dangerous to adults does not mean it is harmless to the developing brain.

In one study researchers at Washington State University in Pullman showed rat pups born to mothers exposed to high amounts of cannabis vapor during pregnancy had trouble with cognitive flexibility. Twice a day the scientists filled the pregnant rats’ containers with





marijuana vapor from an e-cigarette, elevating levels of the psychoactive chemical THC (tetrahydrocannabinol) in the rats' blood to roughly the human equivalent of smoking a joint. After the pups grew up the researchers trained them on a task that measured their ability to think flexibly and learn new rules. The young rats first learned to follow a light cue to push one of two levers in order to receive a sugary treat. The next day, pushing only the left lever would deliver the reward, regardless of which side the light had been on.

The rats exposed to cannabis in utero learned the first rule (following the light cue) without a problem, but they took significantly longer to learn the new rule (pushing the left lever) than did rats not exposed to the drug. The cannabis-exposed rats also made many more mistakes on the second day. They would respond correctly for a couple rounds, making it seem like they knew the new rule, but then they would press the wrong lever again. "It was like something wasn't really clicking with them," says Ryan McLaughlin, an assistant professor of integrative physiology and neuroscience at Washington State and lead author of

the study, which has not yet been published. He says they never got that "Aha!" moment, where it's like, "Oh, this is what I'm supposed to do."

In a similar study, scientists at Auburn University in Alabama found rats born to mothers that had been injected with a low, continuous dose of synthetic cannabis during pregnancy were significantly impaired on several different memory tasks involving mazes. "The rats that were exposed to cannabinoids [chemicals like those found in marijuana] prenatally were performing less efficiently than the control rats" that were not exposed, says Priyanka Pinky, a graduate student at Auburn who conducted the research. "There was a gap in the acquisition of the memory and the consolidation of the memory."

The young rats whose mothers were dosed with the drug also had abnormalities in the hippocampus, the brain's primary memory center. Specifically, they had difficulty creating new connections between neurons—the basis for forming new memories. The researchers think the differences in the hippocampus stem from changes in levels of glutamate, the brain's main excitato-

**“Given that more pregnant women today are starting to smoke marijuana, it’s really important for us to get that word out.”**

**—Yasmin Hurd**

ry neurochemical involved in learning and memory.

In the third study researchers at the University of Maryland School of Medicine and the University of Ferrara again found impairments in memory and changes in levels of glutamate in the brains of rats exposed to THC in the womb. They also discovered an increase in another molecule in the brain, which they think may be the missing link between prenatal cannabis exposure, glutamate and cognitive impairments: kynurenic acid. This chemical acts like a puppet master in the brain, regulating glutamate and other important neurochemicals; high levels of the molecule result in lower glutamate levels. Kynurenic acid has also previously been

implicated in cognitive impairments in both people and animals.

"We think that prenatal marijuana exposure can induce an increase in kynurenic acid, and this may be responsible for the cognitive impairment observed in the offspring of marijuana users," says Sarah Beggiato, a postdoctoral researcher at the University of Ferrara in Italy and co-author of the study. "Why is glutamate going down? It's because kynurenic acid is going up." The scientists are now researching drugs that block the acid's synthesis, which may help defend against the problems associated with prenatal cannabis exposure.

The findings, which are in rodents, may not necessarily translate to humans. Mount Sinai's Hurd, who has been researching the effects of marijuana on the developing brain in both humans and animals for 15 years, says the new studies do not reveal anything "shockingly new." But they show "that there are indeed multiple systems being affected," she says, "and given that more pregnant women today are starting to smoke marijuana, it's really important for us to get that word out."

**—Dana G. Smith**

## How Might the Appendix Play a Key Role in Parkinson's Disease?

Those who've had it removed get the neurodegenerative disorder later or not at all, study finds

MOST PEOPLE FORGET they even have an appendix unless it bursts or becomes inflamed, but a new study suggests the organ may play a key role in the development of Parkinson's disease. Those who have their appendixes removed in young adulthood run a nearly 20 percent lower risk of developing Parkinson's decades later, according to a study published last October in *Science Translational Medicine*.

The new finding helps solidify the developing view Parkinson's is not just a motor disorder characterized by tremors, stiffness and imbalanced walking—but a whole-body condition that often involves the digestive system, says lead author Viviane Labrie, an assistant professor at the Van Andel Research Institute's Center for Neurodegenerative Science. The



appendix is attached to the large intestine and houses gut bacteria, she notes. The fingerlike pouch of tissue, which used to be considered a useless vestige of our evolutionary past, is now believed to play an important role in immune function—particularly early in life. It is not yet known what initiates Parkinson's, although a growing body of research suggests inflammation plays a key role, Labrie and others say.

The multipart study looked at a database of 1.6 million people in Sweden and found a lower risk of Parkinson's among those whose appendixes had been removed,

co-author Lena Brundin said in a news conference. She added that the difference was particularly pronounced among people living in rural parts of the country—potential reasons for this remain unclear, although pesticide exposure has been shown to be linked to Parkinson's, says Brundin, an associate professor at Van Andel, an independent research and science education organization in Grand Rapids, Mich.

The researchers also looked at a much-smaller database of about 850 people whose Parkinson's has been carefully followed, and found those who had undergone appendectomies

developed the disease 3.6 years later on average than those who still had an appendix. They also found the protein alpha-synuclein, which is misshapen in Parkinson's patients, in the appendixes of 48 out of 50 healthy people—suggesting the protein may play a useful (but still unknown) function there. Patrik Brundin, who is associate director of research at Van Andel and director of its Neurodegenerative Science center, says he was surprised to find so much alpha-synuclein in healthy people, and also that the protein was equally abundant in both old and young study subjects. “Those are all, for boring scientists like us, sufficiently surprising to make us excited,” he says.

According to Labrie, deformed clumps of alpha-synuclein might travel up the vagus nerve, which connects the digestive system to the brain, and then seed the brain with this destructive protein. Clumps of it are thought to block the production of the chemical dopamine, causing the tremors and stiffness that define Parkinson's.

Ole Isacson, a professor of neurology at Harvard Medical School who was not involved in the research, has a different view. He believes removing

the appendix may help prevent or delay Parkinson's by blocking inflammation, which he sees as the true bad actor. Inflammatory bowel disease and inflammation of the gut have been linked to Parkinson's, and one recent study found treating inflammatory bowel disease patients with an anti-inflammatory called anti-tumor necrosis factor reduced their likelihood of developing Parkinson's by nearly 80 percent. There are many causes of Parkinson's, says Isacson, who also directs the Neuroregeneration Laboratories and Neuroregeneration Research Institute at McLean Hospital. But he notes "maybe half or more of the patients with Parkinson's disease have had some kind of inflammatory condition that has accelerated that pathology."

Malú Tansey, a professor of physiology at Emory University who did not take part of the study, agrees research into the connection between inflammation and Parkinson's might eventually lead the way to treatments and better diagnosis. She says it is possible that avoiding inflammation in the gut—through good diet and exercise, medications or probiotics—might be protective against Parkinson's.

Many people who develop Parkinson's suffer earlier in their lives from constipation, loss of smell, low blood pressure and sleep disorders such as acting out their dreams, says Rachel Dolhun, a movement disorder specialist and vice president of medical communications for the Michael J. Fox Foundation, which supports Parkinson's research. People should not be concerned if they have occasional constipation in midlife, she notes, but a constellation of these symptoms may mean someone is at higher risk for developing the disorder. She hopes people will eventually be able to get risk scores early enough to let them to make lifestyle or medication changes in attempt to prevent the disease, she says.

Both Dolhun and Labrie say people should not get their appendixes removed because of the new findings. A study like this can only identify an association—not a clear cause-and-effect relationship between appendix removal and reduced risk of Parkinson's. "You wouldn't want anybody to run out and get their appendix taken out just because that might lower their risk of Parkinson's," Dolhun says.

—Karen Weintraub



## A New Connection between the Gut and Brain

**A surprising way that diet leads risks of stroke and cognitive impairment**

IT IS WELL KNOWN that a high salt diet leads to high blood pressure, a risk factor for an array of health problems, including heart disease and stroke. But over the last decade, studies across human populations

have reported the association between salt intake and stroke irrespective of high blood pressure and risk of heart disease, suggesting a missing link between salt intake and brain health.

Interestingly, there is a growing body of work showing that there is communication between the gut and brain, now commonly dubbed the gut-brain axis. The disruption of the gut-brain axis contributes to a diverse range of diseases, including Parkinson's disease and irritable bowel syndrome. Consequently, the



developing field of gut-brain axis research is rapidly growing and evolving. Five years ago, a couple of studies showed that high salt intake leads to profound immune changes in the gut, resulting in increased vulnerability of the brain to autoimmunity—when the immune system attacks its own healthy cells and tissues by mistake, suggesting that perhaps the gut can communicate with the brain via immune signaling.

Now, new research shows another connection: immune signals sent from the gut can compromise the brain’s blood vessels, leading to deteriorated brain health and cognitive impairment. Surprisingly, the research unveils a previously undescribed gut-brain connection mediated by the immune system and indicates that excessive salt might negatively impact brain health in humans through impairing the brain’s blood vessels regardless of its effect on blood pressure.

This research proposes new therapeutic targets for countering stroke—the second leading cause of death worldwide—and cognitive dysfunction. Reducing salt intake is applicable to people around the globe, as nearly every adult consumes too much salt: on average

9 to 12 grams per day or around twice the recommended maximum level of intake (5 grams) by the World Health Organization.

The researchers used mice, and found that immune responses in the small intestines set off a cascade of chemical responses reaching the brain’s blood vessels, reducing blood flow to the cortex and hippocampus, two brain regions crucial for learning and memory. This, in turn, brought a decline in tests of cognitive performance. The impairment in learning and memory was clear even in the absence of high blood pressure; they observed that the gut is reacting to the salt overload and directing immune signals that lay the basis for deterioration throughout the brain’s vital vascular complex and compromise cognitive function. While this study has only been carried out on research animals so far, the scientists believe it’s likely that much of the same applies to people.

Lowering salt intake has been shown to have beneficial effects to overall health, so the researchers wanted to know whether these effects extend to this newly identified signaling cascade that begins in the

gut and targets the brain’s blood vessels to, ultimately, affect cognitive function. When the mice were returned to a normal diet after being on a high salt diet, the detrimental health effects caused by excess salt intake were erased. A pharmacological intervention that disrupted the immune signals also reversed the effects.

The implications of this newly identified gut-brain connection extend to several autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease, that have been shown to activate the same immune signaling pathway implicated in this study. These autoimmune disorders have a high stroke risk and are linked to poorly functioning blood vessels in the nervous system. This research is also a demonstration that what we eat affects how we think, and that seemingly isolated parts of the body can play vital roles in brain health. These results motivate research on how everyday stressors to our digestive systems and blood vessels might change the brain and, consequently, how we see, and experience, the world.

—Jonathan D. Grinstein

## What Do Americans Think about Food Additives and GMOs?

About half think they’re unhealthy; the other half aren’t especially concerned

EVERYBODY EATS—WHICH IS, of course, why food science stands out among scientific fields for its direct relevance to everyday citizens. Food serves as a source of nourishment, a means to achieving better health and a centerpiece of social gatherings.

Food is also undergoing constant change, as new technologies raise ongoing questions for consumers looking to make “safe” choices for their long-term health. A new Pew Research Center report shows an American public that is closely divided over two broad types of food technologies: additives, and genetically modified (GM) crops or other GM ingredients. What’s more, a closer look at these public divides tells a larger story about how Americans assess science.

About half of the public (51



percent) believes the average person faces a serious health risk over the long term from eating foods with additives, while 48 percent say potentially threatening additives exist in such small amounts that there is no serious health risk.

More specifically, the center asked people to evaluate the potential risk of four types of additives associated with the production and processing of food: meat from animals given hormones or antibiotics, produce grown with pesticides and artificial preservatives or artificial coloring. The public was evenly divided with half (50 percent) saying at least one of the four poses a great deal of health risk to the average person and half saying none of these pose a great deal of health risk.

Similarly, there is a close division among the public about the health effects of GM, also known as genetically engineered, foods; about half (49 percent) consider such foods to be worse for one's health than foods with no GM ingredients, while 44 percent say GM foods are neither better nor worse than non-GM foods, and 5 percent say they are better for one's health.

These beliefs do not exist in

isolation from one another. Rather, they tend to be closely connected. That is, those who see more health risk from food additives also tend to see GM foods as worse for one's health than non-GM foods. Further, this is an area where people's beliefs tend to align with their eating habits. For example, people who estimate that a larger share of their diet is organic—foods which, by design, are intended to eliminate artificial preservatives, flavors and colors as well as pesticides and genetically modified ingredients—are more inclined to see serious health risks for the average person from additives in foods and to consider GM foods worse for one's health than foods with no GM ingredients.

It might be easy to discount the public's differences over food. After all, the divides do not fall along the familiar fault lines of public opinion seen on many other civic issues. We are living in an age of polarization, but there are no more than modest differences about food issues by political party. Nor are there consistent divides by age or generation. Women are consistently warier than men about both food additives and GM foods. But the correlation is not

## U.S. Public Is Closely Divided over Health Risk from Food Additives and Genetically Modified Foods

Percent of U.S. adults



Note: Respondents who did not give an answer are not shown. Beliefs about the health effects of genetically modified (GM) foods include those who lean toward each response. Respondents who said GM foods are better for one's health are not shown. Source: Survey conducted April 23 to May 6, 2018. "Public Perspectives on Food Risks"

so large that you could easily pinpoint a person's point of view by knowing simply whether they are male or female.

Nonetheless, these latest surveys indicate that people have their own

set of beliefs about these issues—and these beliefs are consequential when it comes to their assessments of science. For example, among those who say that *all four types* of food additives considered in the survey

pose a great deal of health risk, 56 percent believe the effect of science on the quality of food has been mostly negative, while 44 percent say the effect has been mostly positive. By contrast, 81 percent of those who say *none of the four types* of food additives pose a great deal of health risk believe that science has had a positive effect on food quality in the U.S.

