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The Pain Gap

THE LATEST FINDINGS SHOW SIGNIFICANT DIFFERENCES IN HOW THE SEXES PROCESS PAIN

Plus:

FIGHTING CANCER WITHOUT CHEMO

A SMELL TEST FOR PARKINSON'S

CAN WE HACK CELLS TO CURE DISEASE?

WITH COVERAGE FROM nature

LIZ TORMES

Win-Wins Everywhere

In a special report on sex and gender in the September 2017 issue of Scientific American, Stanford University professor of medicine Marcia L. Stefanick wrote that “medical researchers and physicians have a lot of untangling to do before they can offer better health care to women.” The tangle she was referring to? The woeful lack of data on how women experience diseases, how they respond to medications and the widespread bias in the medical field when diagnosing women. Change in a positive direction over the past several decades has been slow but steady, leading to more women in clinical trials and new rules that require scientists to justify their choices in the sex of their experimental animals. And these improvements have been leading to some fascinating new information about how the sexes are wired. For example, as Amber Dance writes in “The Pain Gap,” the latest findings suggest that genetics, hormone levels and anatomical development may all be at work in how individuals across the sexes experience pain. Such discoveries illuminate beyond women’s experience, too. “A deeper understanding of sex differences will improve health directives for men,” Stefanick writes. It’s a win-win.

Elsewhere in this issue, social media is having a dramatic impact on how clinical trials are recruiting and are being run—patients and their families are having more of a say than ever (see “A Question of Control”). And a theoretical physicist and microbiologist have teamed up to make the case that those who forgo vaccinations should be barred from public or private schools, workplaces or other institutions in the U.S. (see “Opting Out of Vaccines Should Opt You Out of American Society”). After all, your vaccination protects not only you from deadly disease but all those around you. Sounds like another win-win.

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Health & Medicine

Your Opinion Matters!

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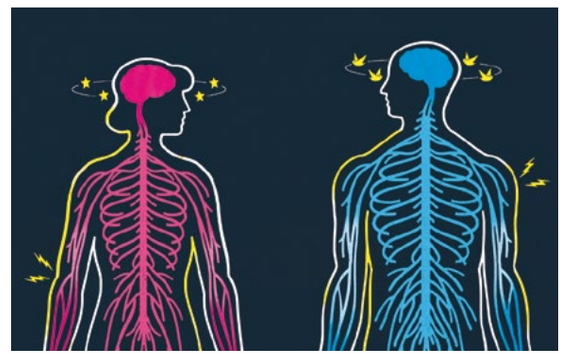
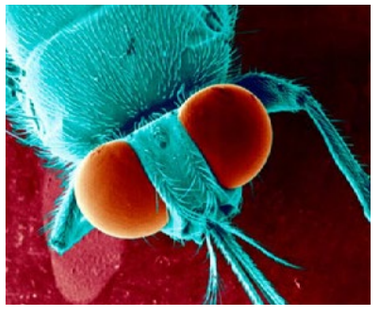


CHRIS GASH

On the Cover

The latest findings show significant differences in how the sexes process pain



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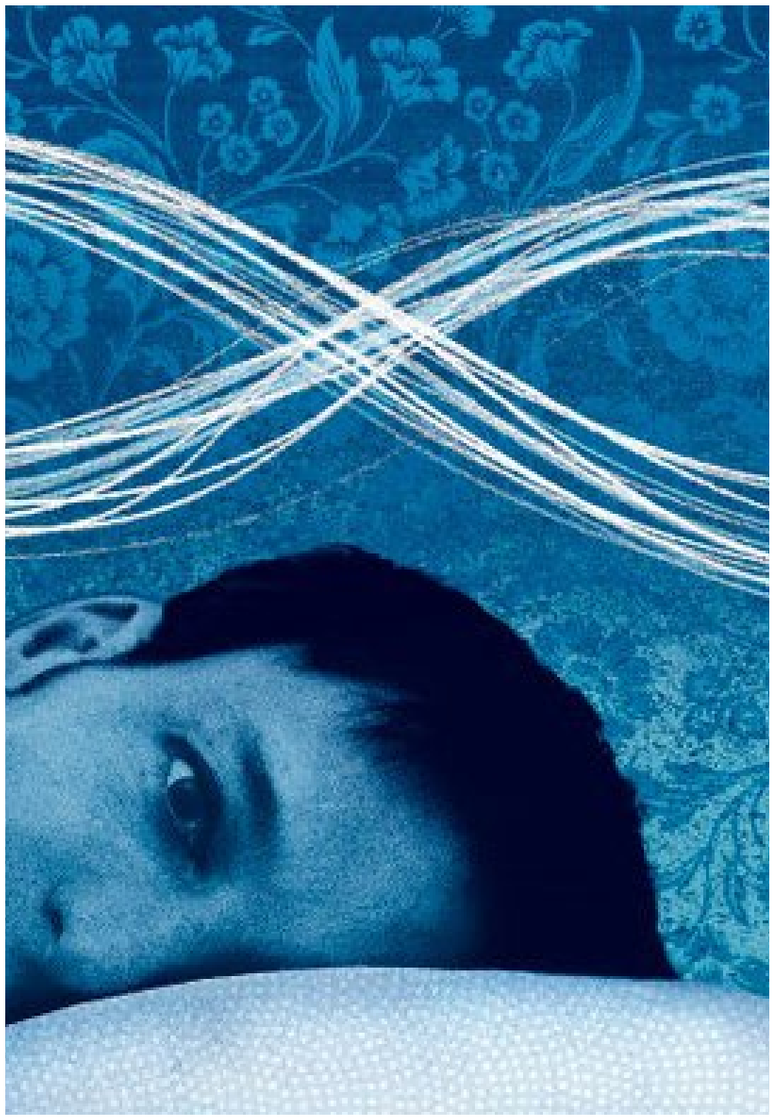

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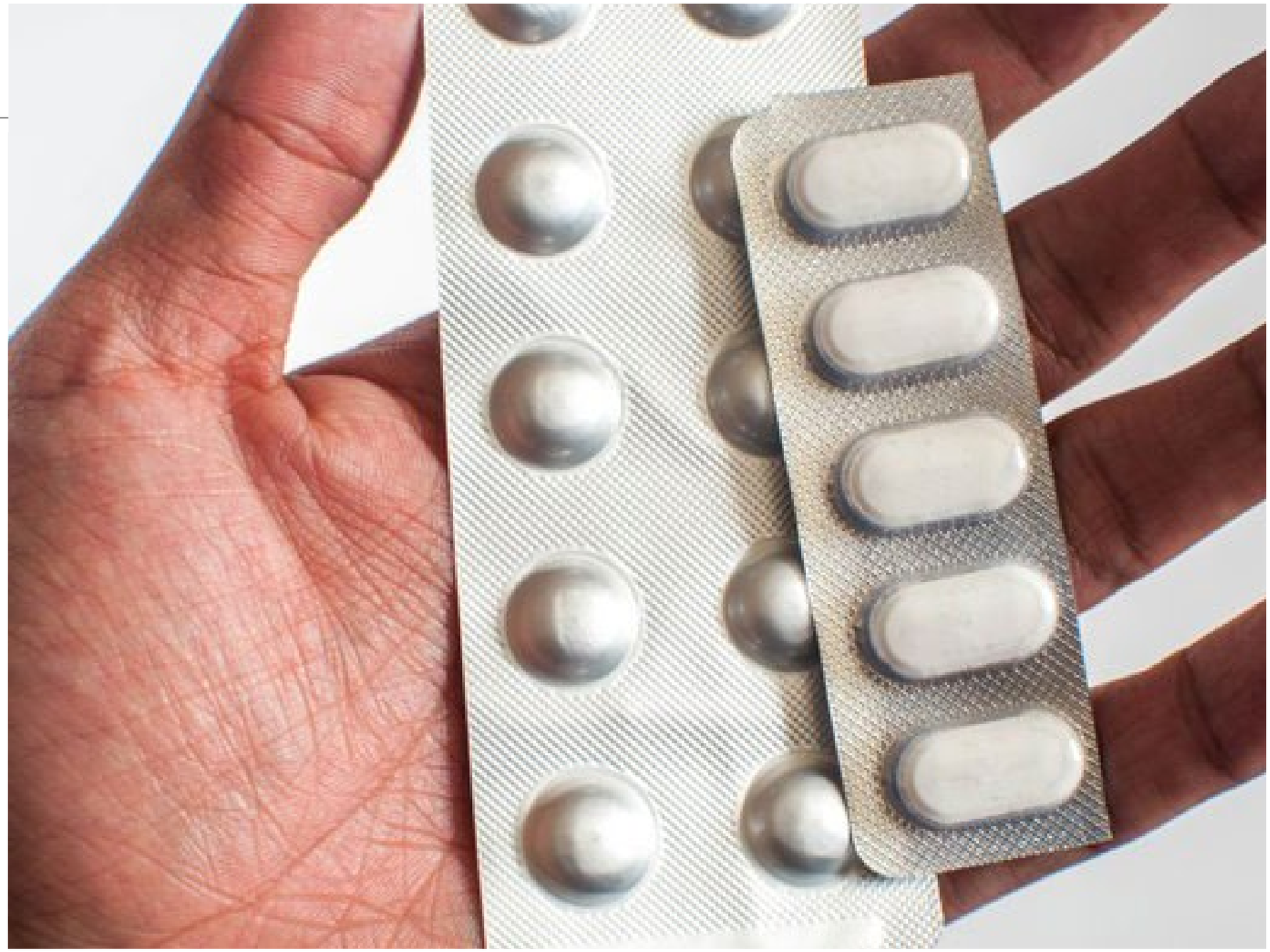
How Drug Company Ads Downplay Risks

A study shows the power of the "argument dilution effect"



KARL TAPALES *GETTY IMAGES*

"FEELING DOWN," "Feeling irritable," "Trouble getting up in the morning?" "Depression hurts," "Drug X can help," "Speak to your doctor about Drug X." These 60-second appeals are an ubiquitous part of the U.S. television experience. This is because, in the U.S., pharmaceutical companies can lawfully market prescription medications to the public through direct-to-consumer (DTC) advertising. Critics have charged that doctors should decide prescription medications without being influenced by patient requests. Citing their proliferation as the main culprit for increasing patient demand for advertised drugs, the American Medical Association has advocated for a ban on DTC ads. But the pharmaceutical companies argue that patients have the right to know their options and thus benefit from these commercials.

The ability to market prescription drugs creates an incentive for pharmaceutical companies to amplify the benefits of a drug without discussing its potential side effects. To counteract this, in the late 1990s the U.S. Food and Drug Administration regulated these ads by stipulating they present a fair balance between the benefits and risks (that is, side effects and contraindications) associated with a drug: the space in print media, and the airtime on broadcast media, allotted to listing its risks or side effects should be equivalent to the space and time allotted to its benefits. The assumption was that listing all side effects of a drug balances an inflated impres-

sion of its efficacy, allowing consumers to make an informed decision.

But the FDA's belief that more risk information leads to greater concern about risk is misplaced. Across six experiments, comprising more than 3,000 U.S. participants, we reliably found that when drug commercials included all side effects (both major and minor), in line with the FDA's regulations, consumers judged the overall severity of the side effects to be *lower* than when they were exposed to only major ones. This lowered assessment of severity led consumers to prefer the drug more—and made them willing to pay more for it.

It is well established that people are susceptible to a range of cognitive and psychological biases that stray decisions from rationality. One such bias is the argument dilution effect. This bias is especially consequential when making social and nonsocial judgments about a target with an array of information that is both relevant and irrelevant to the decision. In such situations, our conclusions about the target are roughly based on averaging both the relevant and irrelevant information instead of ignoring the latter. In other words, the irrelevant information dilutes the value and importance of the relevant information. Initially documented by Richard Nisbett of the University of Michigan and his colleagues, the argument dilution effect's ubiquity in impacting social and nonsocial judgments is well established. For instance, imagine having to assess the grade point average of the following two students. You are either told that "Tim spends about 31 hours studying outside of class in an average week," or that "Tom spends 31 hours studying outside of class in an average week. Tom has one brother and two sisters. He visits his grandparents once every three months. He once went on a blind date and shoots pool about once every two months." When participants in a study by Henry Zukier, then at the New School for Social Research, were presented with these options, Tim was rated as having a significantly higher GPA than Tom. The irrelevant information around Tom's grandparents and his casual play of pool "*diluted*" the value and importance of the relevant information—his study habits.

We wanted to know if the dilution effect also plays a role in DTC commercials. The FDA regulation to list all potential side effects of the drugs in a DTC commercial inadvertently resulted in these commercials describing both major (for example, stroke, heart attack, thoughts of suicide) and comparatively minor (for example, dry mouth and headache) side effects. Building on argument dilution as the underlying psychological bias, we hypothesized that listing both major and minor side effects would dilute consumers' judgments of the overall severity of the drug's side effects, compared with when only major side effects are presented.

In one experiment, American participants heard an audio commercial for Cymbalta—a drug that treats depression and has been marketed via DTC advertising. Half of the participants heard the original commercial in its entirety (78 seconds), while the other half heard a 4 percent shorter commercial (75 seconds) that removed mention of the three minor side effects. Those who heard the commercial in its entirety rated the drug lower in its overall severity of side effects, compared with those who heard the 4 percent shorter version. In addition, the lower overall assessment of severity increased the attractiveness of the drug for that group in comparison with those who heard the shorter commercial.

A follow-up study employed a different advertising medium by having participants read an actual print ad for the drug Lunesta, which is used to treat sleep disorders. Once again, half of the participants read the entire ad, which included four side effects (two major and two minor), while the other half read an ad that included just the two major ones. Again, reading the ad with more side effects, including minor ones, caused participants to rate the drug less in overall severity and more in appeal.

These findings raise the ethical and practical dilemma of achieving transparency with the consumers by sharing all potential side effects, while safeguarding them against argument dilution bias. Hence, we performed an additional study to explore how this might be achieved. If individuals can cognitively place greater weight to the major side effects than the minor ones, the averaging process of the argument dilution effect should attenuate. Thus, to draw greater attention and emphasis to the major side effects, we listed them in a red boldfaced font and set minor ones in

a black regular font. Participants who saw major and minor side effects in different fonts rated the drug similar in severity, compared with those who only saw the major side effects. So by drawing greater attention to the major side effects, we were able to overcome the argument dilution effect while ensuring that all side effects associated with the drug were communicated to consumers.

With the industry annually spending billions of dollars on DTC ads, it is not surprising that they have resulted in increased patient demands for the drugs featured in them. These results add to the chorus for the redrafting of policies surrounding the communication of pharmaceutical drugs' risk. More broadly, this work draws caution to other forms of risk communication that extends beyond DTC: from physicians who have to communicate varying risks of an experimental procedure, to financial advisers who need to make retirees aware of different perils in the financial products they intend to invest in, to public service advertisements that attempt to highlight the risk associated with life choices.

—Niro Sivanathan and Hemant Kakkar

Should We Kill Off Disease-Causing Pests? Not So Fast

Eradicating harmful species may have unintended consequences

SLEEPING SICKNESS (or trypanosomiasis), endemic to sub-Saharan Africa, is a horribly debilitating disease. When the parasitic protozoan that causes it gets into the nervous system and brain, weeks or months after being transmitted by the blood-eating tsetse fly, it sends the victim into a steep decline marked by depression, aggressiveness, psychotic behavior, disrupted sleep patterns and—if untreated—death.

Happily, a concerted multinational effort has reduced the reported incidence of the disease by 92 percent in this century, from 26,550 cases in 2000 to just 2,164 cases in 2016. That puts the fight against sleeping sickness on track to meet the World Health Organization (WHO) goal of eliminating it by 2020, according to a study published last December in *PLOS Neglected Tropical Diseases.* Thanks to increasingly sophisticated methods of reducing the population of tsetse flies, the area where people are at risk of infection has also decreased by 61 percent in the same period.

Why not just finish the job and end sleeping sickness by eradicating the tsetse (pronounced TET-see) fly from the entire African continent? This is the stated goal of the African Union's Pan African Tsetse and Trypanosomiasis Eradication Campaign. But another new study, published last December in *BioScience*, calls for reexamining that approach. "The important ethical question remains: Is tsetse fly elimination morally appropriate?" entomologist Jérémy Bouyer and his co-authors wrote. The study lays out a protocol for properly considering a question that is less simple and more momentous than it seems at first glance, says Bouyer, who spent seven years in tsetse control in Senegal and now works on pest-control programs for the International Atomic Energy Agency (IAEA).

For one thing, tsetse fly eradication is not about getting rid of a single species—but rather an entire taxonomic family called Glossinidae, with 31 species and subspecies across Africa. Conservationists commonly eradicate introduced or invasive

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species from habitats where they do not belong; but tsetse flies are native to Africa, the study notes, and have "a complex biology and unique evolutionary history."

The female rears one larva at a time in her abdomen and "lactates," a little like a mammal, to feed it in utero. When she eventually evicts the larva, she has provisioned it with enough food to burrow underground, mature as a pupa and emerge as an adult fly a month or so later. These traits help demonstrate what conservationists call "intrinsic value"—meaning both the worth a species gives to its own life experience and the worth of its evolutionary and ecological character as a unique species.

But making a case for intrinsic value proved elusive as the researchers were developing their protocol for thinking about tsetse fly eradication, says study co-author Neil Carter of Boise State University. It is easier to quantify "instrumental value"—the costs and benefits of a species for humans, other species and ecosystems. On the one hand, for example, tsetse flies can be devastating for livestock as well as people; eliminating these insects on the island of Zanzibar made it possible for many more small farmers there to keep cattle, raising their income by 30 percent. On the other hand, getting rid of tsetse flies can lead to increased cattle encroachment into natural areas where they conflict with wildlife.

After considering a long list of such pros and cons, the study concludes, "arguments predicated entirely on instrumental value do not provide compelling support for global tsetse fly eradication." But the study says it is "morally justified" to identify areas where tsetse flies pose a threat and then control or eliminate local populations.

For the authors, the main point is it is important to think through the ethical and practical implications rather than simply acting on the initial impulse to eradicate a pest. For instance, Carter says, it might seem like common sense to eliminate leopards from a national park in the middle of Mumbai, India—which has grown up around the park into a city of 20 million people. But it turns out the leopards feed largely on the city's thriving population of feral dogs. So losing the predators could dramatically increase incidence of dog bites and rabies.

It is almost impossible to predict the future instrumental value of a species. The fer-de-lance, for instance, was once considered just another deadly South American viper. But beginning in the 1980s its venom became the source for the first ACE inhibitor drugs, a life-changing treatment for cardiovascular disease. Carter says he is optimistic about humans' increasing willingness "to be transparent about all the benefits and costs" of a pest species "and come to a conclusion as a community, rather than having to say, 'Oops, it's too late.'"

Glyn Vale, former director of Tsetse and Trypanosomiasis Control for Zimbabwe's Department of Veterinary Services, says he welcomes the study's stand against eradication. But he is also sharply critical of Bouyer's employer, the IAEA, for heavily promoting the "sterile insect technique"—a method for disrupting insect reproduction by releasing large numbers of flies that have been sterilized by irradiation. That technique is far too expensive, he says, adding it is ineffective in tsetse flies and does more to boost the IAEA's agenda of demonstrating peaceful uses of atomic energy than it does to improve the health of people in Africa. Bouyer says he began work on the study well before joining the IAEA, and the study is not about the sterile insect technique but about the ethics of eradication.

"People have been trying to get rid of tsetse flies for 100 years, and they haven't succeeded so far," says Michael Barrett, a University of Glasgow trypanosomiasis expert who was not involved in the study. The biggest recent successes, he says, have come from "insecticide-impregnated tiny targets"—inexpensive handkerchief-size bits of blue fabric set out on sticks in areas infested by the tsetse fly. The flies are attracted to the color and pick up the insecticide on landing, resulting in "incredible decreases in the number of tsetse flies and the incidence of disease," he notes.

Barrett, who chaired the WHO's 2018 working group to eliminate the disease, is also optimistic about an epidemiological technique that calculates how frequently the disease gets transmitted by tsetse fly bite from one person to another. Mathematical modeling of the infection makes it possible to estimate the required reduction in tsetse fly

numbers to bring transmission down to zero. It eliminates the disease, but not necessarily the flies themselves.

One other cause for optimism stems from improving treatments for sleeping sickness, which comes in two varieties. Current treatments are inconvenient at best. One type of the disease requires intravenous injection two to four times a day for at least a week—a challenge in the remote, isolated and impoverished areas where sleeping sickness is most common. Another type requires an injection so painful it has been likened to having chili peppers injected straight into the heart; it also kills one patient in 20. But late last year the European Medicines Agency approved a new drug called fexinidazole in pill form, for use in the first type of sleeping sickness. Approval for its use in treating the other type is expected soon, and approval for use by individual countries in Africa appears likely to follow.

Such developments could make the proposed eradication of tsetse flies seem not just impractical but also, in the not too distant future, irrelevant.

—Richard Conniff

A Genetic Basis for Insomnia Emerges from the Twilight

Gargantuan studies show links between sleep difficulties and cardiovascular and psychiatric illnesses

AROUND A THIRD OF people complain of some sleeplessness, and one in 10 meets diagnostic criteria for clinical insomnia. The costs, in terms of well-being, physical health and productivity, are enormous. From twin studies, researchers know the inability to fall or stay asleep has a genetic component, but the identities of the culprits were mostly unknown.

Now, two studies published in March in *Nature Genetics* provide first peeks at the biological basis of insomnia, implicating specific brain regions and biological processes, and revealing links with heart disease and psychiatric disorders like depression. Both are genome-wide association studies (GWASs), which examine DNA from many thousands of individuals to determine where genetic markers related to health, disease or a particular trait reside.

The first study, from a team led by geneticist Danielle Posthuma of Vrije University Amsterdam, analyzed the genomes of over 1.3 million people, making it the largest GWAS of any complex trait to date. They used data from the UK Biobank, a large, long-term genetics project, and from the direct-to-consumer genetics company 23andMe to identify 202 areas of the genome linked to insomnia, implicating 956 genes, a big advance from the seven found previously. "I'm pretty confident the vast majority of these are real," says geneticist Stephan Ripke, a GWAS expert at the Berlin Institute of Health who was not involved

LIZZIE ROBERTS *GETTY IMAGES*

in either study. “But we need to confirm this in more, separate cohorts from different countries and researchers.”

The researchers then investigated which brain regions and cells these genes frequently turn up in. This analysis implicated the axons (output connections) of neurons as well as parts of the cortex and deeper “subcortical” brain regions like the striatum, involved in movement. It also tagged “medium spiny neurons,” which occupy most of the striatum as well as neurons in other regions, including the hypothalamus. These findings tally with brain-imaging studies suggesting dysfunction of some regions in insomnia and with animal studies implicating these cells in sleep regulation. “Before our study we knew little about which genes, pathways and cells were involved,” Posthuma says. “We now have concrete hypotheses that can be tested.”

The second study, from a team led by geneticist Richa Saxena of Massachusetts General Hospital, interrogated over 450,000 genomes, again from the UK Biobank. They identified 57 regions, implicating 236 genes, and confirmed these results in analyses of two separate data sets. One of these used clinically diagnosed patients, a contrast to the other data compendium that was based on less reliable, self-reported symptoms. The team went further by analyzing data from nearly 84,000 UK Biobank participants who had worn motion detectors for a week to observe tossing and turning or sleepwalking, enabling them to link genetic findings with actual measures of sleep. “This shows the findings are valid for different definitions of insomnia-related symptoms, including some that are measured objectively,” according to Virginia Commonwealth University statistical geneticist Mackenzie Lind.

The two studies found significant overlap between genes implicated in insomnia and those related to psychiatric and metabolic traits. Genes for traits, including depression, anxiety, schizophrenia, coronary artery disease and type 2 diabetes, were sometimes the same. The findings suggest insomnia is more strongly related to neuropsychiatric disorders than to other sleep-related traits such as whether someone is a morning person. “That was a big surprise,” Saxena says. “Implying that at the genetic level it’s a disorder that’s likely linked to psychiatric disease and mood regulation, and it’s not necessarily just about sleep regulation.”

“The genetic overlap is sound. But there’s debate about these Mendelian randomization tests; I wouldn’t take this for granted.”
—Stephen Ripke

Both teams also used a technique (Mendelian randomization) that allowed them to infer what might be causing what by comparing their findings with GWAS results for other conditions. The two studies found insomnia may cause depression and coronary artery disease, and the larger study also found causal risk effects for BMI (body mass index) and type 2 diabetes. “One of the motivations for using genetics to study sleep was to tease apart where it’s causal where it’s not,” Saxena says. “So eventually interventions can be targeted to areas where things are causal.” Not all researchers are confident in these tests, however. “The genetic overlap is sound,” Ripke says. “But there’s debate about these Mendelian randomization tests; I wouldn’t take this for granted.”