Similarly, the 17 percent of Americans who believe that GM foods are worse for one's health and say they care a great deal about the GM foods issue are far more negative in their assessment. Among this group, 44 percent say the effect of science on the quality of food in the U.S. has been mostly positive, while 56 percent say it has been negative. For comparison, those who say that GM foods are neither better nor worse than other foods are largely positive about the effect of science; 85 percent of this group says science has had a mostly positive effect on the quality of food in the U.S.

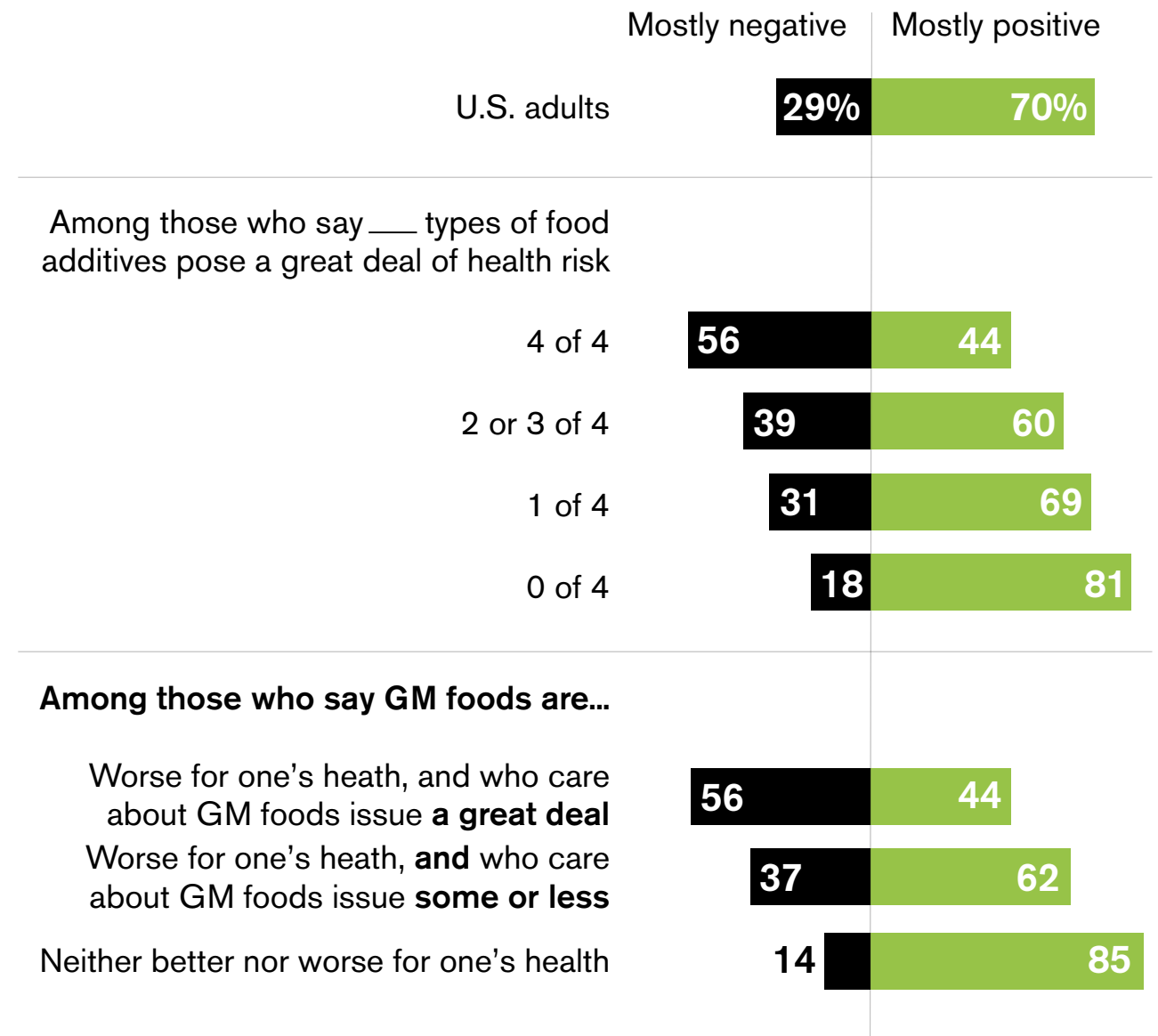
Food scientists, industry groups and health care professionals are themselves often at odds over which foods are safe and how foods

connect with health. Indeed, the back-and-forth, conflicting media reports about the health effects of what we eat and drink are often cited as sources of public confusion over food issues. But a key insight from the center's public opinion research is that, against the backdrop of ongoing developments, Americans have their own set of interconnecting beliefs about food issues, often converging with their own personal eating habits. These findings suggest that those interested in reaching wide audiences would do well to engage with those holding deep concerns about these issues to better understand their perspective and how it ties into their assessment of the scientific enterprise.

—Cary Funk

## Beliefs about Additives, GM Foods Tie with More Negative Views of How Science Influences Food in U.S.

Percent of U.S. adults who say science has had a \_\_\_ effect on the quality of food in the U.S.



Note: Respondents who did not give an answer are not shown. Beliefs about the health effects of genetically modified (GM) foods include those who lean toward each response. Respondents who said GM foods are better for one's health are not shown. Source: Survey conducted April 23 to May 6, 2018. "Public Perspectives on Food Risks"



## Too Good to Be True? A Nonaddictive Opioid without Lethal Side Effects Shows Promise

A still-experimental drug demonstrates the qualities of an ideal painkiller in a test in monkeys

WITH NEARLY 50,000 DRUG overdose deaths from opioids in 2017 and an estimated two million Americans addicted, the opioid crisis continues to rage throughout the U.S. This statistic must be contrasted with another: 25 million Americans live with daily chronic pain, for which few treatment options are available apart from opioid medications.

Opioid drugs like morphine and Oxycontin are still held as the gold standard when it comes to relieving pain. But it has become brutally obvious that opioids have dangerous side effects, including physical dependence, addiction and the impaired breathing that too often leads to death from an overdose. Researchers have long been search-

ing for a drug that would relieve pain without such a heavy toll, with few results so far.

Now a study in monkeys published in *Science Translational Medicine* shows a new type of opioid drug met all the criteria on drug developers' wish list. The findings even suggest that instead of causing addiction, the new compound might be used to curb addiction and pain all at once. The study was led by Mei-Chuan

(Holden) Ko, a researcher at Wake Forest University, and medical chemist Nurulain Zaveri, founder of California-based Astraera Therapeutics. "They've got something here that's really important," says William Schmidt, a pharmaceutical consultant based in Davis, Calif., who was not involved in the work. "I think the chances of a compound with these properties moving forward are high, and simultaneously pretty exciting."

Opioid drugs relieve pain by acting at four types of opioid receptors found throughout the nervous system. The mu opioid receptor is primarily responsible for opioids' pain-relieving effects—and for their side effects as well. Delta and kappa opioid receptors can also modulate pain signals, but they come with their own side effects. A fourth receptor, called the nociceptin/orphanin FQ peptide (NOP) receptor, was discovered relatively recently, in the 1990s, and researchers are still figuring out how it works.

Studies of NOP have shown that it too has analgesic effects in rodents—but seemingly without the side effects that come with mu receptor activation. And an additional benefit comes when the two receptors interact with each other. The inspiration for the new compound, called AT-121, came when Ko discovered that by activating NOP, he could enhance the pain-relieving effects at the mu receptor. "We hypothesized that if we could find a single molecule that activated both receptors, NOP could enhance mu's analgesic effects and mediate the abuse potential," he says.

The researchers investigated the



effects of AT-121 in rhesus monkeys with tests commonly used to compare new painkiller drug candidates with opioids such as morphine. Monkeys were trained to sit with their tails in a bath of hot water, which they normally tolerate for only a couple of seconds. After an injection of AT-121 they kept their tails in hot water for up to 20 seconds, indicating a potent analgesic effect. After monkeys' tails were treated with capsaicin, the ingredient that makes hot chilis hot, they developed pain hypersensitivity, making them even less tolerant of the hot water. But after receiving AT-121 they could keep their tails in the water much longer than expected.

Even at higher doses, AT-121 did not cause the side effects that make most opioids so dangerous—suppression of breathing and heart rate, itch and physical dependence (in which stopping use leads to withdrawal symptoms). Even after several doses AT-121 retained its analgesic effect, whereas most opioids require an increasing dosage over time to achieve pain relief.

To test the compound's addictive potential, the researchers allowed monkeys to self-administer a variety of drugs. With remifentanyl, powerful

**“To have the combination of analgesia and the lack of mu receptor-related side effects, plus the ability to block the euphoric effects of Oxycontin—that’s unique.”**

*—William Schmidt*

opioids or cocaine, monkeys pressed a lever repeatedly to receive increasing doses of the drugs, a hallmark of rewarding substances. In contrast, monkeys only pressed a lever to receive AT-121 at a similar rate as injections of a saline solution, indicating that the drug was not rewarding.

More surprising was the finding pretreatment with AT-121 reduced the monkeys' lever-pressing to receive Oxycontin, a widely used and highly addictive opioid. That suggests AT-121 could reduce the addictive properties of other opioids. “To have the combination of analgesia and the lack of mu receptor-related side

effects, plus the ability to block the euphoric effects of Oxycontin—that’s unique,” Schmidt says.

“It gave very effective pain relief, the rewarding effects were not there and it suppressed the addictive potential of Oxycontin,” Zaveri says. “That suggests it could be a replacement for prescription pain opioids, and it could actually be given to someone who is addicted.”

The concept of trying to finesse pain relief by activating multiple opioid receptors is not new. A drug called cebranopadol, for example, also activates both the NOP and mu opioid receptors, and is in clinical trials for several pain conditions, but the drug might still be addictive.

There is little evidence traditional opioids provide benefits for people with chronic pain, and this drug might not either. The timing of the drug's actions, Schmidt says, “is ideal for acute, postoperative pain. It might have the ideal properties for use in the hospital, but for broader use as a nonaddictive chronic pain drug, you would want an oral drug that works longer.”

*—Stephani Sutherland*

## The Biology of Sugars Points to a Sweet Strategy for Treating Cancer

**Long-ignored field attracts interest from companies trying to develop next-generation immune therapies**

OVER THE LAST FEW decades, researchers tinkering with molecules that turn an immune cell on and off have created a revolutionary approach to fighting cancer. Instead of taking aim at the tumor directly, this new class of medicines harnesses the patient's own immune cells to tackle the disease. Immune-based cancer therapies are saving thousands of lives, and the science behind them earned the 2018 Nobel Prize in Physiology or Medicine.

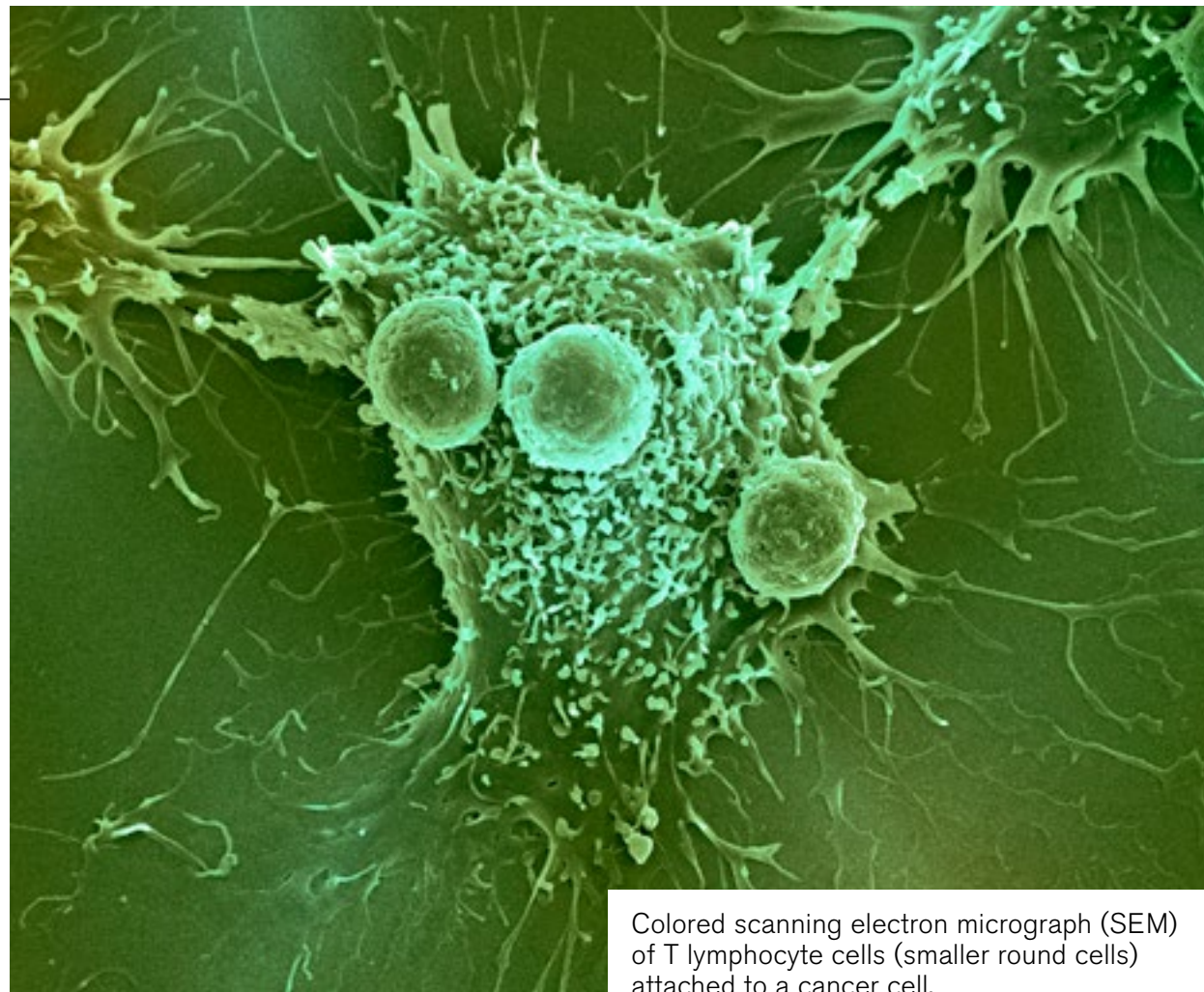
These drugs, called checkpoint blockers, appeared after scientists discovered molecules that help cancer cells block immune processes that would otherwise attack a tumor. The secret lies with several “brake” proteins on white blood cells, T cells, that prevent the immune system from overreacting to microbial



threats. Tumor cells have learned to survive by engaging the brake molecules, sending T cells into a stupor that allows cancer to gain a foothold. By thwarting this hijacking maneuver, checkpoint blockers release the brakes and awaken T cells to attack the tumor. A clever trick—except that so far, these immune-based drugs only work in about a fifth of cancer patients and for certain tumors, barely at all.

To push past those limits, a few companies are venturing into a new frontier—glycobiology, the science of the sugars that stud the surface of cells. Sugars act like switches and knobs that control where and when a cell’s biological machines, proteins and lipids, do their jobs. Yet for all their fine-tuning finesse and power, sugars are highly complex molecules that have often eluded a deeper understanding of their workings because they are so hard to study in the lab.

Recently, though, the science has caught up and biotech companies have begun to build on these findings to develop anti-cancer drugs. Last November at an American Association for Cancer Research meeting in Miami, Palleon Pharmaceuticals, a



Colored scanning electron micrograph (SEM) of T lymphocyte cells (smaller round cells) attached to a cancer cell.

Massachusetts startup, unveiled new data from experiments in rodents on a profoundly different set of checkpoint blockers that target sugars.

These experimental drugs work by interfering with complex sugars called glycans that coat the surface of tumor cells and let them pass unnoticed by the otherwise vigilant immune system. It’s an “underappreciated mechanism of immune evasion,” says Michael O’Dwyer, a clinician-researcher at National University of Ireland, Galway, who has no ties to Palleon. Many researchers are going

after the T cells’ braking systems, he says, but “probably with diminishing returns.” He adds: “There’s only so much you can get out of the T cells.”

Jim Broderick, chief executive and founder of Palleon, compares the immune system to a football team. Defending against threats—whether bacteria, viruses or cancer—requires a coordinated effort from many cell types with different roles. Following the game analogy, the current wave of cancer immunotherapies focuses on the quarterback. “But Tom Brady can’t win the Super Bowl if he has

third graders on his offensive line,” Broderick says.

Palleon launched in 2015 on the strength of research by a handful of labs suggesting that structured patterns of cell-surface glycans—a molecular fingerprint on virtually all cells—might hold the key to rousing a host of additional cancer-fighting immune cells. These macrophages, natural killer cells and other cells make up a different arm of the immune system. Known as innate immune cells, these cells form the body’s first line of defense, which sets the stage for a subsequent T-cell attack.

One particular glycan, sialic acid, is sensed by a family of surface proteins found mostly on innate immune cells but also on activated T cells at tumor sites. These proteins, called Siglecs, act as molecular brakes. When Siglecs bind to sialic acids, coating the surface of a tumor, the immune cell goes to sleep. Several companies—including Innate Pharma in Marseille, France, and South San Francisco-based Alector—are hoping to wake those drowsy cells with therapies that block Siglecs.

A team of researchers led by Palleon co-founder Carolyn Bertozzi,



a Stanford chemist, went after these same molecular pathways with a radically different approach. Rather than trying to block individual Siglec molecules on the surface of immune cells, the researchers designed a therapeutic that stymies all Sigslecs by trimming sialic acids off the tumor cell. In a 2016 proof-of-concept study, the team showed that treating a dish of breast cancer cells with the experimental drug exposed them to killing by natural killer cells.

At another immunotherapy meeting in Washington, D.C., in November, Palleon vice president Li Peng presented data showing this strategy can work in mice with implanted tumors—even in ones that draw weak responses with FDA-approved check-point-blocking drugs. In separate experiments, the team confirmed that T cells, macrophages and natural killer cells all contribute to the drug’s benefit. Cancer cells “are like wolves in sheep’s clothing—bad guys disguising themselves with the glycan code,” Peng says. By removing sialic acids from glycans on the surface

of tumor cells, the drug “reveals their real identity so immune cells can see the bad guys.”

Dong Zhang, director of immunology at the German company EMD Serono, considered Peng’s talk “one of the most exciting findings” at that meeting.

To make the original version of the therapeutic, Bertozzi and colleagues chemically fused the sialic acid-trimming enzyme to an antibody that recognizes a hallmark protein (HER2) on the surface of breast cancer cells. The antibody is needed to restrict the enzyme’s activity to the tumor. Otherwise the enzyme would cut indiscriminately and wreak havoc, since sialic acids also play vital roles on healthy cells.

With an eye toward human trials by 2020, Peng’s team at Palleon has created a means to produce the antibody-enzyme combo without a tricky chemical synthesis. All they have to do is take an existing tumor-targeting antibody and hook it onto the enzyme, says Jason Luke, a medical oncologist at the University of Chicago School of Medicine, who leads a Palleon-funded research project

to see if glycan-modifying enzymes correlate with clinical outcomes. “This is about as straightforward a drug development program as you could want. It’s translatable to other surface proteins, and they could easily make additional therapies.”

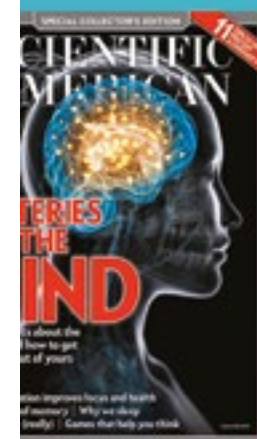
Whereas the vast majority of immune therapies target a single molecular interaction, Bertozzi’s is a broader approach that is “much more robust because sialic acids are recognized by multiple receptors on different immune cells,” says Yvette van Kooyk, an immunologist at VU University Medical Center in the Netherlands, who wrote a recent review about cancer’s “glyco-code” and learned about Palleon’s drug program at an earlier cancer conference in September 2018. The cancer field has really neglected the importance of glycans,” van Kooyk says. “But they have a very immune-suppressing function. To overcome that, it’s necessary for new treatments to also do something with these glyco-codes.”

—Esther Landhuis

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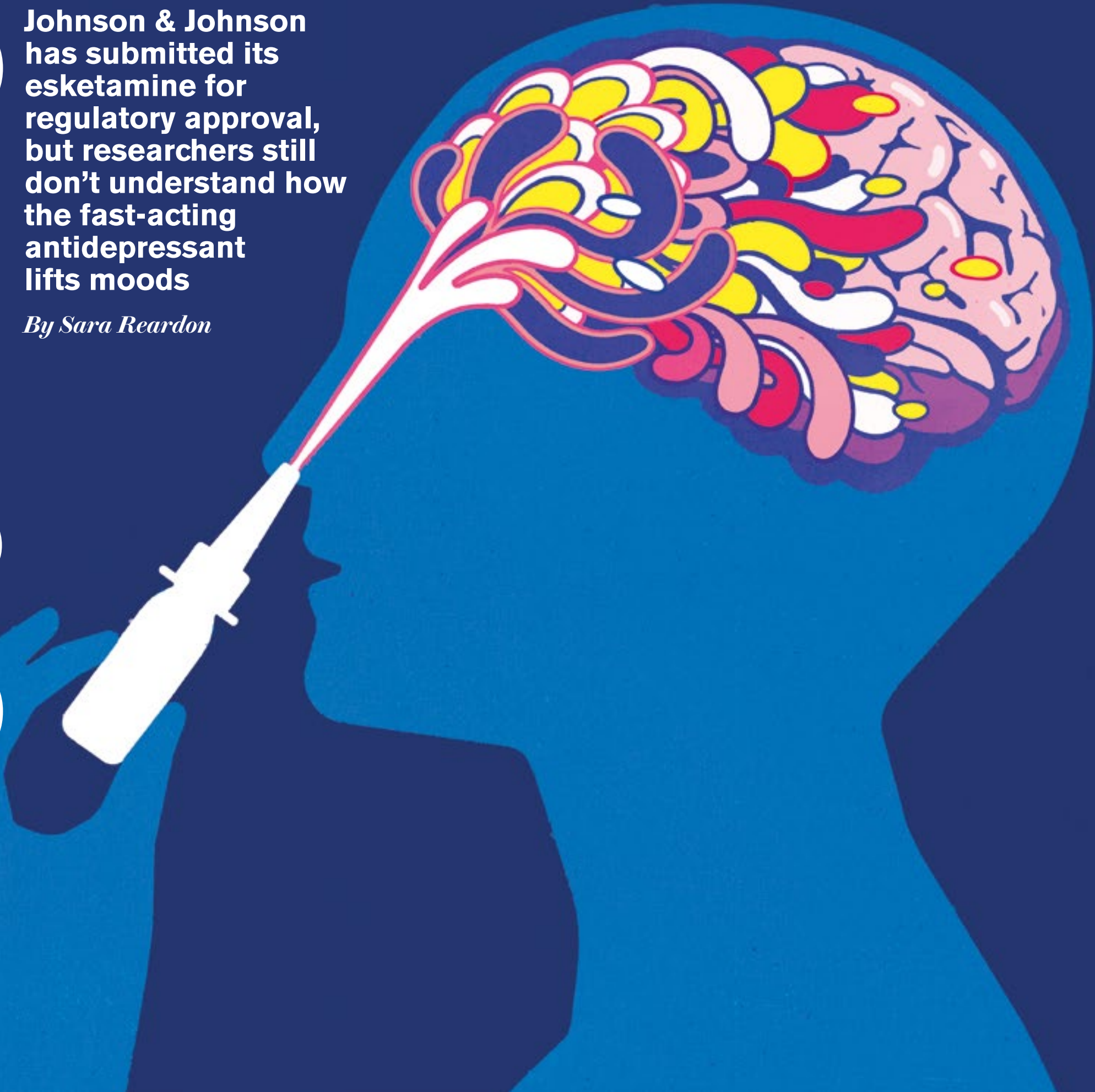




# Generatation Ketamine

Johnson & Johnson has submitted its esketamine for regulatory approval, but researchers still don't understand how the fast-acting antidepressant lifts moods

*By Sara Reardon*



# W

HEN RESEARCHERS SHOWED IN 2006 THAT THE ANESTHETIC KETAMINE—also known as the club drug Special K—was a rapid and potent antidepressant, big pharmaceutical companies quickly jumped into the game. Extensive efforts to improve on decades-old antidepressants had floundered, but ketamine finally promised a novel mechanism of action and the potential to help treatment-resistant patients.

Because ketamine is an old drug and difficult to commercialize for a new indication, early entrants into this space set out to build ketamine mimetics that could replicate the anesthetic's effect, ideally without its hallucinatory side effects. A few of these ketamine-inspired drugs are now nearing the finish line. In September, Johnson & Johnson (J&J) filed for FDA approval of a nasal spray containing esketamine—an isomer of ketamine that the company has patented. Despite some lingering questions about its efficacy compared with ketamine, experts in the field expect the drug will be approved, providing the first antidepressant breakthrough in decades.

“What’s exciting is not that there’s going to be a new drug approved, but that we’re going to have a whole new class of drug approved,” says psychiatrist James Murchio at Mount Sinai Hospital. “Everyone’s waiting with bated breath.”

This is fostering high hopes that psychiatric drug development—which has seen an exodus of major pharma companies owing to continuing failures—could be poised for a renaissance. The number of ketamine trials has skyrocketed, not only for depression but also for obsessive-compulsive disorder, post-traumatic stress disorder and even chronic pain. “If ketamine works and we understand the effects of ketamine on these different disorders, it could really open the way for drug discovery,” says Lisa Monteggia, a neuroscientist at Vanderbilt University.

Yet it is far from clear how this work will play out. Whereas early evidence suggested that ketamine acted through the NMDA receptor, many of the first-generation ketamine mimetics that were designed to act on this target failed in clinical trials. Accumulating evidence now suggests that ketamine’s antidepressant activity may be more complicated.

As a result, some companies are quietly going back to the drawing board. “My sense is that NMDA-receptor-blocking studies are diminishing quite quickly and people are looking at other mechanisms,” says psychiatrist Carlos Zarate at the National Institute of Mental Health (NIMH). While NMDA blockers haven’t been abandoned, he says, “companies are just giving a second thought to whether they want to continue pursuing these pro-

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**Sara Reardon** is a senior reporter at *Nature* in Washington, D.C., covering biomedical research and policy. She has previously written for *New Scientist* and *Science* and has a master’s degree in molecular biology from the University of Washington.

grams.” Until a clearer picture of the mechanism is worked out, the field may be doomed to a trial-and-error hunt for better-than-ketamine mimetics.

### NOVEL ANTIDEPRESSANT ACTIVITY

The most commonly used antidepressants target signaling by the monoamine neurotransmitters serotonin, dopamine and noradrenaline. But starting in the 1950s, researchers using the antibiotic D-cycloserine to treat tuberculosis found that the drug alleviated patient melancholy. Researchers later learned that the antibiotic, at low doses, blocks the NMDA receptor, a glutamate receptor. Then in the late 1990s, when psychiatrist John Krystal of Yale University was curious about whether the neurotransmitter glutamate contributed to schizophrenia, he decided to test the known NMDA receptor antagonist ketamine in nine depressed patients.

At the time, glutamate had mostly been studied for its role in learning and memory. But Krystal’s group found that ketamine induced a rapid improvement in mood in patients.

Zarate and Hussein Manji, who is now head neuroscience researcher at J&J, set out to replicate the surprising findings at the NIMH in a larger trial, enrolling 18 subjects with major depression. The results from this small study suggested that ketamine was a miracle drug—lifting a person’s mood almost immediately. Reporting in the *Archives of General Psychiatry*, they showed that 70 percent of depressed patients respond-



ed to ketamine within 24 hours. By contrast, in one of the largest studies of people with depression, only one-third of patients responded to selective serotonin reuptake inhibitors (SSRIs) after eight weeks.