Both studies implicated a gene involved in restless leg syndrome, which “makes sense, given it’s also a sleep disturbance,” Saxena says, although her team also found this may have been partly due to undiagnosed cases of RLS in their data sets. In fact, it is probable insomnia is not a singular condition but a cluster of symptoms grouped together, which can have a range of underlying causes. It could be a consequence of childhood trauma in one patient, due to disrupted circadian processes in another or just resulting from restless leg syndrome in another. “If that’s the case, then we’ll really be able to dissect that with the genetics,” she says. “Understanding if there are different types of insomnia, and how can we study them and maybe treat them separately, that’s the hope for the whole field.”

Going forward, these findings provide entry points for researchers

to dive into the biology of insomnia. "We're following two strategies now," Posthuma says. Implementation is proceeding by "increasing sample size even further," she notes, "and setting up lab experiments to prove causation and show how implicated cell types influence insomnia." Studies like this may illuminate new therapeutic targets. Although treatments exist, access to therapies like cognitive-behavioral therapy cannot meet existing demand.

The behavioral therapy demonstrates, however, why this line of research is worth pursuing. The genetic overlap between insomnia and mood disorders may point toward why cognitive-behavioral therapy may be effective for both sleep and anxiety. Current drugs, for their part, have limited efficacy, can be addictive and have side effects. "Identifying new variants that contribute to risk helps pinpoint new biological targets," Lind says. This search, she adds, is "a step toward the eventual goal of using genetic information to predict risk and treatment outcomes, although we're not at this point yet."

—*Simon Makin*

The Adult Brain Does Grow New Neurons After All, Study Says

Study points toward lifelong neuron formation in the human brain's hippocampus, with implications for memory and disease

IF THE MEMORY CENTER of the human brain can grow new cells, it might help people recover from depression and post-traumatic stress disorder (PTSD), delay the onset of Alzheimer's, deepen our understanding of epilepsy and offer new insights into memory and learning. If not, well then, it's just one other way people are different from rodents and birds.

For decades, scientists have debated whether the birth of new neurons—called neurogenesis—was possible in an area of the brain that is responsible for learning, memory and mood regulation. A growing body of research suggested they could, but then a *Nature* paper last year raised doubts.

Now, a new study published in March in another of the Nature family of journals—*Nature Medicine*—tips the balance back toward "yes." In light of the new study, "I would say that there is an overwhelming case for the neurogenesis throughout life in humans," Jonas Frisén, a professor at the Karolinska Institute in Sweden, said in an e-mail. Frisén, who was not involved in the new research, wrote a News and Views about the study in the March issue of *Nature Medicine*.

Not everyone was convinced. Arturo Alvarez-Buylla was the senior author on last year's *Nature* paper, which questioned the existence of neurogenesis. Alvarez-Buylla, a professor of neurological surgery at the University of California, San Francisco, says he still doubts that new neurons develop in the brain's hippocampus after toddlerhood.

"I don't think this at all settles things out," he says. "I've been studying adult neurogenesis all my life. I wish I could

Cerebral cortical neuron.

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find a place [in humans] where it does happen convincingly."

For decades, some researchers have thought that the brain circuits of primates—including humans—would be too disrupted by the growth of substantial numbers of new neurons. Alvarez-Buylla says he thinks the scientific debate over the existence of neurogenesis should continue. "Basic knowledge is fundamental. Just knowing whether adult neurons get replaced is a fascinating basic problem," he says.

New technologies that can locate cells in the living brain and measure the cells' individual activity, none of which were used in the *Nature Medicine* study, may eventually put to rest any lingering questions.

A number of researchers praised the new study as thoughtful and carefully conducted. It's a "technical tour de force" and addresses the concerns raised by last year's paper, says Michael Bonaguidi, an assistant professor at the University of Southern California Keck School of Medicine.

The researchers, from Spain, tested a variety of methods of preserving brain tissue from 58 newly deceased people. They found that different methods of preservation led to different conclusions about whether new neurons could develop in the adult and aging brain.

Brain tissue has to be preserved within a few hours after death, and specific chemicals used to preserve the tissue, or the proteins that identify newly developing cells will be destroyed, said María Llorens-Martín, the paper's senior author. Other researchers have missed the presence of these cells, because their brain tissue was not as precisely preserved, says Llorens-Martín, a neuroscientist at the Autonomous University of Madrid in Spain.

Jenny Hsieh, a professor at the University of Texas San Antonio who was not involved in the new research, said the study provides a lesson for all scientists who rely on the generosity of brain donations. "If and when we go and look at something in human postmortem, we have to be very cautious about these technical issues."

Llorens-Martín said she began carefully collecting and preserving brain samples in 2010, when she realized that many brains stored in brain banks were not adequately preserved for this kind of research. In their study, she and her colleagues examined the brains of people who died with their memories intact, and those who died at different stages of Alzheimer's disease. She found that the brains of people with Alzheimer's showed few if any signs of new neurons in the hippocampus—with less signal the further along the people were in the course of the disease. This suggests that the loss of new neurons—if it could be detected in the living brain—would be an early indicator of the onset of Alzheimer's, and that promoting new neuronal growth could delay or prevent the disease that now affects more than 5.5 million Americans.

Rusty Gage, president of the Salk Institute for Biological Studies and a neuroscientist and professor there, says he was impressed by the researchers' attention to detail. "Methodologically, it sets the bar for future studies," says Gage, who was not involved in the new research but was the senior author in 1998 of a paper that found the first evidence for neurogenesis. Gage says this new study addresses the concerns raised by Alvarez-Buylla's research. "From my view, this puts to rest that one blip that occurred," he says. "This paper in a very nice way… systematically evaluates all the issues that we all feel are very important."

Neurogenesis in the hippocampus matters, Gage says, because evidence in animals shows that it is essential for pattern separation, "allowing an animal to distinguish between two events that are closely associated with each other." In people, Gage says, the inability to distinguish between two similar events could explain why patients with PTSD keep reliving the same experiences, even though their circumstances have changed. Also, many deficits seen in the early stages of cognitive decline are similar to those seen in animals whose neurogenesis has been halted, he says.

In healthy animals, neurogenesis promotes resilience in stressful situations, Gage says. Mood disorders, including depression, have also been linked to neurogenesis.

Hsieh says her research on epilepsy has found that newborn neurons get miswired, disrupting brain circuits and causing seizures and potential

memory loss. In rodents with epilepsy, if researchers prevent the abnormal growth of new neurons, they prevent seizures, Hsieh says, giving her hope that something similar could someday help human patients. Epilepsy increases someone's risk of Alzheimer's as well as depression and anxiety, she says. "So, it's all connected somehow. We believe that the new neurons play a vital role connecting all of these pieces," Hsieh says.

In mice and rats, researchers can stimulate the growth of new neurons by getting the rodents to exercise more or by providing them with environments that are more cognitively or socially stimulating, Llorens-Martín says. "This could not be applied to advanced stages of Alzheimer's disease. But if we could act at earlier stages where mobility is not yet compromised," she says, "who knows, maybe we could slow down or prevent some of the loss of plasticity [in the brain]."

—Karen Weintraub

Antiaging Discovery Could Lead to Restorative Skin Treatments

Loss of collagen protein depletes renewal cells that serve as skin's fountain of youth

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DESPITE A MULTIBILLION-DOLLAR skin care industry and plenty of marketing claims, nothing exists that can prevent our skin from turning into tissue paper as we age—except, perhaps, religiously wearing sunscreen. Accumulated damage from UV radiation and other age-related stressors drains the skin's pool of renewal cells—or stem cells—and there is no way to stop or slow this process.

But hope for skin care junkies is on the horizon. A study published April 3 in *Nature* provides new insight into how stem cell loss occurs and even identifies two chemicals that may be able to prevent it.

The research, led by Emi Nishimura, a professor of stem cell biology at Tokyo Medical and Dental University in Japan, revealed that aging and UV exposure deplete stem cells of a crucial collagen protein. Skin aficionados may recognize collagen as a key player in maintaining strong, youthful, elastic skin. The weakened stem cells no longer divide normally and are ultimately forced to turn into adult skin cells. Over time, so many stem cells become damaged that there aren't enough healthy ones to replace them.

"I think it's a beautiful study," says David Fisher, a professor of dermatology at Harvard Medical School who was not involved in the research. "I think it's a very elegant analysis, but also it has some very practical mechanistic insights into how this is happening, and even potentially actionable ones to promote youthfulness."

Our skin is divided into two sections: the epidermis on top and the dermis underneath. The epidermis is what we conventionally think of as our skin and is made up of many layers of cells, while the dermis consists of connective tissue, hair follicles, blood vessels, and sweat glands.

As part of normal skin health, the top layer of the epidermis is constantly being sloughed off and replaced from a self-replenishing pool of stem cells that hangs out on the bottom (or basal) layer. These stem cells have roots that anchor them to a thin piece of tissue called the basement membrane that connects the epidermis and the dermis. The tether to the basement membrane is essential for maintaining a cell's "steminess"—its ability to replicate and mature into another type of cell.

Most of the time, the stem cells in the epidermis divide horizontally, cloning themselves and adding to the renewal pool. Sometimes, though, they divide vertically, and the new cell starts to mature into an adult skin cell, which is gradually pushed up through the layers of the epidermis.

This type of cell turnover—replacing older cells at the top of the epidermis with younger cells from the bottom—explains how cuts heal and skin stays young-looking. As people age, however, the pool of stem cells becomes depleted and cell turnover slows, eventually leaving people with thin, fragile skin.

"The ultimate question, which [the study is] trying to address, is why are there fewer cells? Why do we lose stem cells as we get older?" says Terry Lechler, an associate professor of dermatology at Duke University who was not involved in the research. "I think that's the real crux and the really interesting question."

The study suggests that the stem cells that divide vertically do so because they are damaged through regular aging and the normal cell turnover process, as well as exposure to UV light or other types of toxins. And not only does the new adult cell start its journey through the epidermis, the original stem cell also gets pushed off of the basal layer, forcing it to mature. This is because the damaged stem cell's roots have become weakened, so it can no longer sufficiently anchor to the basement membrane. The researchers describe this step as a kind of competition, the neighboring healthy stem cells banding together and forcing the weak stem cell off of the island.

"It appears that this is due to a quality-control mechanism whereby a skin stem cell that gets damaged is basically purged from the skin," says James DeGregori, a professor of biochemistry at the University of Colorado Denver who wrote a commentary article to accompany the paper. "You could almost imagine all of these stem cells are kind of jostling for position, and if you're really gripping that basement membrane, you're going to do better."

At first this competition is beneficial, ridding the skin of malfunctioning cells or even cancer-causing mutations. At a certain point, however, too many stem cells become damaged, and they begin to outnumber the healthy ones. When this happens, the skin can no longer effectively rejuvenate itself or respond to injury. "Stem cell competition between epidermal stem cells sustains skin youthfulness, but the decline of the competition ends up with skin aging," Nishimura explains.

The linchpin in this process is collagen 17, a specific type of collagen protein that is critical for rooting the stem cell to the basement membrane. As stem cells become damaged, they lose precious amounts of collagen 17. The more protein they lose, the weaker their bond to the basement membrane, until eventually they are forced out by neighboring healthy cells.

The good news is that there may be a way to increase or preserve levels of collagen 17 in stem cells, staving off this process of skin aging. Nishimura showed that two experimental chemicals, Y27632 and apocynin, applied topically can increase collagen 17 levels in cells and even promote wound healing.

This does not mean you should purchase the next skin care product you see that has "collagen" or "stem cells" on the label—there is no evidence that anything on the market affects this pathway. But it does suggest a scientifically backed rejuvenating cream could be on the horizon.

—Dana G. Smith

A New Way to Detect Parkinson's—by Smell

Discovery of odorous markers for neurodegenerative disease

SCENT HAS BEEN USED as a diagnostic tool by physicians for thousands of years. But smell tests are not common in modern medicine—when's the last time you were smelled by your doctor or received a batch of smell results back from the lab? Now, new research suggests that odors can be used to screen for Parkinson's disease, which currently is without a definitive diagnostic.

In the animal kingdom, scents emitted from a body often signal information about an individual's mental or physical state. For example, stressed rodents have been shown to excrete distinctive odors. Human body odors also have this function, emitting a wide array of odor- and nonodor-related chemicals called volatile organic compounds. These compounds are emitted from different areas of the human body and vary with age, diet, sex and possibly genetic background. Moreover, disease processes can influence our daily odor by changing these compounds.

So, it is perhaps not surprising that physicians have used their sense of smell to diagnose patients. In ancient Greece, Hippocrates—of the eponymous medical oath—recognized the diagnostic usefulness of body odors and reported on several disease-specific smells from urine. In an experiment published in 1776, English doctor Matthew Dobson evaporated a diabetes patient's urine, yielding a white, granulated powder that smelled and tasted like sugar. More recently, the composition of exhaled breath was shown to be different in patients with lung cancer, inflammatory lung or liver disease, hepatic or renal dysfunction, or diabetes. However, there has been little evidence to tie scent to diseases of the nervous system, with the possible exception of schizophrenia—although controversial, it has long been claimed that these patients have a particular peculiar odor.

Here's where Joy Milne comes in, a woman who first noticed a "musky" smell on her husband, Les, who was diagnosed years later with Parkinson's disease. It turns out that Joy

GETTY IMAGES

can distinguish the unique Parkinson's odor before clinical symptoms appear in a person's sebum—the moisturizing, waterproofing wax that protects the skin produced by sebaceous glands. Characterizing the compounds linked to this distinctive odor in sebum could enable rapid, early screening of Parkinson's disease as well as provide insights into changes that occur as the disease progresses. Which is exactly what researchers were able to do—chemically define the scent in sebum that Milne is picking up on in Parkinson's patients.

In preliminary tests to identify the origin of the scent, Joy inspected T-shirts and medical gauze that had sampled the upper backs of Parkinson's patients. The odor was not present in the armpits and instead was on the forehead and upper back—not surprisingly, areas of high

sebum production. The researchers then tested and compared the sebum samples from the upper backs of 43 Parkinson's patients and 21 matched healthy subjects to discover volatile organic compounds linked to disease. To investigate the aroma-causing chemicals, the researchers used a sophisticated analytical technology: thermal desorption-gas chromatography-mass spectrometry. With it, the researchers shortened the list of Parkinson's smell-causing candidates from the hundreds to just 17. Joy confirmed that mixing all 17 identified chemicals, or specific combinations of just nine or four, closely matched the musky fragrance she smelled on Parkinson's patients, demonstrating that, indeed, these chemicals contribute to the unique smell associated with Parkinson's.

This study highlights the potential of analyzing the sebum from Parkinson's patients and raises the possibility that individuals can be screened noninvasively using a diagnostic device with a nose for these odor-based biomarkers. Such a device could allow earlier diagnosis and treatment to prevent the disease from progressing to stages with severe symptoms. However, with samples from just over 60 people, the current study is limited by sample size. The next steps are to study the sebum of more patients for an odor signature to establish a panel of odor-based biomarkers associated with Parkinson's disease.

Without an objective test, such as a blood test or brain scan, to make a definitive diagnosis of Parkinson's disease, doctors instead look for key neurological symptoms. But the misdiagnosis rate remains significant because the symptoms are similar to other neurological conditions, and patients cannot be treated until symptoms manifest. As the foundation of a diagnostic medical device, odorous biomarkers for Parkinson's can open new avenues for facilitating earlier detection of the disease to prevent progressive neurodegeneration and motor symptoms, such as tremor.

However, the concept of using disease-associated odorous biomarkers as the basis for a medical device has been simmering for nearly 40 years but has so far come up empty-handed. Since the 1980s, devices called "electronic noses" that mimic the human olfactory system have been developed but have only been used for research purposes. In the future, the development of new sensors with improved sensitivity could make the electronic nose an effective clinical tool for the early detection of Parkinson's and other health problems such as infections, tumors and exposure to toxic agents. An electronic nose with the accuracy to identify specific volatile organic compounds has the potential to yield a catalog of diagnostic odorous biomarkers for patients with diseases that cannot be diagnosed with traditional clinical tools.

—Jonathan D. Grinstein

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After decades of assuming that pain processing is equivalent in all sexes, scientists are finding that different biological pathways can produce an "ouch!"

By Amber Dance

The Pain Gap

CHRIS GASH

Amber Dance is a freelance writer in Los Angeles.

ROBERT SORGE WAS STUDYING PAIN IN MICE IN 2009, but he was the one who ended up with a headache.

At McGill University in Montreal, Canada, Sorge was investigating how animals develop an extreme sensitivity to touch. To test for this response, Sorge poked the paws of mice using fine hairs, ones that wouldn't ordinarily bother them. The males behaved as the scientific literature said they would: they yanked their paws back from even the finest of threads.

But females remained stoic to Sorge's gentle pokes and prods. "It just didn't work in the females," recalls Sorge, now a behaviorist at the University of Alabama at Birmingham. "We couldn't figure out why." Sorge and his adviser at McGill University, pain researcher Jeffrey Mogil, would go on to determine that this kind of pain hypersensitivity results from remarkably different pathways in male and female mice, with distinct immune-cell types contributing to discomfort.

Sorge and Mogil would never have made their discovery if they had followed the conventions of most pain researchers. By including male and female mice, they were going against the crowd. At the time, many pain scientists worried that females' hormone cycles would complicate results. Others stuck with males because, well, that's how things were done.

Today, inspired in part by Sorge and Mogil's work and spurred on by funders, pain researchers are opening their eyes to the spectrum of responses across sexes. Results are starting to trickle out, and it's clear that certain pain pathways vary considerably, with immune cells and hormones having key roles in differing responses.

This push is part of a broader movement to consider sex as an important variable in biomedical research, to ensure that studies cover the range of possibilities rather than gleaning results from a single population. A major change came in 2016, when the U.S. National Institutes of Health (NIH) made it a requirement for grant applicants to justify their choice of the sex of animals used in experiments. The discoveries in pain research are among the most exciting to emerge, says Cara Tannenbaum, scientific director of the Institute of Gender and Health in Montreal, part of the Canadian Institutes of Health Research. And of Sorge and Mogil's work, she adds, "To my knowledge, no other field of science has identified this type of sex difference."

The research could open the door for new medical advances, adds Tannenbaum. These are sorely needed: some 20 percent of people worldwide experience chronic pain—and the majority are women. Today, the pharmaceutical market offers the same pain drugs to everyone. But if the roots of pain are different, some drugs might work better in some people than in others.

Moreover, people might require different pain medications when hormone levels fluctuate through life. And a person's sex doesn't always fit clearly into the categories of male and female: it is determined by a spectrum of characteristics, including genetics, anatomical development and hormone levels, each of which might affect a person's needs in pain therapy. The picture is a long way from complete, and studies—most in rodents—have so far focused on biological sex, as opposed to gender, a psychosocial concept that doesn't necessarily match sex.

Iain Chessel, vice president and head of neuroscience at AstraZeneca in Cambridge, U.K., predicts that future pain medications will be tailored to individuals—and that sex will be a key factor in those personalized prescriptions. "But we don't understand it yet," he adds.

IMMUNE TO THE PAIN

Pain happens when neural sensors in the skin, muscles, joints or organs register a potentially harmful sensation, such as heat or tissue damage. They send signals through peripheral nerves to the spinal cord, activating other nerves that send signals to the brain stem and on to the cerebral cortex, which interprets those signals as "ouch!" But pain happens in many ways, and diverse chemical pathways contribute. Some pain types are distinguished by timing. There's the acute response to something hot, sharp or otherwise noxious, and there's long-term, chronic pain that might persist even after the initial injury has healed.

Chronic pain can manifest as hypersensitivity to otherwise nonpainful stimuli, as in the case of Sorge's male mice. Back in 2009, he and Mogil were studying a model of chronic pain triggered by inflammation.

Injecting a bacterial molecule called lipopolysaccharide into the spines of mice drew the attention of microglia, the nervous system's resident immune cells. But in Sorge's studies, this led to inflammation only in the males, explaining why they were so sensitive to the hair-prick test, Sorge and Mogil reported in 2011. The microglia remained qui-

et in females, which seemed to account for their indifference to Sorge poking their paws with fine hairs.

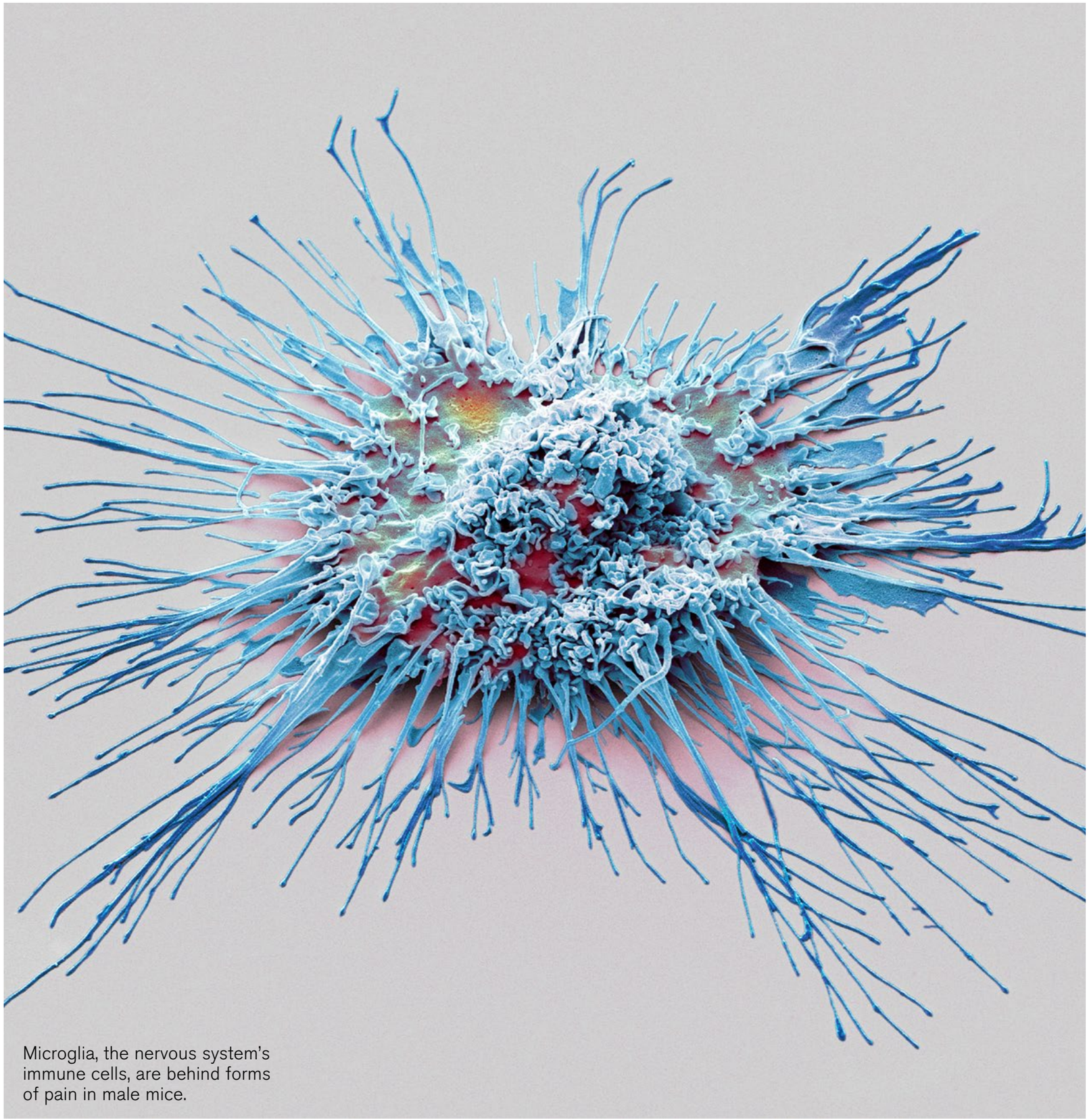
To better understand why male and female mice dealt with pain so differently, Sorge and Mogil turned to a pain source that affects all mice. They injured the animals' sciatic nerves, which run from the lower back down each leg. This led to a form of chronic pain that happens when the body's pain-detecting system is damaged or malfunctioning. It caused both male and female mice to become extra sensitive to touch.

Yet even in this case, there were differences. Microglia seemed to have a prominent role in the pain of males, but not in that of female mice. Sorge and a team of collaborators from three institutions found that, no matter how they blocked microglia, this eliminated the pain hypersensitivity in males alone.

It's not that females were immune to pain. They were just as bothered by nerve injury as the males were, but they weren't using microglia to become hypersensitive to touch. Mogil and Sorge wondered whether another immune component, called a T cell, was behind the chronic pain in females. These cells have a known role in pain sensitization in mice.

Sorge tried the same nerve injury in female mice lacking T cells. They still became hypersensitive to the fine hairs, but the mechanism now seemed to occur through microglia. In females lacking T cells, blocking the activity of microglia prevented this pain response, just as it did in males. And when the researchers transferred T cells back to female mice that were lacking them, the animals stopped using microglia in nerve-injury pain (*see Two Routes to Pain on next page*).