Ketamine also appears to reduce suicidal thoughts—something that no other drug is known to do—and its effects last for weeks to months.

“Ketamine works so well it would be hard to do better,” says neuroscientist Todd Gould of the University of Maryland. Some clinics have taken this conclusion to heart, and are already offering ketamine to depressed patients on an off-label basis. Drug developers have meanwhile been working hard to make next-generation alternatives, armed with a preliminary hypothesis for how the drug lifts moods.

When ketamine is used as an anesthetic or a hallucinogen, it blocks the NMDA receptor. This in turn stimulates the release of a glutamate burst, which is believed to be responsible for the drug’s hallucinatory effects. The neurotransmitter then stimulates other receptors that control gene transcription to enable rapid rewiring of brain circuits. This rewiring, or plasticity, is thought to cause the antidepressant effect.

When developing a pharmaceutical version of ketamine, companies have generally decided to target the start of this pathway. J&J, for instance, chose to develop the *S*-enantiomer of ketamine because it is four times as potent at blocking the NMDA receptor as regular ketamine, which is a mix of *R*- and *S*-enantiomers. J&J’s Manji says that the company has no plans to compare its product directly with ketamine in a clinical trial. But overall, esketamine’s side effects—including hallucinations—seem similar to the original drug.

The company recently published results from two phase III studies on depression, and will conclude a suicidal ideation trial next year. Clinical trial results were mixed, however. In one study of 223 participants, esket-

**“I think once esketamine is approved, and it becomes likely a multibillion-dollar drug, you’ll see big pharma coming back.”**

**—Ronald Duman**

amine significantly reduced depression at 28 days. But the results were not as strong as the company had anticipated, and esketamine took longer to take effect than ketamine and missed its secondary end point of lifting mood within 24 hours. In the second study in 138 people over 65 years old, the drug missed its primary end point.

Nevertheless, these results have buoyed hopes for glutamate-based antidepressants. Whereas Pfizer, AstraZeneca, Roche and others terminated development of NMDA receptor modulators for mood disorder in recent years owing to failed trials or severe side effects, researchers hope that success for J&J will lift all boats.

“I think once esketamine is approved, and it becomes likely a multibillion-dollar drug, you’ll see big pharma coming back,” says drug researcher Ronald Duman at Yale University.

#### UPPING THE AMPA?

Basic research on ketamine’s mechanism of action complicates future ketamine-mimetic discovery plans, however. In 2016, Gould and Zarate published a startling paper in *Nature*, proposing that a metabolic byproduct of ketamine—not the drug itself—was responsible for the mood-altering activity in mice. The metabolite (2R,6R)-hydroxynorketamine, or HNK, didn’t seem to interact with the NMDA receptor at all. Nor did it appear to cause the hallucinatory side effects of esketamine,

even at doses nearly 40 times greater than the normal dose of ketamine.

The result suggested that drug developers may have been going after the wrong target all along. “It definitely created a stir,” says Murrough. “It contributed to a realization that we don’t really know how ketamine is working, and whatever the mechanism is, it’s not simple.”

Others aren’t ready to give up on NMDA inhibition just yet. Monteggia reported in 2018 in *Neuropsychopharmacology* that when she repeated a similar experiment, she found that very high levels of HNK could indirectly block the NMDA receptor through an as-yet-unknown mechanism.

J&J’s Manji is also skeptical about reading too much into the effect of HNK in mice. If the NMDA receptor is uninvolved, the company’s esketamine nasal spray should not work as well as it has, Manji says. He suspects that previous NMDA antagonist failures can largely be chalked up to dosing problems and side effect profiles, rather than a problem with the target itself.

Researchers are trying to reconcile these various results. For instance, ketamine might quickly reverse depression by blocking the NMDA receptor, but perhaps HNK is responsible for maintaining the effect over time, says Monteggia. Zarate and Gould are planning to file for FDA permission to start clinical trials with HNK in 2019, which they say should be able to answer some of these questions.

Other studies add further complications. In August, a 12-patient study led by Alan Schatzberg of Stanford University suggested that ketamine might be acting through the opioid system and not the glutamatergic system at all. The researchers gave depressed patients naltrexone to block the opioid receptor before administering ketamine, and found that this eliminated ketamine’s antidepressant effects but not its hallucinatory side effects.

Promising data from Allergan's lead antidepressant rapastinel, an intravenous drug in phase III trials for depression and suicidality, add another wrinkle. Whereas ketamine and esketamine block the NMDA receptor, rapastinel is a partial agonist of the NMDA receptor. Phase II data suggest that the drug relieves depression quickly and that its effects last for several weeks. Phase III trials are currently underway, with first pivotal results expected 2019.

And Allergan is doubling down on the mechanism. In May 2018, the company bought rights to an experimental oral drug AGN-241751, which targets the NMDA receptor and is currently in phase II trials for depression.

"It's really hard to reconcile all those different studies into a unified model," says Gerard Sanacora, a psychiatrist at Yale University.

But he, Gould and others believe that studies are beginning to home in on one convergent mechanism: a glutamate receptor known as AMPA, which is activated when glutamate levels increase and that stimulates brain rewiring. Ketamine, HNK and rapastinel all acti-

vate AMPA receptors, and animal studies have shown that directly blocking AMPA receptors eliminates the antidepressant effects of these drugs. Yet targeting AMPA receptors directly tends to raise the risk of seizures, Sanacora cautions, making it unlikely that AMPA receptor agonists could be turned into therapeutics.

Allergan's chief R&D officer David Nicholson, meanwhile, remains unfazed by the lingering uncertainty about the mechanism of action of ketamine-inspired drugs—as long as the drugs work. "We didn't know really how tricyclic [antidepressants] were working, or how SSRIs were working," he says. "You can debate if we really know that today, to be frank."

*This article is reproduced with permission and was first published in Nature on October 30, 2018.*

## Ketamine Clinics

Although the FDA has not approved ketamine for depression and most insurance companies do not cover it, an estimated 300 clinics are already providing off-label ketamine to depression patients.

Some researchers consequently question the need for next-generation drugs such as esketamine. "It's not going to do anything ketamine doesn't do, but it will cost 10 to 100 times as much as ketamine," says Scott Thompson, a neurobiologist at the University of Maryland. "If esketamine is safe enough to release into the general population, then ketamine is safe enough. It's a backwards way to get a drug approved."

But ketamine is not a perfect drug, either. In 2017, researchers published a consensus paper for the American Psychiatric Association that included guidelines for physicians prescribing ketamine for depression. Among other recommendations, the paper said that ketamine should only be used in the clinic and not sent home with patients because of the potential for abuse. It also warned about the lack of long-term data and the acute risks for people with heart conditions.

Esketamine faces similar limitations, and if approved will also be administered in the clinic.

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A crowded market day in Uganda. Rates of hepatitis B are surging in several sub-Saharan African nations.

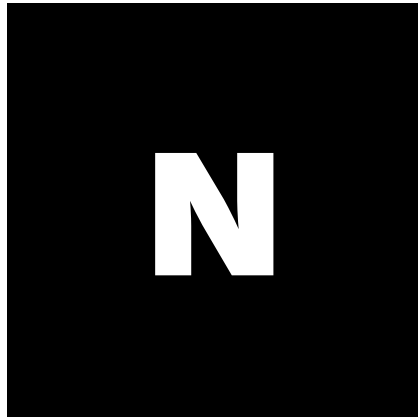


# The Silent Epidemic Killing More People Than HIV, Malaria or TB

Viral hepatitis is on the rise. Tackling hepatitis B in Africa is key to fighting back

*By Ian Graber-Stiehl*





URU WAS PREPARED for the worst when she went to get screened for HIV eight years ago. After caring for her mother in Uganda, who died as a result of the virus, Nuru moved to the United Kingdom to study, and decided to take her health into her

own hands. “I was ready to be told I had HIV,” she says. “I felt, ‘That’s okay. I’ve looked up to my mother.’”

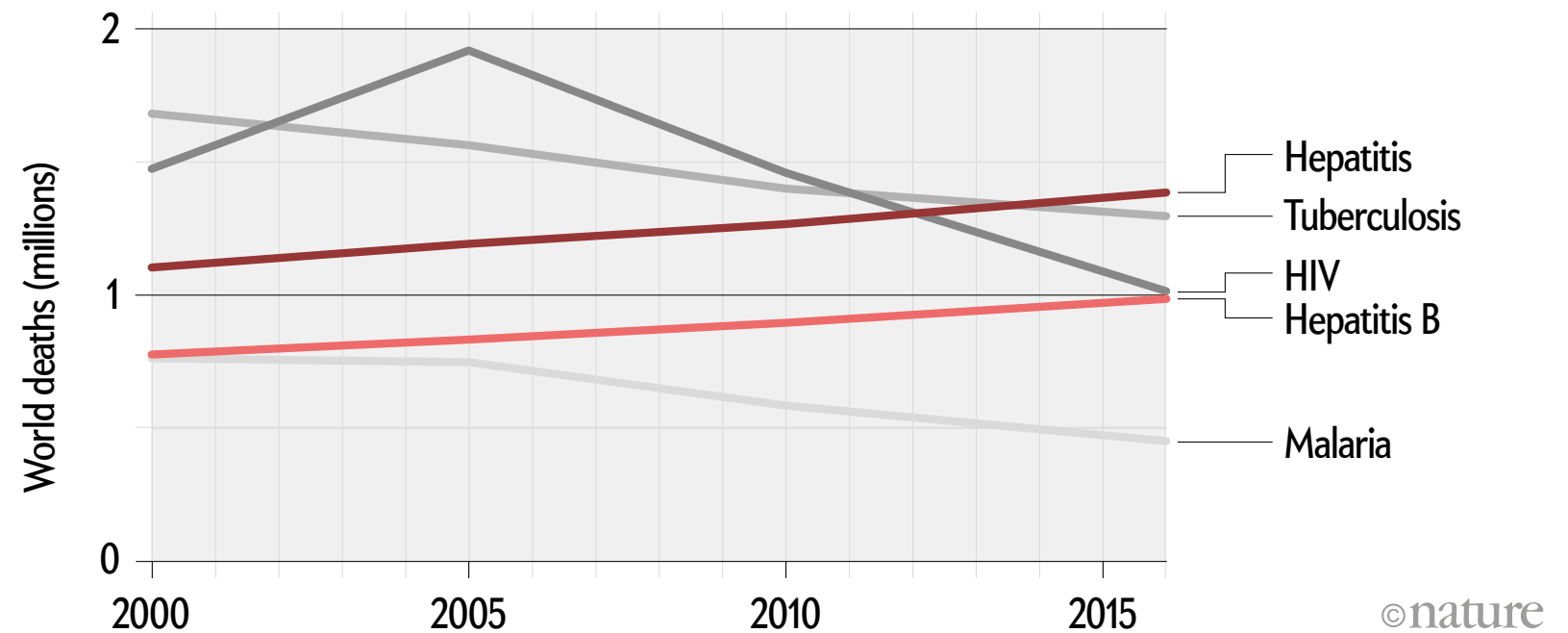
What she didn’t expect was to be diagnosed with a different viral infection altogether: hepatitis B. “The way the health worker delivered it to me, it was like, ‘It’s worse than HIV. I was confused, I was suicidal,’” says Nuru (who asked that her real name not be used for this article). “I just didn’t understand what it was because no one ever talks about hep B—they talk about HIV. That’s well researched, it’s well talked about, well documented. It’s all over the television. But hep B is not.”

The hepatitis B virus (HBV), which spreads through blood and bodily fluids and invades liver cells, is thought to kill just under 1 million people every year around the world, mostly from cancer or scarring (cirrhosis) of the liver. HBV is less likely to be fatal than HIV, and many people who carry the virus don’t have symptoms. But because more than 250 million people live with chronic HBV infections, more than seven times the number with HIV, its global death toll now rivals that of the more-feared virus.

Hepatitis—or liver inflammation—is caused by a number of viruses, but types B and C are associated with the

## RISING DEATH TOLL

Hepatitis infections are now associated with more deaths globally than are tuberculosis, HIV or malaria.



most deaths. In 2016, the most recent year for which estimates are available, the number of deaths worldwide from viral hepatitis rose to 1.4 million, outstripping those from tuberculosis, HIV or malaria individually.

This is despite the fact that HBV infection can be prevented by vaccination early in childhood and treated with the same antiretroviral drugs used to combat HIV. “HIV has been an acute pandemic with resources thrown at it. That’s a completely different picture than hep B, which has traveled with humankind for tens of thousands of years—and by dint of that invisible carriage, has

never had that injection of political advocacy, funding, energy and education that’s gone into HIV,” says Philippa Matthews, an immunologist at the University of Oxford, U.K., who studies viral infections such as HBV.

Researchers and health workers are now hoping to change that. Two years ago, the World Health Assembly endorsed a World Health Organization (WHO) strategy to eliminate hepatitis as a public-health threat by 2030, which the WHO defined as reducing new infections by 90 percent and deaths by 65 percent.

A major focus is to combat the growing HBV crisis in

sub-Saharan Africa. Other high-risk regions, such as the Western Pacific (which stretches from China to New Zealand), have long inoculated children against the virus, following a 1992 WHO decision to include HBV in routine vaccination protocols. As a result, although around 6 percent of people in the region are still living with HBV, most children and teenagers there are protected. But in sub-Saharan Africa, where it's also estimated that about 6 percent of the population are currently infected, fewer than one-tenth of children receive the necessary inoculations. The region also ranks last in every other intervention, including screening and diagnosis, and in treating those living with the virus.

“Hepatitis B has been, to a large extent, neglected,” says Ponsiano Ocama, a hepatologist at Makerere University in Kampala, Uganda. Health care workers, he says, are generally undereducated and ill-equipped to treat the virus. Matthews adds that priority for antiretroviral drugs is weighted so heavily in favor of people with HIV that some health care workers think those with HBV stand a better chance of receiving adequate care if they contract HIV as well, even though having both infections increases the chance of early death.