The team's findings, reported in 2015, had a big influence on the pain field, says Greg Dussor, a neuropharmacologist at the University of Texas at Dallas. The results showed that even though everybody's pain might look similar from the outside, scientists can't assume it's the same on the inside.



Microglia, the nervous system's immune cells, are behind forms of pain in male mice.

STEVE GSCHMEISSNER *GETTY IMAGES*

PAIN POINTS

If animals can switch between pain pathways, what controls the switch? Researchers have long attributed sex differences in pain perception to estrogen, a hormone that controls the development of the uterus, ovaries and breasts and that regulates the menstrual cycle. Estrogen can either exacerbate or dull pain, depending on its concentration and location. Testosterone, the hormone involved in development of the penis, testes and prostate, as well as of secondary characteristics such as body hair, has received much less attention from pain researchers, although studies suggest it can reduce pain, and some people with chronic pain take testosterone treatments.

In the case of microglia and pain hypersensitivity, Mogil's research points squarely at testosterone as the control switch for pain pathways. In the 2011 and 2015 studies, when Sorge tested castrated male mice, which have low testosterone levels, the animals exhibited a response similar to females. And when the researchers provided testosterone to castrated males, or to females, the pain pathway switched to one dependent on microglia.

Since then, researchers have continued to find evidence shoring up the importance of microglia—and the cells' enzymes and receptors—in male mice experiencing pain. And the phenomenon isn't restricted to mice: one of Mogil's collaborators, neuroscientist Michael Salter, also found microglial receptors at work in male rats that had hypersensitivity from nerve injury. Salter, who is chief of research at the Hospital for Sick Children in Toronto, Canada, is now investigating the question in macaques, which are likely to process pain in a more similar way to humans.

It's much harder to investigate these pain pathways in people, but clues are emerging. Neuropharmacologist Ted Price of the University of Texas at Dallas, and his collaborators have found preliminary evidence, published in March, of differences in how immune cells contribute to pain in people.

They're working with nerve tissue removed from individuals with cancer, whose tumors had invaded their spines. In nerves excised from men experiencing pain, Price's team found signs of inflammation caused by an immune cell called a macrophage. These cells serve a similar function to microglia. In women who were in pain, however, the more important players seemed to be nerve cells themselves and a short stretch of protein building blocks (called a peptide) that stimulates nerve growth. The results suggest parallels between human and rodent sex differences, says Price.

But immune cells and hormones don't fully explain pain differences. For instance, Sarah Linnstaedt, a translational biologist at the University of North Carolina Medical Center in Chapel Hill, has found hints that some women might have a genetic predisposition to chronic pain. Her team has identified a suite of RNA molecules in the bloodstream that are more likely to be elevated in women who develop chronic neck, shoulder or back pain after a motor-vehicle accident. Many of these RNA molecules are encoded by genes on the X chromosome, of which there are two copies in most women.

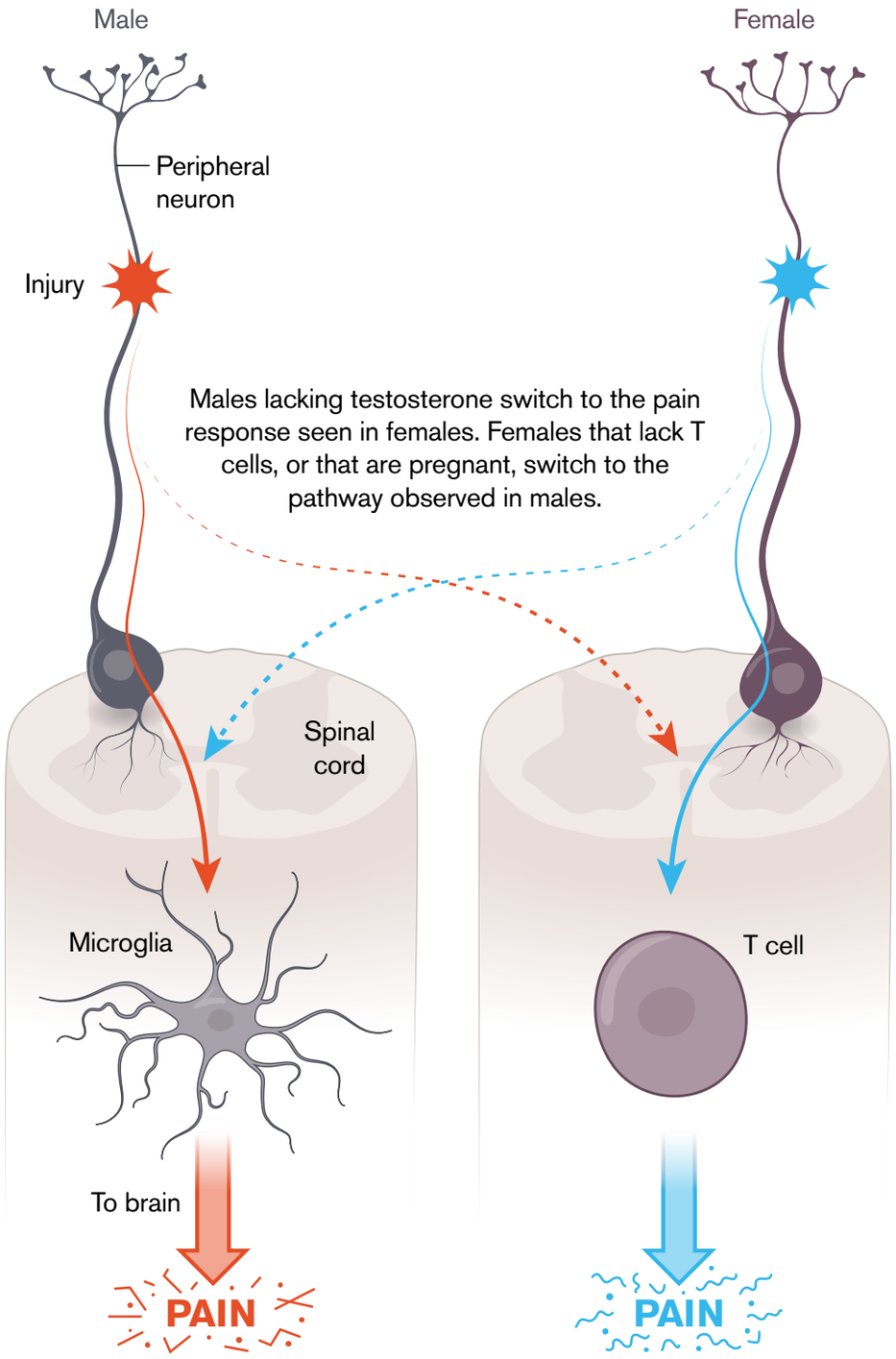
That's useful information, says Linnstaedt. "It will enable us to develop new therapeutics that can either be used specifically in women, or at higher doses in women."

DRUG DIFFERENTIAL

Others are thinking about sex-specific pain treat-

TWO ROUTES TO PAIN

Injuries to peripheral nerves—those connecting the brain and the spinal cord to the rest of the body—can cause increased sensitivity to pain. In male mice, this response depends on immune cells in the spinal cord called microglia. In females, it is T cells that seem to control pain.



NATURE

ments, too. In a study published online in November 2018, Price and his team reported that a diabetes drug called metformin reduces microglial populations surrounding sensory neurons in the spinal cord. They also showed that the drug blocks pain hypersensitivity from nerve damage only in male mice. "It didn't do anything in the females; in fact, it got a little bit worse," says Price, who has a theory as to why: to enter the nervous system, metformin relies on a protein that's expressed at higher levels in cells from males. Higher doses didn't make a difference in females, however, presumably because the medication was trapped outside the nerves.

Higher doses do help females receiving one of the oldest pain drugs in the pharmacy: morphine. Women and female rodents both usually require higher doses of morphine to achieve the same pain relief as men and male rodents, says Anne Murphy, a neuroscientist at Georgia State University in Atlanta. She's one of a handful of researchers who was studying sex differences well before the NIH changed its guidelines.

Microglia are also behind morphine's differing effects, Murphy's team reported in 2017. The drug dulls pain by blocking neurons in a brain region called the periaqueductal gray, or PAG. But the drug can also activate microglia there, counteracting morphine's pain-relieving effects. This is exactly what happens in female rats, which have more active microglia in the PAG than males have. When rats were treated with morphine before the scientists applied a hot light beam to their paws, the female animals had more inflammation in the PAG and pulled back their legs more quickly than did males given the same dose. When Murphy's team blocked morphine's effects on microglia, males and females responded to the pain in a similar way.

There's at least one drug already on the market that scientists have reason to think might work differently across sexes. In 2018, the U.S. Food and Drug Administration approved migraine treatments based on antibodies against CGRP, a peptide found in the nervous system that is involved in these kinds of headache. Migraines affect three times as many women as men.

In an as-yet-unpublished study of mice and rats, a team led by Price and Dussor applied CGRP to the thick membrane surrounding the brain. In females, the peptide created a response that looked like a migraine: the animals grimaced and their faces were hypersensitive to touch. In males: "Nothing," says Dussor. Modern anti-CGRP medicines might work better in women than in men, he adds—but the drug's clinical trials didn't check for such effects.

That's typical of many drug trials. They usually include men and women, but the numbers of each often aren't high enough to suss out differences. There's a real possibility that pain drugs that failed clinical trials in the past might have succeeded if they had been tested separately by sex, says Price. "It seems really obvious," he adds, "but nobody was really doing it."

PERSONALIZED PILLS

Chessel, at AstraZeneca, would be happy to develop a pain drug that works only in people of a certain sex. But the sex of study participants and animal subjects is driven by practicality, ethical concerns and government regulations, he says. AstraZeneca uses female rodents in most of its preclinical pain research because they're less aggressive and easier to house and handle than males. In early clinical trials, safety is the focus, so companies often exclude people who could become pregnant. As a result, drugs are mostly trialed on men and on women who are past menopause.

Even if scientists develop drugs that are targeted to male- or female-specific pain pathways, these might not be enough. It might be best to customize drugs more closely, to take into account the spectrum of genetics, hormone levels and anatomical development.

Little research has been done on pain mechanisms in people who don't fit into a binary definition of sex and gender. In one study, researchers in Italy surveyed transgender people undergoing hormone treatment. They found that 11 out of 47 people who transitioned from male to female reported pain issues that arose after the transition. Six out of 26 people transitioning from female to male reported that their pain problems lessened after taking testosterone.

On the basis of his team's experiments with castration and testosterone treatments in mice, Mogil thinks that pain pathways will be determined by hormone levels. He predicts that people with more than a certain threshold of testosterone will have pain mechanisms associated with males, and those whose testosterone falls below that level will experience pain through mechanisms common in females.

Pain responses also seem to change throughout life, around the time hormone levels rise or fall. Studies looking only at biological sex have found that, at puberty, the rates of pain conditions rise more in girls than in boys. And as people age, and some hit menopause, hormonal levels change again, and sex differences in chronic pain rates begin to disappear. Pregnancy changes pain responses, too. Mogil's group reported in 2017 that, early in pregnancy, mice switch from a typically female, microglia-independent mechanism of pain sensitization to a more male-associated one that involves microglia. By late pregnancy, the animals don't seem to feel chronic pain at all.

But he's no longer one of a few scientists looking for such sex differences. "People are finding this left, right and center now," says Mogil. "I don't think we know the half of it at this point."

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Amber Sapp (*left*) looks to many places for guidance on experimental treatments for her son, Garrett (*second from right*), who has Duchenne muscular dystrophy.

A Question of Control

Clinical-trial participants and their carers are gaining influence over how experiments are run. As they take to social media, that could make things messy for the science

By Heidi Ledford

ABIGAIL BOBO

Heidi Ledford works for *Nature* magazine.

Amber Sapp was browsing the Internet late one night in August when she happened to find out that her 12-year-old son's clinical trial had failed.

Every four weeks for two-and-a-half years, she had shuttled Garrett to a hospital nearly six hours away. There, he was prodded and pricked with needles in the hope that the antibody treatment being tested would reverse a devastating genetic disease called Duchenne muscular dystrophy. But an early data analysis, Sapp learned, had shown that the treatment wasn't working.

The thought of wasting Garrett's limited time with a failed trial was hard enough. The news was all the more disturbing because it didn't come from the trial organizers, but through a Facebook post from another parent. "It was upsetting that we found out that way," says Amber. "It sent everybody on Facebook into a tizzy." Even Garrett's local clinical-trial coordinator, someone who should have had intimate knowledge of what was happening with the research, hadn't yet heard the news.

Some members of the Facebook group had regularly discussed how their children were faring in the trial, even speculating as to who was in the control arm of the study, receiving a placebo instead of the experimental treatment. Social-media interactions can empower those living with disease, and their families, to make informed choices about their health care and clinical trials. Some people have even united on social media to launch trials of their own.

It's part of a major shift in clinical research. A 2016 survey found that three out of every four major pharmaceutical companies had used a patient-advisory board to gather feedback on clinical-trial designs. And several scientific journals, including the *BMJ*, have included patients as peer reviewers of submitted manuscripts.

But Amber's experience also shows how trial participants are disrupting the usual flow of information in clinical studies. As participants become more empowered, the natural tensions between their goals and those of the researchers become more pronounced. Online discussions threaten to compromise trial integrity when participants join forces to work out who is receiving a placebo. Discussing potential side effects can also influence results, particularly when the symptoms are subjective. Drug companies have yet to report any cases of such actions causing irrevocable damage to a trial, but some researchers worry that information-sharing by participants could sink trials or weaken their findings.

Now, scientists are grappling with how best to work with—and for—the people they are trying to study. "The fallback for most researchers is, 'I have to get these patients to change,'" says Craig Lipset, head of clinical innovation at Pfizer, a pharmaceutical company based in New York City. "But I think there are other things we'll have to take more seriously in the design of studies."

TRIALS AND TRIBULATIONS

By the time Garrett turned three, Amber, who works as a physical therapist in Nashville, Tennessee, noticed that something was off. When he tried to jump, he couldn't get his feet off the ground, and he looked unstable climbing stairs. Amber asked Garrett's pediatrician for answers, but was told that, in time, he would probably catch up with his peers.

One day, she watched Garrett stand up from sitting on the floor, and the answer came to her. The way that he used his arms to help raise his body was not just a quirk: it was a hallmark of muscular dystrophy that she had studied in school. "It just took me out of the blue," she says. "I thought, 'Oh my God, that's what it is.'"

Duchenne muscular dystrophy (DMD) is a genetic disorder that affects mainly boys, and is caused by mutations in a gene called DMD. The dystrophin pro-

tein that it encodes is important for maintaining healthy muscle cells; without it, muscles gradually deteriorate. Many people with the disorder need a wheelchair by the time they are 12, and will have difficulty breathing by their late teens.

Amber and her husband spent the next four years consumed by grief. “We refer to them as the dark days,” she says. “We couldn’t do anything: couldn’t function, couldn’t talk to other parents, couldn’t reach out for resources.”

When Garrett was about seven, Amber began to open up. She ventured online and met other carers, chatting to parents of older boys who were grappling with later stages of the disease. “Watching them go through that process of clinical trials and the difficulties—I guess maybe that’s where we learned about clinical trials,” she says.

Medical centers and pharmaceutical companies have noticed the power of social media to draw in patients. Some have launched efforts to advertise trials, for example, to targeted Facebook groups. The hope is that it could help trial recruiters to tackle a growing problem: a shortage of participants that has been stretching the time required to do clinical research.

As companies increasingly focus on rare diseases and precision medicine tailored to a specific subset of patients, it has become more difficult to find willing volunteers who meet the necessary criteria. Recruitment and retention rates are the worst that they’ve been since the Tufts Center for the Study of Drug Development started tracking them 20 years ago, says Kenneth Getz, who studies clinical trials at the center in Boston, Massachusetts.

“Industry-wide, everybody recognizes this as a huge problem,” says James Nolan, chief executive at InClinica, a contract-research organization in Wayne, Pennsylvania, that conducts clinical trials. “It’s not going away—it’s going to get much worse.”

Garrett already takes a variety of medications and supplements every day, which sometimes makes the prospect of adding new pills and procedures difficult.

ABIGAIL BOBO

The recruiting problem has given potential participants leverage and altered their relationship with clinical researchers: a trial that is too burdensome, or forces many participants into a control group, could be doomed to failure from the start. “Many of the companies understand that we can’t do this now without patients being equal partners,” says Sohini Chowdhury, deputy chief executive of the Michael J. Fox Foundation for Parkinson’s Research in New York City.

So drug firms and medical centers have enlisted the aid of patient advisory boards to evaluate clinical trials. Participants are getting the opportunity to demand trials with fewer procedures or more comfortable conditions. Lipset recalls a protocol for a trial in atopic dermatitis, a form of eczema, that would have required participants to stop using all their usual medications for six weeks to clear their system of drugs. A panel of people with dermatitis was shocked: going that long without relief was

unfathomable. “The washout period made perfect sense scientifically,” Lipset says. “But to the humans involved it was completely intolerable.”

The team adjusted the protocol, rather than risk launching a trial that was destined to fail. An evaluation of 30 patient advisory boards found that many were making recommendations about the convenience and feasibility of study visits, and the schedule of procedures performed. The advisory boards have good cause to push back. Getz says that as many as one-third of procedures—such as blood tests or biopsies—performed during clinical trials are not crucial to the applications for drug approval.

“Part of the balance is recognizing that although good science is great, it also has to be feasible and convenient,” says Getz. “That’s where patient engagement has completely changed the philosophy.”

In some cases, patients and their advocates band together to launch clinical studies of their own. When Katherine Leon had a heart attack in 2003, soon after the birth of her second child, she was told that it was just something that can happen after having a baby. But Leon eventually learned that she had spontaneous coronary artery dissection (SCAD), a rare condition that few community physicians are familiar with.

Leon says that she was “randomly googling around” one night when she stumbled on a message board for women with heart disease. Over time, a community of people with SCAD emerged. Then she started keeping a record of their symptoms and disease course: at what age were they diagnosed, which artery was affected and whether it might have been related to pregnancy. She took her data to a physician and convinced her to launch a research project to catalogue features of SCAD. “It was huge, because we felt as patients that we had definitely initiated it,” Leon says. “When I compare what they’ve discovered so far with the anecdotal data in my little proposal, it jibes pretty well—and that’s all just from people having conversations.”

“Many of the companies understand that we can’t do this now without patients being equal partners.”
—Sohini Chowdhury

A PLACEBO EFFECT

Garrett’s first clinical trial was designed to test whether a drug called tadalafil (Cialis) would help to keep boys with DMD walking. The protocol was relatively simple: just a few pills in the morning with a spoonful of apple sauce.

But Garrett’s ability to walk continued to decline. Faced with a degenerative disease and a ticking clock, the family wrestled with worries that he should move on to another trial. Eventually, Amber called the coordinator and said it was time to consider leaving the trial and to look ahead to the next one.

Online, Amber could see carers facing the same decision in various clinical studies. Some parents posted videos of their children walking or climbing stairs, and speculated as to whether they were receiving the active drug. If they suspected that their child was taking the placebo, a number of parents openly talked about their plans to withdraw from a study. “Nobody wants to be in the control,” says Amber. “We don’t have a lot of time with our boys. Nobody has time to waste.”

Trial participants have long sought to avoid being in the placebo group; they would rather have the chance to benefit from an experimental drug. The advent of social media has made it much easier to “unblind” a study, says Pat Furlong, founding president and chief executive of Parent Project Muscular Dystrophy, an advocacy group based in Hackensack, New Jersey. “Before social media, you wouldn’t know the other people in that trial,” says Furlong, whose two sons had DMD.

Bioethicist Lindsay McNair first became aware of the phenomenon while working for Vertex Pharmaceuticals, which is now in Boston. The company was running a clinical trial of a potential treatment for the hepatitis C virus in 2007 when a researcher reported activity from its participants on MedHelp.org, a health-related social-media site. Some participants said that they were having their blood tested by an outside laboratory to find out their levels of virus, to guess who was receiving the active drug and who the placebo.

McNair, who is now the chief medical officer at WIRB-Copernicus Group in Boston, a company that performs ethical reviews of clinical trials, decided to take a closer look with her colleagues. They read publicly available online health discussions over the course of about a year, noting any that might affect a study’s outcome. They found that participants were comparing the appearance and taste of their pills, even crushing them up to get a better look. Some of the activity, McNair recalls, was on

Yahoo Finance company message boards—and at least one financial analyst cited data from these boards in his or her predictions about the trial and in recommendations about Vertex stock.

There is no evidence that online unblinding affected any of these trials. But anecdotes such as these are troubling drug-makers. “We have largely turned a blind eye to the use of social media,” says Lipset. “It’s only a matter of time before Facebook jeopardizes the scientific integrity of a study.”

Sharon Terry, president and chief executive of the advocacy group Genetic Alliance in Washington, D.C., recalls working on a 2013 trial testing high doses of magnesium in 44 people with a rare genetic disease, pseudoxanthoma elasticum, which affects elastic fibers in connective tissue. “The group of individuals all got on Facebook and figured out pretty fast which were in the control,” she says.

In some online conversations that Furlong and McNair have seen, parents discussed leaving a trial if they didn’t see any improvement. “Dropouts are super frustrating,” says Brian Loew, founder and chief executive of Inspire, a social-media site that caters to people with medical conditions and their carers. This can delay the completion of a trial and raise warning flags to reviewers at regulatory agencies.

And when participants share details about which side effects they might be experiencing, they can induce others to wonder about—and then perhaps report—similar symptoms. The same could be true of a key clinical end point of the trial, particularly if that end point is somewhat subjective, such as a ranking on a pain scale. And, sometimes, participants swap information about entry criteria, such as the score on a cognitive test that might be required to join an Alzheimer’s disease study, says Lipset. Armed with that knowledge, those who want to join the study can prepare accordingly.

As Amber weighs the options for future clinical trials for her son, she must consider how invasive the procedures will be and how much Garrett will be away from friends and family.

ABIGAIL BOBO

Amber says that she generally stayed quiet during such online discussions, but it was still painful to see other families talking about possible improvements in their sons’ ability to walk or climb stairs. Garrett had experienced no such progress.

After the first clinical trial, the family began shuttling Garrett to Cincinnati, Ohio, for the antibody trial. The drive, the needles and the time spent in the hospital all took their toll. “Clinical trials are exciting, frustrating and frightening,” says Furlong. “There is certainly some altruism. But I can say to you—especially in rare disease, especially when so many people with rare disease are children—what you want, as a caregiver, is benefit.”

When Garrett turned 11, Amber held her breath. At that age, he would have to give his own assent to remain in the antibody trial. Garrett agreed, but Amber suspects he bowed to his parents’ wishes.

Furlong recognizes that anxiety. “There’s a moment

when your son looks at you and says, 'I don't think I want to do this. I miss my friends. I don't want them to stick me another time.'" she says. "As a parent, you are second-guessing: 'Is this the right thing?'" Often, parents of children with DMD will share information online because they are desperate to hear someone, anyone, tell them that their child is improving, she says.

Researchers are still grappling with how best to handle such online discussions. Inspire, which displays targeted advertisements for clinical trials to some of its 1.5 million members, expressly prohibits discussions that could affect clinical-trial results, such as comparing possible side effects or discussing ways to game eligibility criteria to gain entry to a trial. The site employs moderators to check posts after they go live.

"We had a lot of internal debate about it," says Loew of the policy. "On the one hand, people should be able to talk about whatever they want. But we decided that you can actually do harm to the science." Other sites, however, such as Twitter and Facebook, have no such policies.

Some companies running trials have inserted guidance about such communications in the consent forms that study participants sign. But that can backfire and cause undue worry, or limit participants' ability to find support online, says Lipset. "You can see in online communities where participants are scared that they have just signed a confidentiality agreement and will be thrown in jail for posting."

Lipset says that investigators will have to become savvier about how they set up their trials. This could include firming up eligibility criteria for a study, he says, to make them less subjective—and harder for a potential participant to game.

Some firms are hiring outside companies that specialize in listening in on social media, to report back when conversations veer towards unblinding a trial. Others are looking to facilitate the groups. Bristol-Myers Squibb, headquartered in New York City, partnered with Inspire to launch a moderated online community in April, in which patients in a given trial can support one another and discuss their condition, says Loew. This idea is catching on, says Lipset. "We're maturing to a place where people have to take seriously even the potential to create online communities for your research participants, so that people can have a safe place to share. Because they want to share."

"We're maturing to a place where people have to take seriously even the potential to create online communities for your research participants, so that people can have a safe place to share. Because they want to share."

—Brian Loew

THE TOUGH DECISIONS

When Amber learned that Garrett's second trial had ended, it was time to weigh options for the next one. But Garrett's choices are narrowing. He stopped walking this summer, and few trials will take boys who are no longer able to walk.