With little routine screening, there are also many gaps in researchers' understanding of the prevalence and outcomes of hepatitis in vulnerable populations. While the fight against hepatitis is buoyed by progress in Western Pacific nations, the crisis in sub-Saharan Africa is flying under the radar. “It's a critical time for the region,” says Matthews.

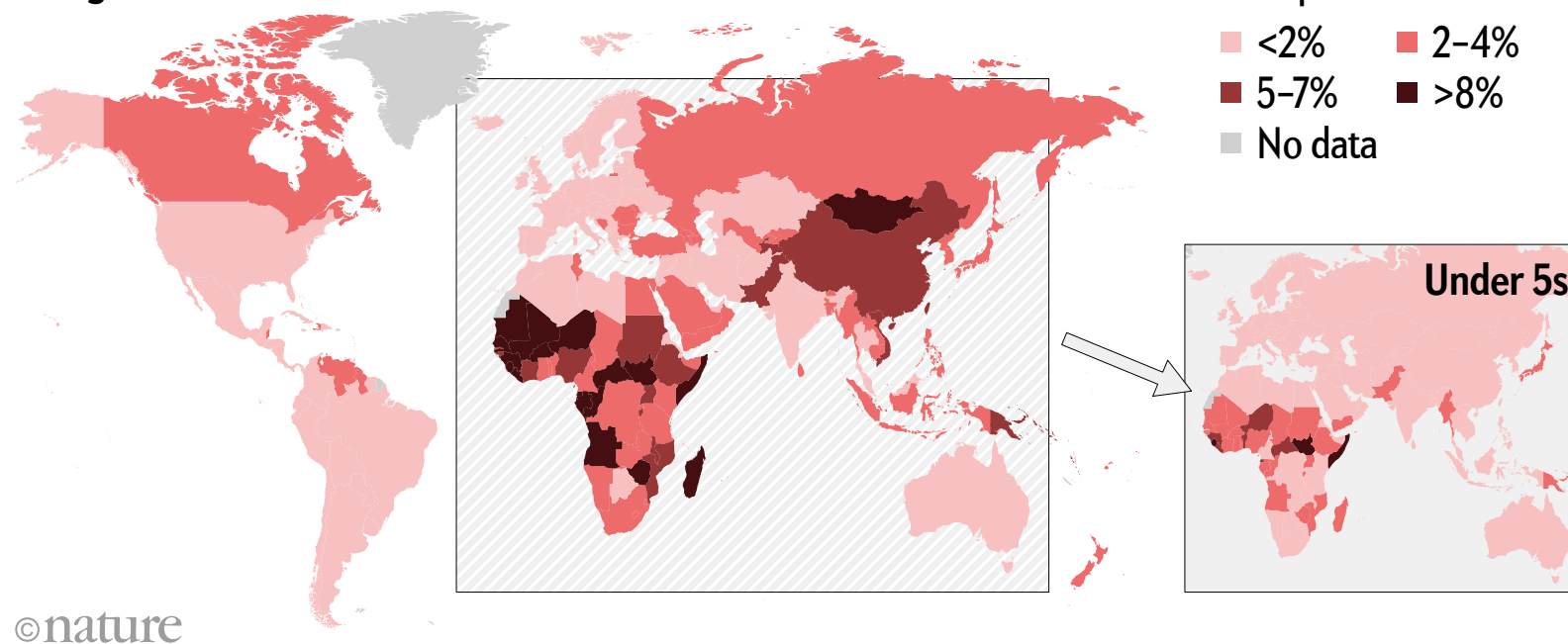
### KNOWLEDGE GAP

Nuru left her U.K. screening appointment dejected, and feeling that she knew little about her infection. She turned to the Internet to answer questions she felt had been glossed over by the health care professionals she saw. Public ignorance about transmission, but awareness

## AN UNEQUAL BURDEN

The hepatitis B virus (HBV) is most prevalent in Africa and the Western Pacific, but in infants (inset), it is found mainly in Africa.

### All ages



that HBV can be passed on during unprotected sex, has given the infection a stigma that, says Nuru, smacks of the whispers that emerged around HIV when that virus first came to light in sub-Saharan Africa. Nuru's body is suppressing the virus well enough that she does not need treatment, but she doesn't talk openly about it. If news that she has HBV spreads back to Uganda, she says, then she worries people will regard her family there with suspicion. “They will be segregated, isolated—they won't get jobs,” she says.

Kenneth Kabagambe, who founded Uganda's National Organization for People Living with Hepatitis B (NOPLHB) in 2011, after a friend died with the infection, says he had a similar experience when he himself was diagnosed in 2012. His doctor, he said, left him wondering whether the

disease might even be comparable to Ebola.

As Kabagambe and Nuru would learn, hepatitis is sometimes referred to as the silent epidemic, because its carriers do not initially show symptoms. In some cases, the virus responsible can sabotage the liver's function over years without causing noticeable problems, until eventually a viral takeover causes cirrhosis or liver cancer.

Hepatitis C virus (HCV) is an RNA virus that is spread largely through blood—usually through unsterilized blood donations, drug use, reuse of unsterilized equipment in hospitals and, to a lesser extent, unprotected sex. There is no vaccine against it, but antiviral medications can cure a chronic infection in most people. By contrast, HBV (a DNA virus, like HIV) is less malignant—in that fewer adults develop chronic infections—but more wide-

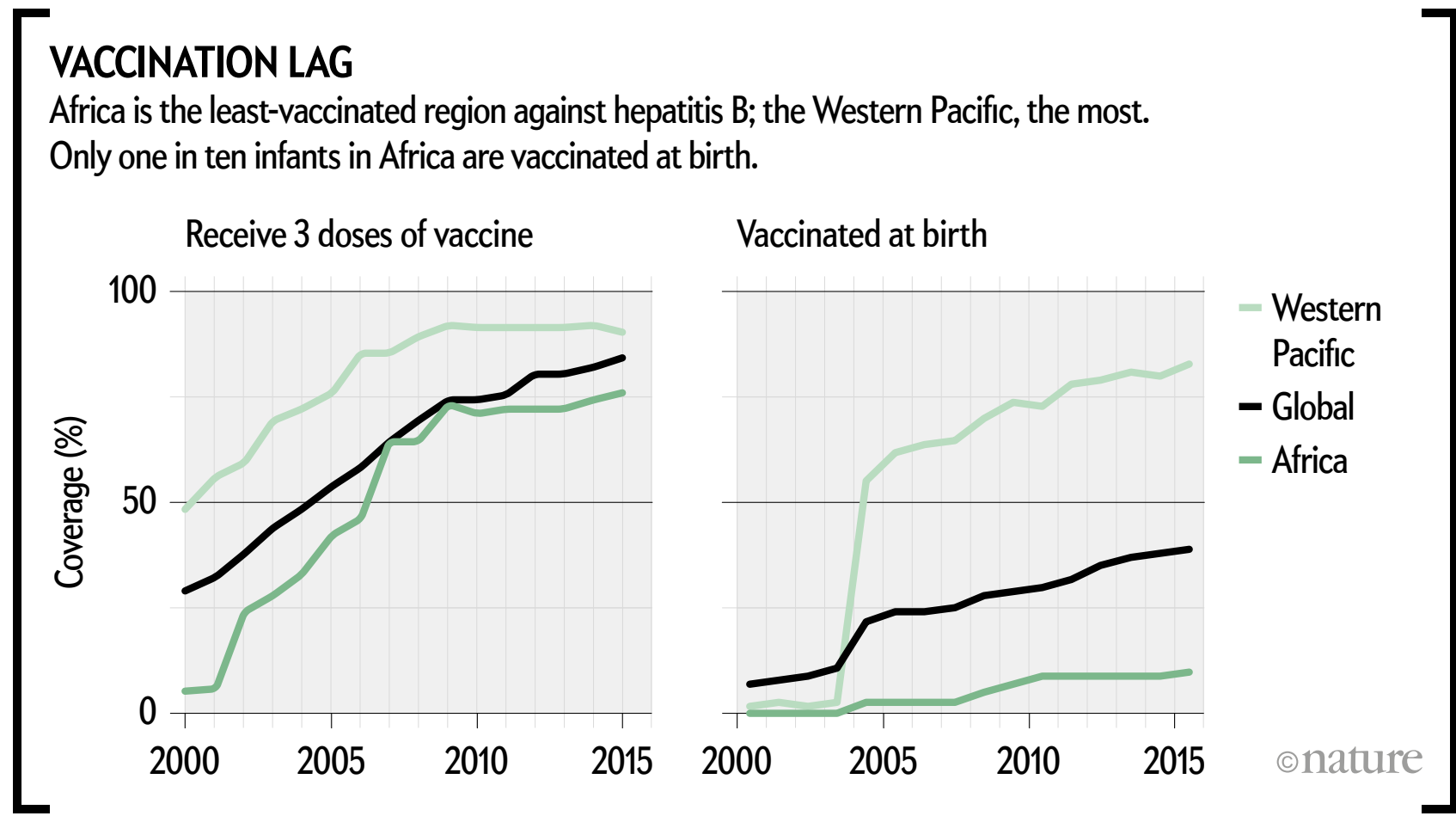
spread. It affects almost four times as many people as HCV, and is more likely than HCV to be spread from mother to baby during pregnancy or birth. HBV infection is also divided more along economic lines: it is, says Oca-ma, largely “a disease of the poor.”

In contrast to people with HIV, adults who don’t already have HBV are unlikely to become infected—and, if they do, there is only a small chance of developing a chronic infection or passing it on to other adults. The group at highest risk of becoming infected and transmitting HBV is infants, who have weaker immune systems. Compared with adults with HBV, toddlers “teem with the virus,” says Mark Sonderup, a hepatitis researcher at the University of Cape Town, South Africa. So, screening and treating infected mothers, and vaccinating babies, is key to cracking down on HBV. Yet, myths still circulate among health workers in Africa about how HBV is transmitted, including that adults with the virus should be isolated. This perpetuates the infection’s stigma, says Oca-ma.

There are some subtleties to this picture. In Western Pacific nations, the main transmission route for strains of HBV tends to be from mother to baby, according to research that dovetailed with the vaccination campaigns there in the 1990s. In sub-Saharan Africa, however—which has different HBV strains—mothers with the infection tend to have lower viral loads, making it slightly less likely that they will infect their babies during pregnancy or birth. Viral transmission from child to child, through the usual scratches of rough play and the lackluster hygiene of youth, seems to be a more prominent infection route.

### VACCINE PUSH

For many years, policymakers thought that rolling out vaccinations would be enough to halt HBV, says Maud Lemoine, a hepatologist at Imperial College London. That’s true in principle, but the vaccine’s design makes it difficult to administer. It is generally given in three



parts. The first is a “birth dose,” which is most effective if given within 24 hours of birth. The other two doses are given later and several weeks apart. From 1990 to 2015, the proportion of children getting three HBV inoculations skyrocketed from 1 percent to 84 percent, with the Western Pacific leading the way at more than 90 percent coverage, just above that in the Americas; Africa lags behind at 70 percent.

But in practice, the first dose is not always given at birth—coverage of this dose is only 39 percent globally—and its timing is not always reported. In Africa, coverage at birth is just 10 percent. Administering a birth dose within 24 hours, and follow-up vaccinations on schedule, poses a monumental challenge in a region where many births are not supervised by medical professionals.

The challenge of accessing mothers in time has been

compounded by a reliance on Gavi, the Vaccine Alliance, an international organization that connects public and private sectors to roll out vaccines. Gavi has been a driving force in expanding HBV vaccination in sub-Saharan Africa. But it does this through a compound inoculation that immunizes against diphtheria, pertussis, tetanus, HBV and influenza, but which isn’t given until six to eight weeks of age. A spokesperson says that the organization has not focused on providing the birth-dose vaccine, in part because it had not seen evidence that distribution systems could get the inoculations to infants within 24 hours of birth, and because it felt the more expensive five-fold vaccine was a better target for subsidy.

Last November, however, Gavi’s board voted to prioritize investment in HBV birth-dose vaccines, as part of a strategy targeting six new vaccine programs from 2021 to



2025. And success in other vaccination campaigns shows that it should be possible to overcome distribution challenges. In the 1990s, researchers in Indonesia gave pre-packaged single-use hepatitis B vaccines to local midwives so that they could administer an inoculation after home births, an approach now used more widely. And two years ago, researchers in Laos demonstrated that providing mobile phones to vigilant health workers and local volunteers helped keep track of births and ensure more infants were vaccinated.