The family then considered a gene-therapy trial. It was a difficult decision. "Gene therapy is huge and promising and terrifying at the same time," Amber says.

It comes with a slew of new challenges, and risks. The virus that is used to deliver genes could raise an immune response that would make Garrett ineligible for future gene-therapy trials. And if he's in the placebo arm, he won't know whether he's eligible to receive the actual treatment until a year has passed. Added to these tensions would be three muscle biopsies performed under general anesthesia, procedures that are particularly unnerving for people whose muscle is wasting away. "If the trial we had just come out of was, to us, pretty invasive, this is ten times that discomfort," Amber says.

It's a gamble. In October, Amber and her family opted to hold off from joining the gene-therapy trial. While they were weighing their options, Amber decided not to rely on other parents on social media to help with the decision. Instead, she stuck to her "board of directors," a few trusted medical professionals. "Social media has such a wide pool of people that you don't always know that the answers you're going to get are on the level," she says. "It's hard," Amber adds. "Time is limited."

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The Protein Slayers

An emerging class of drug could send some of medicine's most troublesome protein targets to the cellular rubbish bin

By Megan Scudellari

DAVID PARKINS

Megan Scudellari is a freelance science journalist based in Durham, North Carolina, specializing in the life sciences. She is a correspondent for the *Scientist* magazine and has contributed to *Technology Review*, *Nature Medicine*, *Pacific Standard* and more. She is currently writing her first textbook, a college biology text.

WHEN CRAIG CREWS FIRST MANAGED TO MAKE proteins disappear on command with a bizarre new compound, the biochemist says that he considered it a "parlor trick," a "cute chemical curiosity."

Today, that cute trick is driving billions of U.S. dollars in investment from pharmaceutical companies such as Roche, Pfizer, Merck, Novartis and GlaxoSmithKline. "I think you can infer that pretty much every company has programs in this area," says Raymond Deshaies, senior vice president of global research at Amgen in Thousand Oaks, California, and one of Crews's early collaborators.

The drug strategy, called targeted protein degradation, capitalizes on the cell's natural system for clearing unwanted or damaged proteins. These protein degraders take many forms, but the type that is heading for clinical trials this year is one that Crews, based at Yale University in New Haven, Connecticut, has spent more than 20 years developing: proteolysis-targeting chimeras, or PROTACs.

Large and unwieldy, PROTACs defy conventional wisdom on what a drug should be. But they also raise the possibility of tackling some of the most indomitable diseases around. Because they destroy rather than inhibit proteins, and can bind to them where other drugs can't, protein degraders could conceivably be used to go after targets that drug developers have long considered "undruggable": cancer-fueling villains such as the protein MYC, or the tau protein that tangles up in Alzheimer's disease.

"This is new territory," says Alessio Ciulli, a biochemist at the University of Dundee, U.K. "We're breaking the rules of what we thought would be druggable."

The field has reason to be optimistic. In 2014, scientists discovered that the myeloma treatment lenalidomide (Revlimid), one of the world's best-selling drugs, works in a similar way to protein degraders to chew up two formerly untouchable proteins.

Yet the field lacks published data confirming that PROTACs and other emerging compounds can make undruggable proteins disappear. And there are questions about where and how these odd-looking molecules will work in the body.

For now, all eyes are on Arvinas, a biotech company in New Haven, Connecticut, founded by Crews. It's scheduled to begin testing a PROTAC for prostate cancer, albeit attacking a protein that's been targeted successfully by other drugs. "We're on the cusp of proving these PROTACs can be drugs," says Ian Taylor, senior vice-president of biology at Arvinas. "Right behind that will be: can we do this with an undruggable?"

AN ACADEMIC EXERCISE

In diagrams, PROTACs often look like dumbbells. They are molecules made up of two binding ends connected by a thin tether.

The action happens on the ends. One grabs on to the target protein, while the other latches on to a ubiquitin ligase—part of the cell's natural rubbish-disposal system that labels defective or damaged proteins by slapping a small protein called ubiquitin onto them (*see Marked for Destruction on next page*). Ubiquitin tags act as sort of "please collect" stickers that instruct the cell's protein shredder, called the proteasome, to do its thing.

Proximity accounts for a lot in biology, so by simply bringing together the ligase and the target protein, a PROTAC ensures that the target will get marked for destruction. Ligases are efficient and ubiquitin, as the name suggests, is plentiful, so a single PROTAC should be able to perform its catch-and-release function repeatedly throughout the cell, suggesting that only a small amount of such a drug is needed for potent activity.

The earliest-known published description of a PROTAC-like molecule is in a patent filed in 1999 by two scientists at Proteinix, a biotechnology company in Gaithersburg, Maryland. In the patent (see go.nature.com/2vyjf9l), John Kenten and Steven Roberts proposed co-opting the cell's protein-degradation system. Colleagues dismissed the idea, saying that Kenten and Roberts were complicating drug discovery by trying to bind to two proteins—the unwanted protein and the ligase—at once. "There was not a lot of enthusiasm internally for

it," recalls Kenten, now research director at Meso Scale Diagnostics in Rockville, Maryland. Proteinix did not pursue the approach.

But on the other side of the United States, another pair of minds was mulling the same idea. During a research retreat in 1998 at a scenic resort on Semiahmoo Bay in northwest Washington, Deshaies paused in front of a poster by Crews to listen to him talk about using small molecules to link two proteins together. Deshaies, then a biochemist at the California Institute of Technology in Pasadena, was knee-deep in the study of ubiquitin ligases. The human genome encodes roughly 600 of them, which need to form a complex with other proteins to do the tagging. About a year earlier, Deshaies had co-discovered a protein family now known to contain 250 ubiquitin ligases.

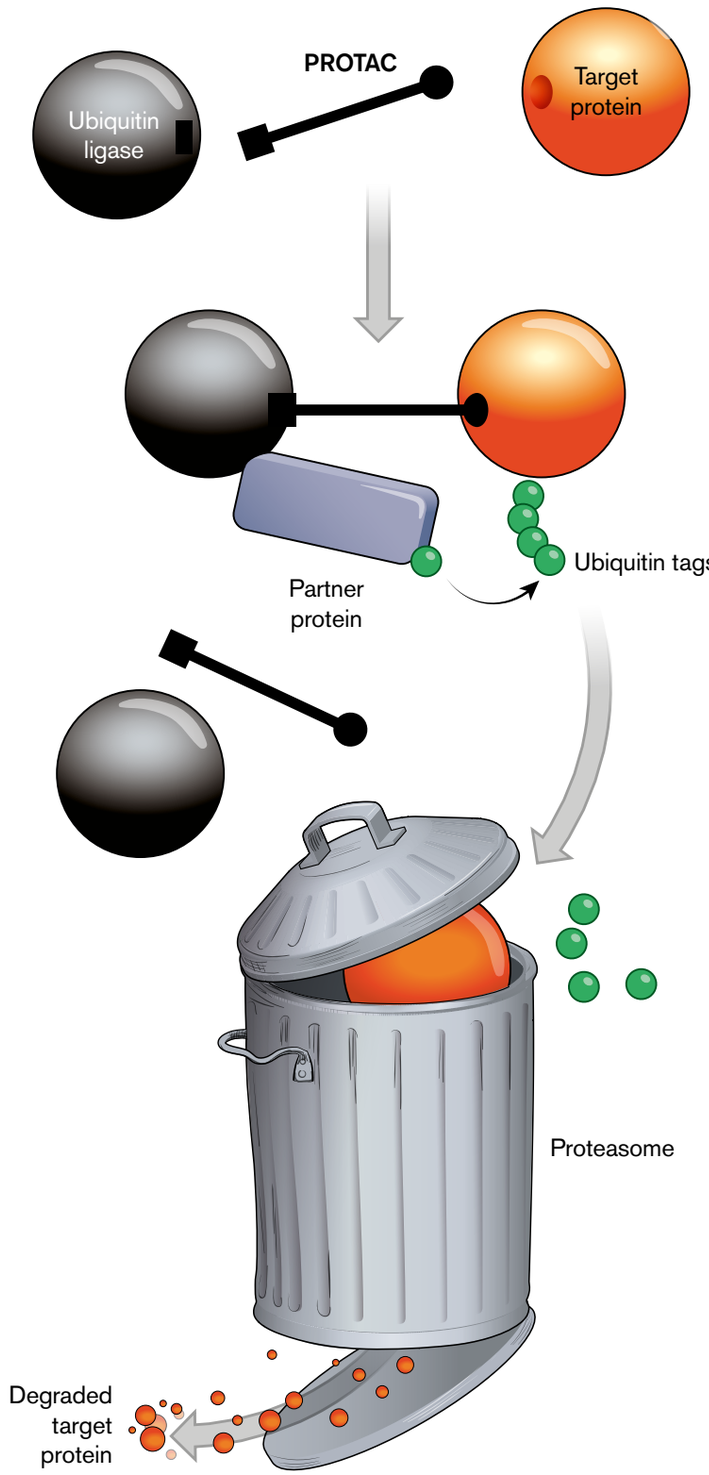
"It wasn't that big of a leap to come to the idea of, well, gee, if you could link things to ubiquitin ligases, then you could potentially drive the ubiquitination of a protein—and its degradation," recalls Deshaies. He and Crews continued to chat all weekend and parted ways with a plan to find funding to explore the idea.

At the time, Crews was developing a drug that worked in the opposite way to PROTACs. It blocked the ubiquitin system in cells, causing proteins to build up to dangerous levels and eventually trigger cell death. The result of that work, carfilzomib (Kyprolis), is now used to treat the blood cancer multiple myeloma. "I thought the flip side would be equally as interesting," says Crews. "That certainly has turned out to be the case."

Crews and Deshaies soon published a study demonstrating that their first PROTAC, Protac-1, successfully grabbed and led to the degradation of a cancer-associated protein called METAP2 in extracts

MARKED FOR DESTRUCTION

Targeted protein degradation uses a drug such as a proteolysis-targeting chimera (PROTAC) to bring together a ubiquitin ligase–and its associated proteins–with a target protein. After this tethering occurs, the ligase attaches ubiquitin tags to the target protein, marking it for degradation.



from *Xenopus* frog eggs.

Still, Protac-1 was far from being a drug, says Crews, who called the paper an "academic exercise." First-generation PROTACs had low activity in human cells, probably because the compounds struggled to get inside. They relied on big, unwieldly peptides to bind to the ligases. The scientists had to find a way to make the ligase-binding ends more drug-like—"Something that had potential to be a pharmaceutical," says Crews. Or they needed to move on.

With funding and research support from GlaxoSmithKline in London, Crews pushed ahead, mainly targeting one particular ligase, the von Hippel–Lindau disease tumor suppressor (VHL). In 2012, Crews, together with his graduate student Dennis Buckley and Ciulli, a former visiting fellow in Crews's lab, reported on a small-molecule binder for VHL. Crews finally began to believe that PROTACs really could become drugs.

FISHING FOR SMALL MOLECULES

Crews wasn't the only one chasing protein degraders. In 2010, while at the Dana-Farber Cancer Institute in Boston, Massachusetts, chemical biologist James Bradner read a paper by a team of researchers in Japan, led by Hiroshi Handa, then at the Tokyo Institute of Technology in Yokohama. Handa had been trying to understand why the infamous drug thalidomide, approved in some countries in the late 1950s and early 1960s to help with nausea in pregnancy, caused problems with limb development. (It is now approved to treat multiple myeloma and a skin condition.) Using thalidomide as the bait to fish for proteins in cells, Handa discovered that the drug hooks on to and blocks the activity of a ubiquitin ligase called cereblon. That inhibition, his team

found, affects limb growth and development in zebrafish and chicks.

Bradner realized that if thalidomide binds to a ubiquitin ligase—no easy feat, because such enzymes are notoriously difficult to grab—then perhaps he could find a way to bind to the same ligase but target it to proteins implicated in disease. In 2013, Buckley joined Bradner's team as a postdoctoral researcher, and they began the search for small molecules that bind to cereblon.

In May and June 2015, three teams—led by Bradner, Ciulli and Crews—published five separate papers describing small-molecule PROTACs with potent, drug-like activity. With Ian Churcher at GlaxoSmithKline, Crews bound a PROTAC to VHL and used it to degrade the levels of several proteins to less than 10 percent of those present in untreated cells. Bradner and his colleagues bound cereblon to their PROTAC to reduce levels of a cancer-causing protein, and Ciulli, by then at the University of Dundee, and his team degraded the same protein, using VHL as the ligase. The protein degraders worked both in cells in a dish and in human tumors in mice.