### SCREENING RESEARCH

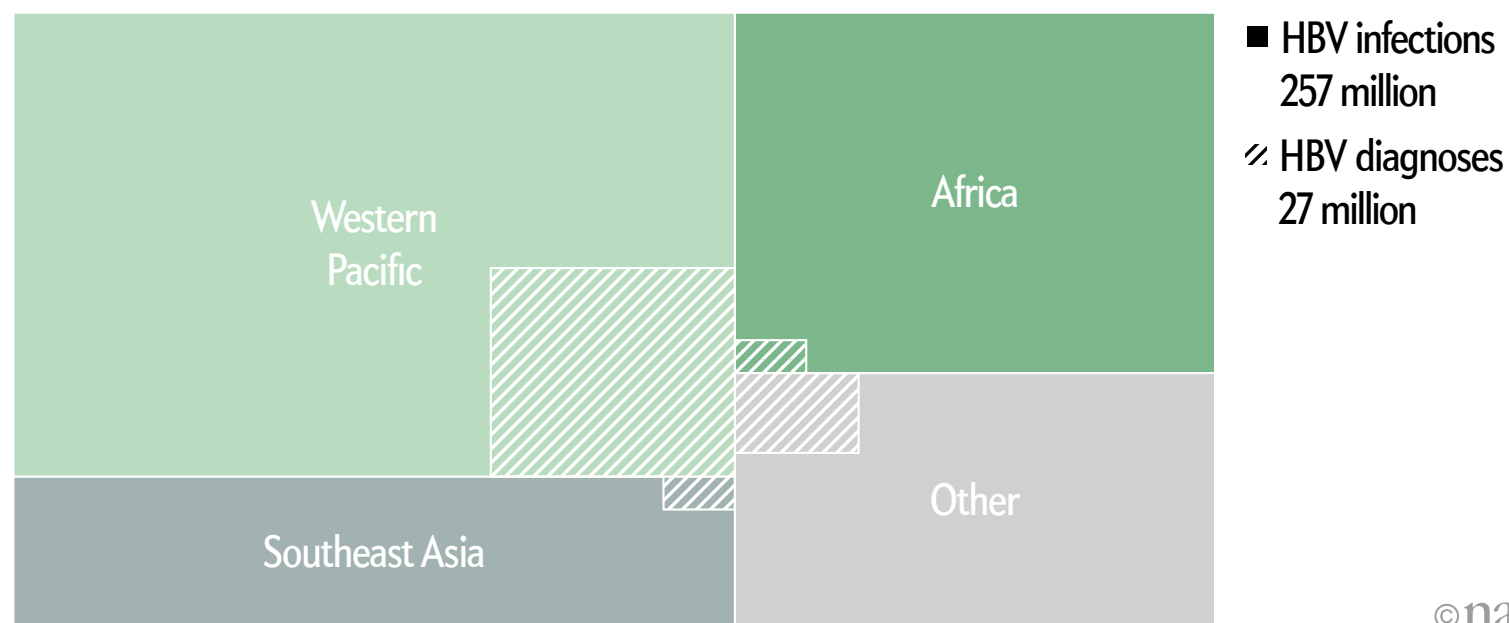
Another key to tackling HBV is screening and diagnosing adults. Mothers are among the most crucial people to check because of their propensity to pass the virus on to their babies. “If you find infected antenatal women, you can also screen their partners. You can vaccinate any household contacts who aren’t infected. You can identify any other household contacts who are infected and treat them,” says Matthews. “It gives you a route into more population-level interventions.”

But mothers are not routinely checked before giving birth. Add to that a paucity of cancer registries with accurate data on liver cancer, and a generally low regional turnout for testing, and it’s of little surprise that researchers’ picture of the prevalence and dynamics of hepatitis viruses are plagued with gaps.

Instead, the populations that are screened most reliably are those who donate blood and people such as Nuru and Kabagambe, who saw firsthand how HIV ravaged their communities and decided to get tested. Many health professionals have criticized initiatives such as Gavi and the U.S. President’s Emergency Plan for AIDS Relief for not doing more to leverage HIV-testing networks to also provide screening for hepatitis. Lemoine points out that one negative HBV test is probably all that an adult needs, because it is so unlikely that they will be

### DIAGNOSIS GAP

The World Health Organization wants to diagnose 90 percent of hepatitis B infections by 2030. The rate is currently 10 percent.



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infected, whereas people might need to be retested for HIV many times.

Initial screens cost only a few dollars: health workers simply check the person’s blood for evidence that their immune system has developed antibodies against the hepatitis viruses. But these checks, says Matthews, test only whether you’ve been exposed to the viruses, not whether you’re currently infected. To get a definitive diagnosis, people need more-expensive nucleic-acid tests that detect the viral DNA of HBV (or, for HCV, viral RNA). The cost can be as high as U.S. \$200—something that few people in sub-Saharan Africa can afford, says Olufunmilayo Lesi, a member of the WHO’s advisory group on viral hepatitis. Fewer than 1 percent of those in the region with HBV, and 6 percent of those with HCV, are diagnosed, according to a WHO estimate.

### DRIVING FORWARD

Several countries in sub-Saharan Africa are now expanding their screening efforts, including Uganda, which hopes to tie its effort to a vaccination drive aimed at mothers and infants, says Ocama. And researchers have been working on more convenient diagnostic tests. In 2017, the WHO approved a test that detects HCV RNA and runs on equipment found in most hospitals in sub-Saharan Africa—the GeneXpert nucleic-acid system. Made by Cepheid, a company in Sunnyvale, California, it is already used to diagnose HIV and tuberculosis. A test for HBV that could be run on the GeneXpert machine is in beta testing, says Sonderup, but has yet to be formally released. (Cepheid did not reply to requests for comment.)

As the world has focused on combating HIV, billions of dollars have been poured into developing antiretrovi-

rals—drugs that people with HIV take indefinitely to inhibit the replication of DNA viruses. In low-income countries, the cost of these drugs is heavily subsidized, and in many cases, the same drugs can treat both HIV and HBV.

But when it comes to access to drugs, people with HBV in many resource-limited regions find themselves overlooked in favor of those with HIV. Ocama says he has known hospital administrators who have allowed physicians to administer drugs reserved for people with HIV to those with HBV—but overall, an abysmally small fraction of people in sub-Saharan Africa with HBV receive treatment.

Some countries are increasingly aware that antiretroviral drugs need to also reach people with hepatitis. In 2012, Uganda became the first sub-Saharan African country to produce a generic form of the antiretroviral tenofovir, through the company Quality Chemicals, and the drug is offered for free at some treatment centers, says Ocama. And in 2017, after years of using HIV programs to secure drugs for people with HBV, the Senegalese Society of Gastroenterology convinced the government to make tenofovir available to them at a price similar to that offered to those with HIV.

Still, the stigma of having HBV can be as problematic as drug scarcity. Patient groups in Africa, Ocama says, are too few and far between. “For many people, I think it is a lonely journey. It is a place of isolation,” says Nuru. But she and Kabagambe are determined to change this. After Nuru was diagnosed, she convinced her siblings to get tested. Three out of six tested positive for HBV. Since then, leveraging her sisters in Uganda as part of a “whisper network,” she has convinced 13 other people to be tested, and paid for the procedure.

Meanwhile, the patient network that Kabagambe founded is dedicated to educating the public about HBV and establishing a community in which people who have the virus can talk about it. “Being diagnosed with hepatitis B does not define your end,” he says. “You can still prosper.”

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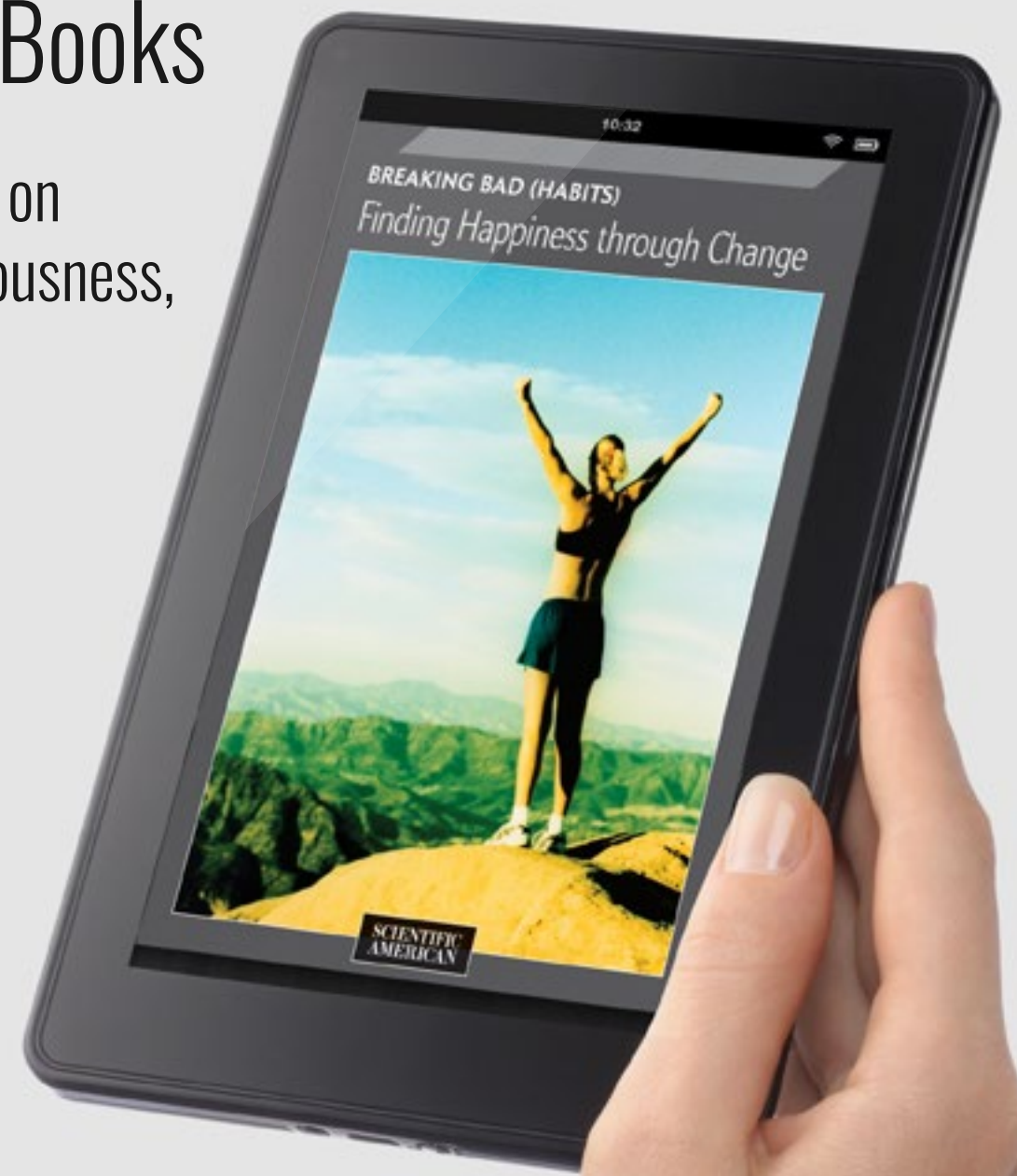
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# Model Citizens

**How digital drug dealers and virtual users are providing clues to help stop the U.S. opioid epidemic**

*By Sara Reardon*

MAN uses heroin under a bridge in Philadelphia.



WITH THE TIP OF HER SYRINGE, BRANDI POKES AT A GRAY LUMP OF HEROIN IN A SPOON. IT'S A NEW variety of the drug that has shown up on the market in the past few days, and Brandi likes it. "I feel this more, I feel more of the pain resistance," she says. Once it has dissolved into a liquid, she injects it into her arm, then uses a fresh needle to inject the skinny arm of another woman. "She does it better than the hospital," the woman comments. "I'll help anybody who needs it," Brandi explains to public health researcher Daniel Ciccarone of the University of California, San Francisco, who has been filming the entire process.

Ciccarone's team has embedded with Brandi—whose name has been changed for this story—in Charleston, W. Va., documenting her interactions without judgment or interference. Later, the group will analyze this video, in addition to half a dozen other videos of drug users from across the city, logging details big and small. Brandi does not heat the solution on the spoon, for instance, and that may increase the likelihood of spreading viruses such as HIV. And tests reveal that what she's taking has been laced with fentanyl, a synthetic drug up to 50 times more powerful than heroin.

The researchers will plug these data into powerful computer simulations of Charleston, populated by thousands of virtual Brandis—heroin users and dealers going about their daily routines. They will watch these digital agents buy more heroin as their tolerance increases, form networks with sellers and users, and, in some cases, accidentally overdose.

Ciccarone's is one of several groups using agent-based models to understand what is driving the U.S. opioid epidemic—the dramatic rise over the past two decades in the

use of opioids, including prescription pain medications and illegal drugs such as heroin. By studying the motivations and practices of real drug dealers and users, the researchers hope to build agents whose behavior in the virtual world mimics that in real life.

Agent-based models promise to provide a more granular view of the opioid crisis than standard modeling, which is based on average populations, and to capture some of the complexity of the driving forces. This could prove important for demonstrating the effects of opening or closing methadone clinics or needle exchanges. The models allow scientists to compare interventions at almost no cost and could help policy makers to decide how to proceed in the real world. "It's a very classic and useful way to try and see where is the best place to deploy an intervention to have the biggest effect," says John Brooks, a medical adviser for the division of HIV/AIDS prevention at the U.S. Centers for Disease Control and Prevention.

Although such simulations have long been used to model disease outbreaks and have, in some instances,

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guided public policy, their track record with more complex social behavior such as drug use is limited, largely because of sparse data and the breadth of parameters to consider.

Still, scientists hope that agent-based models can lay out scenarios for decision makers, who are often driven more by politics than data. "The barriers are not scientific or medical," Ciccarone says. "You can throw \$1 billion at West Virginia, and they may or may not know how to use it well." These virtual worlds can add clarity, says Joshua Epstein, director of the Agent-Based Modeling Lab at New York University. "You can literally watch the thing unfold before your eyes," he says.

### THE DIFFERENCE IN THE DETAILS

The U.S. opioid crisis is estimated to kill 115 people a day through overdoses and has run up \$1 trillion in health care costs and lost productivity since 2001. It is not the first addiction crisis that the U.S. has faced, nor is it the most severe. Alcohol use causes many more deaths, and the rate of cocaine overdose among African-Americans is similar to the rate of opioid overdose in white Americans.

But the opioid crisis does have some different driving factors, including the prevalence of prescription drugs, which many have used on the way to abusing illegal drugs, and the introduction of fentanyl, which is often used to boost the potency of heroin and is responsible for a large share of overdose deaths. The epidemic has also hit hard in rural settings, where services and infrastructure for dealing with addiction are scarce. "The demo-



graphic now encompasses a population that in the past has not been so affected,” says Nora D. Volkow, director of the National Institute on Drug Abuse.

As a result, researchers are coming up with fresh ways of thinking about the crisis. It bears similarities to a disease epidemic, for example, in the way it spreads through networks based on personal relationships and physical proximity, says Georgiy Bobashev, a data scientist at the nonprofit research institute RTI International in Research Triangle Park, N.C. “Nobody is born an addict. Somebody has to teach you how to smoke or how to inject.”

These personal networks can be replicated using agent-based modeling. Unlike other types of models, which may rely on average characteristics or relationships between homogeneous groups to inform algorithms, agent-based models allow researchers to see subtle connections between people. “That’s useful because drug use and overdose is inherently personal,” says epidemiologist Brandon Marshall of Brown University. Factors such as job loss, mental health or genetics can influence how likely a person is to begin using drugs or become addicted, but those factors might fade into the averages if researchers looked at a population as a whole.

To create an agent-based model, researchers first “build” a virtual town or region, sometimes based on a real place, including buildings such as schools and food shops. They then populate it with agents, using census data to give each one its own characteristics, such as age, race and income, and to distribute the agents throughout the virtual town.

The agents are autonomous but operate within preprogrammed routines—going to work five times a week, for instance. Some behaviors may be more random, such as a 5 percent chance per day of skipping work or a 50 percent chance of meeting a certain person in the agent’s network. Once the system is as realistic as possible, the researchers introduce a variable such as a flu virus, with



WARREN, OHIO, has high rates of unemployment and opioid addiction. Here an American flag is painted inside the window of a closed business.

a rate and pattern of spread based on its real-life characteristics. They then run the simulation to test how the agents’ behavior shifts when a school is closed or a vaccination campaign is started, repeating it thousands of times to determine the likelihood of different outcomes.

In 2015 data from an agent-based model developed at the University of Pittsburgh helped California state senator Richard Pan to gain support for a bill on mandatory vaccination in his state. Pan used the simulation to demonstrate to his fellow senators how measles outbreaks could unfold in their home districts. “It certainly made an impact on them,” Pan says. “Instead of just describing it in more abstract terms, [the model] can make it more concrete.” The bill ultimately passed, and

immunization rates increased.

As computers have improved, researchers have begun adapting agent-based models to look at sociological and behavioral trends that require more computing power because of the number of variables they contain. Some groups use the technique for crisis modeling, and Australia has begun intervention studies for child obesity on the basis of the findings of an agent-based model.

In response to the opioid epidemic, Bobashev’s group has constructed Pain Town—a generic city complete with 10,000 people suffering from chronic pain, 70 drug deal-



ers, 30 doctors, 10 emergency rooms and 10 pharmacies. The researchers run the model over five simulated years, recording how the situation changes each virtual day.

During this time, the patients' drug tolerance increases, leading them to find different ways of acquiring drugs. Their behavior is driven by variables such as the chance that a doctor will increase their prescription or the likelihood that a dealer will have enough heroin. At a certain threshold, patients become addicted or more likely to overdose. Bobashev's early data suggest, for example, that requiring doctors to track patients' medication history can be effective over the long term, though not immediately.

The model contains many assumptions and simplifications, Bobashev says. For example, it does not capture the fact that the rate at which people develop tolerance and addiction can depend on factors such as genetics and that whether a person switches from prescription drugs to heroin can depend on the relative availability of the two drugs.

But researchers can adjust models such as Pain Town to test various interventions, such as increasing access to emergency rooms, arresting a dealer or equipping police with naloxone (a drug that reverses opioid overdoses), to see how the system reacts and whether it affects the number of deaths over time. And as models become more sophisticated, the researchers may be able to incorporate more factors, such as people who are not taking pain medications but are susceptible to trying opioids for the first time.

Models can also be useful for understanding why individual places or situations may differ, says Christopher Barrett, a computer scientist at Virginia Tech. For instance, heroin and fentanyl might be easier to come by in cities near ports, whereas doctors may be the main source of opioids in a suburban or rural setting. Interventions focused on prescribing practices, therefore, would have



different effects in each case.

Such models can also reveal feedback loops, such as the link between economic downturns and opioid use. Some epidemiological studies have suggested that factors such as unemployment tend to predict suicide and addiction, especially in white male populations. And addiction can lead to further job loss and lower productivity, harming the economy. Agent-based models could investigate loops such as this, providing ideas for how to mitigate the effects, Barrett says.

In May, Bobashev and Ciccarone presented results from one of their agent-based models at a meeting of the International Society for the Study of Drug Policy in Vancouver,

LAW-ENFORCEMENT OFFICIALS seize 33 kilograms of heroin and two kilograms of fentanyl in a major drug bust in New York State.

B.C. Their findings suggested that the increased prevalence of white-powder heroin—a newer form of the drug in the U.S.—may increase the risk of HIV spreading among injection drug users. The reason, also supported by the model, is that unlike black-tar heroin, users do not need to heat the drug to dissolve it—and heating kills the virus.

Bobashev and Ciccarone are working on models of how younger heroin users begin using the drug. Unlike older users, who experienced the rise of the HIV epidemic in the 1980s, newer users may be less likely to adopt safe

practices. The models suggest that the U.S. may see more localized HIV outbreaks, similar to the recent outbreak in Scott County, Indiana. That region experienced 181 new HIV cases between November 2014 and November 2015, compared with fewer than five cases per year previously. Opioid use is thought to be the cause. Agent-based models might help stem future outbreaks by guiding surveillance priorities.

Law-enforcement officials have been seizing vast quantities of heroin and the powerful synthetic drug fentanyl, but information on the amount in circulation is hard to come by.

One of the most sophisticated agent-based models is the University of Pittsburgh's system, known as FRED (a Framework for Reconstructing Epidemiological Dynamics). It fits population census data to maps of geographical regions around the country, allowing researchers to track virtual individuals in the area in a realistic way. It was data from these models that helped to convince Pan and his fellow state senators to pass legislation on mandatory vaccination. The FRED team is now beginning to use the system for opioid modeling, training it on historical trends. Pan, who is also a physician, says he is intrigued by the prospect. "If there's a way to actually model in different communities which factors would have the biggest impact, that would be helpful," he says.

## DATA DROUGHT

The models face numerous challenges before they will be ready for widespread adoption, primarily data gaps. Marshall says that researchers struggle to get access to data on opioid prescriptions that are held by manufacturers, pharmacies and law-enforcement agencies. It is also difficult to obtain government information on drug cartels and the type and rate of drugs flowing into the country. Other data simply do not exist in usable form: agencies may record deaths from drug overdose, for instance, but

## **After an initial awkward period, drug users tend to become more honest with the researchers, telling them crucial information such as how they form networks with dealers and the cost of drugs.**

fail to specify which drug was responsible.

Observing drug users such as Brandi can provide certain types of information more quickly and accurately. "Drug users know their chemicals intimately," Ciccarone says.

Lee Hoffer, a cultural anthropologist at Case Western Reserve University, studies heroin markets and collaborates with Bobashev. He says that the ethnographic data that his group and others are collecting could help fill some of the information gaps: "We're trying to enter their world as interlopers to see how they see their life." After an initial awkward period, he notes, drug users tend to become more honest with the researchers, telling them crucial information such as how they form networks with dealers and the cost of drugs.

Understanding the psychology of drug users is also crucial, Epstein says. Most decision-making models assume rational behaviors. In reality, emotions, misinformation and irrational calculations play a major part. "When you put them together, you get collections of dynamics that are very dysfunctional."

Epidemiological data may soon be available to buttress the models. The CDC and the National Institute on Drug Abuse have started several major surveys of drug-use pat-

terns. A number of states have also begun collecting epidemiological information on trends in overdose and addiction. And research groups such as the University of Pittsburgh team are working with multiple health agencies to collate their findings in a single database, which can inform FRED and other models.

But no matter how advanced the models become, implementing interventions based on their findings is an enormous challenge. Models may reveal socioeconomic contributors that cannot be easily addressed by policies, and politics can stand in the way of proven solutions. Last April, Ciccarone had to cancel his work in Charleston, at least for the time being, after a needle-exchange clinic with which he had been collaborating closed because of political pressure. "They were seeing 300 people on a Wednesday afternoon because there's a lot of need," he says. "It's a huge loss."

Increasing work is being done to determine the relative impact of interventions. Last April the National Institutes of Health announced \$96 million for a program that will partner with health care systems and local governments to carry out evidence-based public health interventions in different locations, evaluating them as they go. "This is the first time this [has been] done for a particular substance-abuse disorder," Volkow says. The NIH is now asking researchers who want to apply for these funds to justify the size and scope of their proposed studies with data from models, including agent-based models.

But these studies are certain to take many years to complete. And Bobashev says that society cannot afford to wait for the science to be perfect: "By the time these data are collected, tens of thousands, if not hundreds of thousands, more deaths will have occurred."



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OBSERVATIONS

# Has Your Health Insurance Really Got You Covered?

When it comes to making sure patients take their medications as prescribed, the answer is no

Your health insurance is paying for the wrong things. According to both the [World Health Organization](#) and the [Centers for Disease Control and Prevention](#), about 50 percent of people who are prescribed medication for long-term health conditions such as high blood pressure, high cholesterol or diabetes do not take their medications as prescribed.

The reasons are many and vary from person to person, but the result is the same: Many people are not getting the health benefits they need from their medication, either to maintain or improve their health, or to prevent worse health events down the road, such as heart attack or stroke.

As a result, insurers must pay for health care providers to deliver behavioral interventions and case management to improve adherence to medication regimens.



Over my 20 years as a nurse, I have seen many patients struggle to manage medications, often ending up hospitalized as a result. In my research, I have found ways to identify and help patients better manage their medications, but our current health care financing model does not reimburse for such care.

Medication nonadherence is estimated to cost the U.S. health care system between \$100 billion and \$289 billion in direct costs each year, according to research published in the *Annals of Internal Medicine*. The average total cost of a single heart attack

ranges from \$760,000 to about \$1 million per person, depending on severity, according to an article from the National Business Group on Health reported by [CBS News](#).

Research in the journal *Stroke* reports that total costs from a stroke range from \$90,981 to \$228,030, depending on the type of stroke. If we can prevent heart attacks and strokes, the savings to insurance companies, employers, patients and taxpayers is staggering.

We know that many people need help with manag-



ing medications for reasons such as forgetfulness, complex medication regimens, language barriers, inability to obtain medication, or symptoms from health conditions, yet health insurers do not provide coverage to pay for patients to get the help they need.

For instance, researchers have developed many programs through which health care providers can work with patients to improve medication management, but without a financial model to pay for it, such programs will not reach patients who need it. As one example, P. Michael Ho at the Department of Veterans Affairs and colleagues have shown that team-based approaches do lead to significant improvements in how patients use their cardiovascular medications.

Reimbursing health care organizations for medication adherence initiatives delivered by providers, such as registered nurses, nurse practitioners or pharmacists, would improve health outcomes and lower costs overall. While this approach would involve up-front costs, the result would be a net savings due to prevented hospitalizations.

Health care providers typically don't have time during appointments to address whether patients are taking medications correctly, and research repeatedly shows that patients usually think they're doing better with managing their medications than they actually are.

Reliant Medical Group, a network of over 500 health care providers in Massachusetts serving over 320,000 patients, has also demonstrated how a focus on adapting medication regimens to improve adherence in high-risk patients can lead to better rates of blood pressure control. These approaches can work when health care teams are able to devote the time and resources needed to partner with

patients to address the obstacles in the way of improving each patient's health.

To be sure, taking medication when required is not the only important behavior for maintaining and improving health. While other health behaviors such as diet and exercise are important, for most people with chronic health problems, adhering to a medication regimen is going to be the most important health behavior for keeping a person out of the hospital (or worse).

While many insurance companies have their own care management programs, patients tend to be more comfortable working with case managers and nurses from their own health care provider's office. If these programs are housed in individual practices, there is also better continuity of care and ability to make modifications to medication regimens or detect changes in health status needing early intervention to prevent hospitalization.

Yes, this is a change in how we do things.

Having insurance companies pay for services that don't fit the traditional model may be seen as radical. But the health of our nation and the growing cost of our health care system demand new approaches.

There can be no innovations to our health care delivery models if there is no change in how insurance reimburses for health care services and defines what is necessary in health care services.

It is far better in the short term and the long run to pay for proactive care up front for the portion of the population that needs it than to have all of society paying increased insurance costs to pay for health problems we could have prevented.

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**Gina Siddiqui** is an emergency room doctor at Yale New Haven Hospital. Before patching people up in the ER, Gina founded and led a digital health company in Silicon Valley called Remedy. Follow her on Twitter @zaberdasst.

● *Opinion*

OBSERVATIONS

# Why Doctors Reject Tools That Make Their Jobs Easier

**From the thermometer's invention onward, physicians have feared—incorrectly—that new technology would make their jobs obsolete**

I want to tell you about a brouhaha in my field over a “new” medical discipline 300 years ago. Half my fellow doctors thought it weighed them down and wanted nothing to do with it. The other half celebrated it as a means for medicine to finally become modern, objective and scientific. The discipline was thermometry, and its controversial tool a glass tube used to measure body temperature called a thermometer.

This all began in 1717, when Daniel Fahrenheit moved to Amsterdam and offered his newest temperature sensor to the Dutch physician Herman Boerhaave. Boerhaave tried it out and liked it. He proposed using measurements with this device to guide diagnosis and therapy.

Boerhaave's innovation was not embraced.

Doctors were all for detecting fevers to guide diagnosis and treatment, but their determination of whether fever was present was qualitative. “There is, for example, that acrid, irritating quality of feverish heat,” the French physician Jean Charles Grimaud said as he scorned the thermometer's reducing his observations down to numbers. “These [numerical] differences are the least important in practice.”

Grimaud captured the prevailing view of the time when he argued that the physician's touch

captured information richer than any tool, and for more than 100 years doctors were loath to use the glass tube. Researchers among them, however, persevered. They wanted to discover reproducible laws in medicine, and the verbal descriptions from doctors were not getting them there. Words were idiosyncratic; they varied from doctor to doctor and even for the same doctor from day to day. Numbers never wavered.

In 1851 at the Leipzig university hospital in Germany, Carl Reinhold Wunderlich started





recording temperatures of his patients: 100,000 cases and several million readings later, he published the landmark work “On the Temperature in Diseases: a manual of medical thermometry.” His text established an average body temperature of 37 degrees, the variation from this mean which could be considered normal, and the cutoff of 38 degrees as a bona fide fever. Wunderlich’s data were compelling; he could predict the course of illness better when he defined fever by a number than when fever had been defined by feel alone. The qualitative status quo would have to change.

Using a thermometer had previously suggested incompetence in a doctor. By 1886, *not* using one did. “The information obtained by merely placing the hand on the body of the patient is inaccurate and unreliable,” remarked the American physician Austin Flint. “If it be desirable to count the pulse and not trust to the judgment to estimate the number of beats per minute, it is far more desirable to ascertain the animal heat by means of a heat measurer.”

Evidence that temperature signaled disease made patient expectations change too. After listening to the doctor’s exam and evaluations, a patient in England asked, “Doctor, you didn’t try the little glass thing that goes in the mouth? Mrs Mc\_\_\_ told me that you would put a little glass thing in her mouth and that would tell just where the disease was...”

Thermometry was part of a seismic shift in the nineteenth century, along with blood tests, microscopy, and eventually the x-ray, to what we now know as modern medicine. From impressionistic

illnesses that went unnamed and thus had no systematized treatment or cure, modern medicine identified culprit bacteria, trialed antibiotics and other drugs, and targeted diseased organs or even specific parts of organs.

Imagine being a doctor at this watershed moment, trained in an old model and staring a new one in the face. Your patients ask for blood tests and measurements, not for you to feel their skin. Would you use all the new technology even if you didn’t understand it? Would you continue feeling skin, or let the old ways fall to the wayside? And would it trouble you, as the blood tests were drawn and temperatures taken by the nurse, that these tools didn’t need you to report their results. That if those results dictated future tests and prescriptions, doctors may as well be replaced completely?

The original thermometers were a foot long, available only in academic hospitals, and took 20 minutes to get a reading. How wonderful that now they are cheap and ubiquitous, and that pretty much anyone can use one. It’s hard to imagine a medical technology whose diffusion has been more successful. Even so, the thermometer’s takeover has hardly done away with our use for doctors. If we have a fever we want a doctor to tell us what to do about it, and if we don’t have a fever but feel lousy we want a doctor anyway, to figure out what’s wrong.

Still, the same debate about technology replacing doctors rages on. Today patients want not just the doctor’s opinion, but everything from their microbiome array and MRI to tests for their testosterone and B12 levels. Some doctors celebrate this

millimeter and microliter resolution inside patients’ bodies. They proudly brandish their arsenal of tests and say technology has made medicine the best it’s ever been.

The other camp thinks Grimaud was on to something. They resent all these tests because they miss things that listening to and touching the patient would catch. They insist there is more to health and disease than what quantitative testing shows, and try to limit the tests that are ordered. But even if a practiced touch detects things tools miss, it is hard to deny that tools also detect things we would miss that we don’t want to.

Modern CT scans, for example, perform better than even the best surgeons’ palpation of a painful abdomen in detecting appendicitis. As CT scans become cheaper, faster and dose less radiation, they will become even more accurate. The same will happen with genome sequences and other up-and-coming tests that detect what overwhelms our human senses. There is no hope trying to rein in their ascent, nor is it right to. Medicine is better off with them around.

What’s keeping some doctors from celebrating this miraculous era of medicine is the nagging concern that we have nothing to do with its triumphs. We are told the machines’ autopilot outperforms us so we sit quietly and get weaker, yawning and complacent like a mangy tiger in captivity. We wish we could do as Grimaud said: “distinguishing in feverish heat qualities that may be perceived only by a highly practiced touch, and which elude whatever means physics may offer.”

A children's hospital in Philadelphia tried just that. Children often have fevers, as anyone who has had children around them well knows. Usually, they have a simple cold and there's not much to fuss about. But about once in 1,000 cases, feverish kids have deadly infections and need antibiotics, ICU care, all that modern medicine can muster.

An experienced doctor's judgment picks the one-in-1,000 very sick child about three quarters of the time. To try to capture the remainder of these children being missed, hospitals started using quantitative algorithms from their electronic health records to choose which fevers were dangerous based on hard facts alone. And indeed, the computers did better catching the serious infections nine times out of ten, albeit also with ten times the false alarms.

The Philadelphia hospital accepted the computer-based list of worrisome fevers, but then deployed their best doctors and nurses to apply Grimaud's "highly practiced touch" and look over the children before declaring the infection was deadly and bringing them into the hospital for intravenous medications. Their teams were able to weed out the algorithm's false alarms with high accuracy, and in addition find cases the computer missed, bringing their detection rate of deadly infections from 86.2 percent by the algorithm alone, to 99.4 percent by the algorithm in combination with human perception.

Too many doctors have resigned that they

have nothing to add in a world of advanced technology. They thoughtlessly order tests and thoughtlessly obey the results. When, inevitably, the tests give unsatisfying answers they shrug their shoulders. I wish more of them knew about the Philadelphia pediatricians, whose close human attention caught mistakes a purely numerical rules-driven system would miss.

It's true that a doctor's eyes and hands are slower, less precise, and more biased than modern machines and algorithms. But these technologies can count only what they have been programmed to count: human perception is not so constrained.

Our distractible, rebellious, infinitely curious eyes and hands decide moment-by-moment what deserves attention. While this leeway can lead us astray, with the best of training and judgment, it can also lead us to the as of yet undiscovered phenomena that no existing technology knows to look for. My profession and other increasingly automated fields would do better to focus on finding new answers than on fettering old algorithms.

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**Marian W. Wentworth** is president and CEO of Management Sciences for Health, a global nonprofit that works side by side with leaders in low- and middle-income countries to build strong, equitable and sustainable health systems that save lives and improve health outcomes.

● *Opinion*

OBSERVATIONS

# Viruses on a Plane: What Emirates Flight EK203 Teaches Us

**We're good at responding to suspected disease outbreaks, but we're in danger of letting down our guard**

Even before Emirates flight EK203 arrived in New York on September 5, 2018, carrying dozens of ill passengers, the crisis response was under way. Crew members alerted authorities about the sick travelers from the air. Health officials dispatched an emergency response team with mobile diagnostic equipment to the tarmac to await the plane's arrival. Ambulances waited nearby. EMTs notified hospitals about a potential influx of severely ill, potentially infectious patients. And after the flight landed, health officials evaluated more than 500 passengers at the airport and transported at least 10 to a local hospital for further testing.

It was an excellent dry run to test our capabilities for fast detection, reporting and interagency



coordination. Luckily, this happened in the United States, a country with significant resources and one of the strongest health systems in the world.

But what if an airplane carrying passengers harboring an unknown and possibly deadly pathogen landed in a country without a robust health system? Imagine that these people had been forced to stay on the plane, or shuttled through a busy airport and sent to an unprotected hospital ward. If passengers harboring the

virus but without symptoms then returned home to their families or boarded another plane, you'd have the beginnings of an epidemic.

Managing a crisis requires authorities on many levels to mobilize quickly. While the public sees only the flashing lights of an ambulance or people with moon suits dispensing treatments and vaccines, those of us who work in public health see what lies beneath—a web of complex protocols and well-maintained equipment and

treatments, strong leadership and skilled health workers.

Preparedness doesn't happen by chance. A responsive, resilient health system requires commitment and investments of money and time. It is important to stop outbreaks both inside our country and before they reach our borders. The United States engages in thwarting diseases overseas through the Centers for Disease Control and Prevention (CDC) and U.S. Agency for International Development (USAID). We spend \$108.2 million each year through the CDC alone on global health security. Activities include setting up emergency operations centers to manage crises; shoring up leadership and regulations; implementing early warning information systems; and training clinicians, nurses and community health workers on how to spot and contain disease.

These investments pay off. With support from the CDC on disease surveillance, border health screening, logistics and supplies and community engagement, the Democratic Republic of the Congo (DRC) was able to contain the outbreak of Ebola that began last May. These modest investments save lives overseas, keep Americans safe at home and protect our livelihoods. A pandemic would likely crash the U.S. stock market, sending the economy into collapse and society into turmoil. The World Bank estimates that an epidemic such as the 1918 Spanish Flu could cost as much as 5 percent of the global GDP.

The threat comes from the known and the unknown. The World Health Organization has

warned that the next pandemic may be sparked by a pathogen we haven't yet seen, "Disease X," perhaps loitering in a once-hidden cave or mutating in a hog pen. The way to fight a new disease is the same as it is for a known foe: a coordinated response from a strong health system.

However, we are in danger of letting down our guard. Our country's commitment to preventing infectious disease epidemics is weakening. We continue to see proposals to scale back funding for programs designed to prevent, detect and respond to disease threats in the countries where they originate. This is a grave mistake. Even as one Ebola outbreak in the DRC was ending, another more intractable outbreak erupted in a conflict zone that is proving harder to contain. Failing to make necessary investments now will virtually guarantee that a future epidemic will cause great human suffering and be economically disastrous.

We must continue to invest in building strong health systems equipped with sufficient resources to catch the next deadly pathogen before it has a chance to get on an airplane and spread across continents. We need to adequately fund CDC operations overseas to help countries get and stay prepared for worst-case scenarios. And we must continue to fund USAID projects that complement this work with projects that strengthen governance and health services around the globe. Only then will we be safe to fly.

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VOICES

# Addressing Cultural Bias in Medicine

**We must overcome our inherent prejudices if we want to offer the best health care for all**

“What’s the deal with your people?”

As a second-year South Asian–American Muslim OB/GYN resident in training, I looked up through my scrub mask at the Caucasian female attending physician with whom I was operating as she asked this question.

I had an idea what she was referring to. I had overheard her complain earlier about a laboring patient while she was scrubbing with the other Caucasian attending who was operating in the room next door.

“She acts as if she has never had anything in her vagina, but clearly she has.”

The physician was referring to this recently immigrated South Asian patient, Aisha (name changed to protect patient identity), who was like many women I had been asked to examine: She was meek and, like any other woman in her first



labor, she was scared and uncomfortable.

This patient had a small introitus, or opening to the vagina, and had a difficult pelvic exam with an inability to relax her legs during the exam. She had always had pain with intercourse but revealed that she had been told this was normal.

Now, 15 years later, looking back with more knowledge and expertise, I see that this patient clearly had hypertonic pelvic floor muscles secondary to anxiety and fear. This resulted in vaginismus, or a tightening of the muscles of the vagina preventing entry, and it is likely she had a condition

called provoked vestibulodynia, or a type of nerve pain at the entry of the vagina when it is touched.

I would encounter many “Aishas” during my residency, and I always felt like the attending physicians involved would begrudgingly take care of “my people.” Yes, their pelvic exams were difficult, and each patient took extra time. But I found many of them did not receive the empathy and cultural sensitivity they needed in their health care delivery.

Many of the patients were from a culture of deference to the physician, so although they may have been uncomfortable, they went along with

whatever the doctor said. As a young resident, I never felt comfortable with the stereotype but also did not feel brave enough to say anything to these physicians—who were mostly Caucasian.

Regardless of ethnicity or culture, all physicians need to be aware of their inherent racial and gender-based biases and how these may impact managing women's sexual health issues and sexual dysfunction. They should also be aware of the cultural stigmas associated with sexual health and practices of their patient base in order to improve health care delivery.

For instance, sexual health topics such as intercourse, infections and even menstruation are still taboo in certain cultures, such as South Asian communities, Arab communities, native African communities and some conservative religious communities whether they be Muslim, Hindu, Jewish or Christian.

Women are less likely to address these issues of concern given their culture of origin. And even if they were, if a clinician approaches these patients with deep patriarchal perspectives or privileged bias, the patient may be less likely to discuss it with the clinician. In fact, some studies have demonstrated that health care providers' lack of cultural competence compounded with patients' beliefs has resulted in some American Muslim women not seeking cervical cancer screening or breast cancer screening at the same rates as other women.

Some physicians have become aware of their own privilege and bias when it comes to both their career advancements and patient care. In a recent article in the *Annals of Family Medicine*, Max J.

Romano, a Caucasian male doctor at the Johns Hopkins Bloomberg School of Public Health, says he had opportunities in his career and advancements he attributes to white privilege. He also discussed how racial stereotypes and bias have interfered in patient care, health care outcomes and life expectancy.

For instance, studies demonstrate that clinicians prescribe less pain medication to African-Americans than to their Caucasian counterparts for the same medical conditions. This is also attributed to racial stereotypes and pain responses of different races.

I take care of many women of color with chronic pelvic and sexual pain conditions. Many tell me they have never felt heard or adequately responded to by other physicians. Serena Williams recently claimed her race was a factor when she almost died due to postpartum complications of a pulmonary embolus (blood clot in her lungs) despite repeatedly explaining her symptoms to her health care team.

As a brown girl growing up in the South, I was subjected to a significant amount of racism. I always imagined that, once I had attended elite universities, then medical school and started practicing medicine, I would be less likely to see it and would be immune to it.

Working as a Muslim physician in the post-9/11 era, there were many times I would hear blatant racist statements or even subtle ones—such as during Ramadan when fasting—from certain patients and even from attending physicians.

Whether it was a joke about terrorism, discus-

sions about “towelheads” or opinions about female patients, their pelvic exams or their status, these comments were often made with minimal remorse.

It has become apparent that gender biases and sexual harassment are endemic in our culture. Many clinicians are also biased against women who come forward with sexual complaints. As physicians, each of us needs to be aware of his or her own biases in order to serve patients with the promise made during the Hippocratic Oath.

I own and operate a gynecology practice in Chicago; one of my specialties is treating patients with sexual dysfunction. “My people” tend to flock to me for their care and management.

Perhaps it is because of my background, cultural competence and experience, but I do know what’s “the deal” is with “my people.” I like to believe that having been brought up with egalitarian principles and a general calling to serve those in need, I am able to deliver unbiased health care equally to my patients.

This is not an indictment of the entire health care system. It is not broken when it comes to equality in health care delivery. But inherent biases impact how physicians perceive patients. Representation matters. Knowing there are like-minded medical professionals is a start. Empathy and goodwill toward all races and socioeconomic backgrounds cannot always be taught to individuals. Being aware of the discrimination and stereotypes is a stepping stone to breaking these barriers in health care.

That way every patient can best be served, regardless if her physician happens to be one of her own people.



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