As well as designing drug-like protein degraders, Crew's and Bradner's teams have both built systems—HaloPROTACs and dTAG, respectively—that enable researchers to put targeted protein degradation to work as a tool in the laboratory, using genetic tags to mark proteins for destruction in cultured cells and in mice. With dTAG, "you can deplete a protein in minutes or hours and monitor what happens," says Behnam Nabet, a chemical biologist who led development of the system with Nathanael Gray at the Dana-Farber Cancer Institute. "This gives you a lot of power to study oncogenes and kinases and proteins that have very rapid activity." The dTAG materials are currently freely available: more than 150 academic labs use the probe to investigate the effects of depleting specific proteins in cells, says Nabet.

Bradner, who left Dana-Farber in 2016 to become president of the Novartis Institutes for Biomedical Research, estimates that around 30 separate tools already incorporate the technology. "The path to chemical probes is now well established," he says. "But the challenge to make real-world medicines from these ligands is significant."

"We're throwing out preconceived notions we've had about larger-than-average small molecules."
—Ian Taylor

GOLD RUSH

Following the 2015 flurry of small-molecule PROTACs, Deshaies, who had left the field, penned an opinion piece declaring that PROTACs had the potential to become a major new class of drug, possibly surpassing two of the hottest drug-development areas of all time—protein kinase inhibitors and monoclonal antibodies. "The gold rush is on!" Deshaies wrote at the time.

Since then, he says, it has only intensified. He joined Amgen in 2017 and now oversees the company's work in the area.

The Arvinas trial, expected to begin by mid-2019, will include 28 to 36 men with metastatic prostate cancer and will last around nine months, says Taylor. It is usual for any new class of drug to go after a well-known target, where the biology and toxicology are well understood, and Arvinas's first candidate is no exception. It degrades the androgen receptor, a protein that is already targeted by a handful of approved drugs. The company hopes that by degrading rather than inhibiting the receptor, its PROTAC will be able to treat people who have become resistant to or see no benefit from existing drugs. And if the candidate succeeds, the field will finally have the clinical data that everyone is looking for. Arvinas will have shown that a PROTAC can be a drug.

That's crucial because there has been considerable doubt about whether protein degraders can work in humans. Fully assembled PROTACs break well-known rules of thumb for drugs. Chief among them is size. A good small-molecule drug typically has a mass of less than 500 daltons. Current PROTACs range upwards of 1,000 daltons. Yet the molecules can still enter cells. Crews suspects that this is because they are probably recognized by the cell membrane as two smaller molecules that happen to be tethered together, rather than a single large one.

"We're throwing out preconceived notions we've had about larger-than-average small molecules," says Taylor.

Also out of the window are preconceived ideas about undruggables. The problem with many of these tough protein targets is that most small-molecule drugs or monoclonal antibodies need to bind to an active site on an enzyme or a receptor to work. But an estimated 80 percent of proteins in human cells lack such a site. PROTACs, however, can grab a protein by any nook, cranny or crevice—they don't need to be sitting in an active pocket to work. So they could make those proteins accessible.

There's already some evidence to support this approach. Last year, a team at the Institute of Cancer Research in London produced a small molecule that can bind to a transcription-factor regulator that doesn't have an active site. They were able to create a potent PROTAC by attaching a binder for the ubiquitin ligase cereblon.

The field still lacks published evidence of a PROTAC

that can target and degrade a valuable undruggable protein. Deshaies says that Amgen has a PROTAC effective in both cultured cells and animals against an unnamed high-value cancer target that has been historically tough to bind. Arvinas claims to have in vivo evidence of PROTACs degrading tau in the brains of mice. On its Web site, the company says that injecting its tau-protein degrader directly into the mouse hippocampus reduced levels of tau by 50 percent.

By developing PROTACs for an array of diseases, including those that affect the brain, Taylor says that many researchers hope to show that the technology is "therapeutic-area agnostic." Various teams are also working to expand the pool of ligases that protein degraders can recruit. There are only four main ones used at present, including VHL and cereblon, and a wider variety of available ligases could enable drug developers to match the most potent ligase-PROTAC combination with their cell type or protein of interest. "Potentially, any ligase can be hijacked through this approach," says Ciulli, who is collaborating with German pharmaceutical company Boehringer Ingelheim on the development of PROTACs.

Buoyed by fresh targets, improved potency, and a clinical trial about to begin, researchers are ready to prove that protein degraders can be more than a parlor trick. "The sky is the limit," says Ciulli. "It is just a question of when."

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Ethan Siegel is a theoretical astrophysicist and author of *Treknology: The Science of Star Trek from Tricorders to Warp Drive.*
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POLICY & ETHICS

Opting Out of Vaccines Should Opt You Out of American Society

People who are able to take vaccines but refuse to do so are the moral equivalent of drunk drivers

SEAN GALLUP GETTY IMAGES

The ongoing measles outbreaks across the United States and Europe prove definitively that our personal choices affect everybody around us. Although you have a right to your own body, your choice to willfully be sick ends where another's right to be healthy begins. For that reason, people who "opt out" of vaccines should be opted out of American society.

This is America, the Land of the Free. That freedom, however, doesn't mean "I can do whatever I want, whenever I want." When we choose to live in a society, there are certain obligations—both moral and legal—to which we are bound. You cannot inflict harm or infringe on the rights and liberties of those around you.

Those obligations extend even to your constitutional rights. Although we have a First Amendment, you are not allowed to play music as loudly as you want in your apartment. Your neighbors have a legal right to peace and quiet. Even though we have a Second Amendment, you are not allowed to shoot a gun for sport in the middle of a city or town. Stray bullets are not only scary, they're hazardous, and often inadvertently kill people.

Finally, your moral and legal obligations to the safety of others can even curtail combinations of your rights. Even though consuming alcohol and driving are both legal activities, they are not legal when performed together. Nearly 11,000 people die every year because people choose to exercise their "rights" inappropriately.

The exact same reasoning applies to vaccination. There is no moral difference between a drunk driver and a willfully unvaccinated person. Both are selfishly, recklessly and knowingly putting the lives of everyone they encounter at risk. Their behavior endangers the health, safety and livelihood of the

innocent bystanders who happen to have the misfortune of being in their path.

The reasons why are simple and straightforward. Vaccines aren't perfect (e.g., they can wear off over time) and not everyone can be vaccinated. There is one and only one legitimate reason to skip a vaccine: being immunocompromised. Some individuals, because of genetic deficiencies or diseases like cancer, cannot receive vaccines. Other people are too young. Vaccines such as MMR (measles, mumps, rubella) cannot be administered before 12 months of age. These vulnerable people rely on the responsible actions of everyone else in society to protect them, a concept known as "herd immunity."

For their sake, we have a moral—and there should also be a legal—obligation to protect them. Everyone who can be vaccinated must be vaccinated in order to prevent the spread of disease. This is a protection we demand even for our animals: kennels will turn your pet away if they aren't properly vaccinated and on an accepted flea treatment. There are rules we all have to play by and responsibilities we have to live up to if we want to live in a society together.

If this isn't enough to convince a person to become fully vaccinated, then perhaps there is a solution that maintains everybody's freedom: Antivaxxers can opt out of American society. No public or private school, workplace or other institution should allow a nonexempt, unvaccinated person through its doors. A basic concern for the health and safety of others is the price it costs to participate.

Is that too harsh? We don't think so. If a person wants to blast their music loudly, shoot guns aimlessly, and drink and drive, they should be allowed to do exactly as they please: so long as it's on their own property, sufficiently isolated from everyone else. Similarly, if you don't want to be vaccinated, perhaps that should be allowed, too, so long as you agree to permanently live out in the middle of nowhere.

It is inexcusable that society has reached this point. Many of the deadliest diseases known to humankind are caused by bacteria and viruses, and dozens of them are now entirely preventable thanks to the sciences of microbiology and immunology.

People falsely believe that diseases like measles have "gone away," but they have not. They're always there, waiting to strike as soon as our collective guard goes down. Not so long ago, smallpox ran the risk of obliterating entire cities, while polio paralyzed large fractions of a generation. We have forgotten this morbid history because public health has been a victim of its own success.

But misinformation abounds. The Internet, both a blessing and a curse, has allowed devilish lies, propaganda and a discredited fraud masquerading as science to infect the minds of millions of people. Unfortunately, there's no vaccine that can inoculate someone against a counterfactual, unscientific mindset.

There are, however, vaccines that can prevent dozens of harmful diseases. Those who refuse, and recklessly endanger others, should be put in quarantine.

Claire Pomeroy is president of the Albert and Mary Lasker Foundation, which is dedicated to advancing medical research.

PUBLIC HEALTH

Loneliness Is Harmful to Our Nation's Health

Research underscores the role of social isolation in disease and mortality

GETTY IMAGES

Thanks to remarkable new technologies and the widespread use of social media, we are more "connected" than ever before. Yet as a nation, we are also more lonely. In fact, a recent study found that a staggering 47 percent of Americans often feel alone, left out and lacking meaningful connection with others. This is true for all ages, from teenagers to older adults.

The number of people who perceive themselves to be alone, isolated or distant from others has reached epidemic levels both in the United States and in other parts of the world. Indeed, almost two decades ago, the book *Bowling Alone* pointed to the increasing isolation of Americans and our consequent loss of "social capital." In Japan, for example, an estimated half a million (known as *hikikomori*) shut themselves away for months on end. In the United Kingdom, four in 10 citizens report feelings of chronic, profound loneliness, prompting the creation of a new cabinet-level position (the Minister for Loneliness) to combat the problem.

While this "epidemic" of loneliness is increasingly recognized as a social issue, what's less well recognized is the role loneliness plays as a critical determinant of health. Loneliness can be deadly, according to former Surgeon General Vivek Murthy, among others, who has stressed the significant health threat. Loneliness has been estimated to shorten a person's life by 15 years, equivalent in impact to being obese or smoking 15 cigarettes

per day. A recent study revealed a surprising association between loneliness and cancer mortality risk, pointing to the role loneliness plays in cancer's course, including responsiveness to treatments.

Biologists have shown that feelings of loneliness trigger the release of stress hormones that in turn are associated with higher blood pressure, decreased resistance to infection and increased risk of cardiovascular disease and cancer. There's even evidence that this perceived sense of social isolation accelerates cognitive and functional decline and can serve as a preclinical sign for Alzheimer's disease.

It has long been recognized that social support—through the availability of nutritious food, safe housing and job opportunities—positively influences mental and physical health. Studies have repeatedly shown that those with fewer social connections have the highest mortality rates, highlighting that social isolation can threaten health through lack of access to clinical care, social services or needed support.

However, how the subjective sense of loneliness (experienced by many even while surrounded by others) is a threat to health may be less intuitive. It is important to recognize that feelings of social cohesion, mutual trust and respect, within one's community and among different sections of society, are all crucial to well-being. Perhaps this is especially so at a time of great social polarization exacerbated by contentious politics and vitriolic TV news.

These new statistics underscore the urgent need to address this "epidemic" of alienation and despair and to increase social support. For the first time in the U.S., life expectancy is declining, while the numbers of "deaths of despair" (from suicide, drugs and alcohol abuse), especially among white males, is on the rise. The chances of dying from an opioid overdose or suicide are now higher than the odds of dying in a motor vehicle accident.

Biologists have shown that feelings of loneliness trigger the release of stress hormones that in turn are associated with higher blood pressure, decreased resistance to infection and increased risk of cardiovascular disease and cancer.

So what can be done to combat widespread loneliness and anomie? The good news is there are models of success already in place in the U.S. and across the world. Programs such as Meals on Wheels and help lines that arrange phone calls between volunteers and the lonely—whether they be older adults or teens in crisis—offer direct social support to those feeling profoundly isolated. Intergenerational initiatives, like the dementia-friendly villages in the Netherlands, the Intergenerational Learning Center in Seattle, and global home-sharing programs offer unique opportunities for the elderly to make meaningful connections with children and young adults.

Community engagement programs such as improvisational workshops at Chicago's Second City aim to tackle social anxiety and feelings of isolation through laughter. And policy initiatives such as the Aspen Institute's Weave: The Social Fabric project, New York's Age-Friendly and England's National Health Service provide strategic assistance—encouraging patients to engage in social activities rather than resorting to prescription drugs. And certainly information technology can be part of the solution as well: apps to "increase sociability" are being developed to combat loneliness. We have good models. We must prioritize further investment.

But perhaps, equally important, each of us can reach out to someone who may be lonely: the senior next door who never has visitors, the homeless person who feels invisible, or the mother overwhelmed with the responsibility of a new baby. By making a simple human connection, we can save a life.

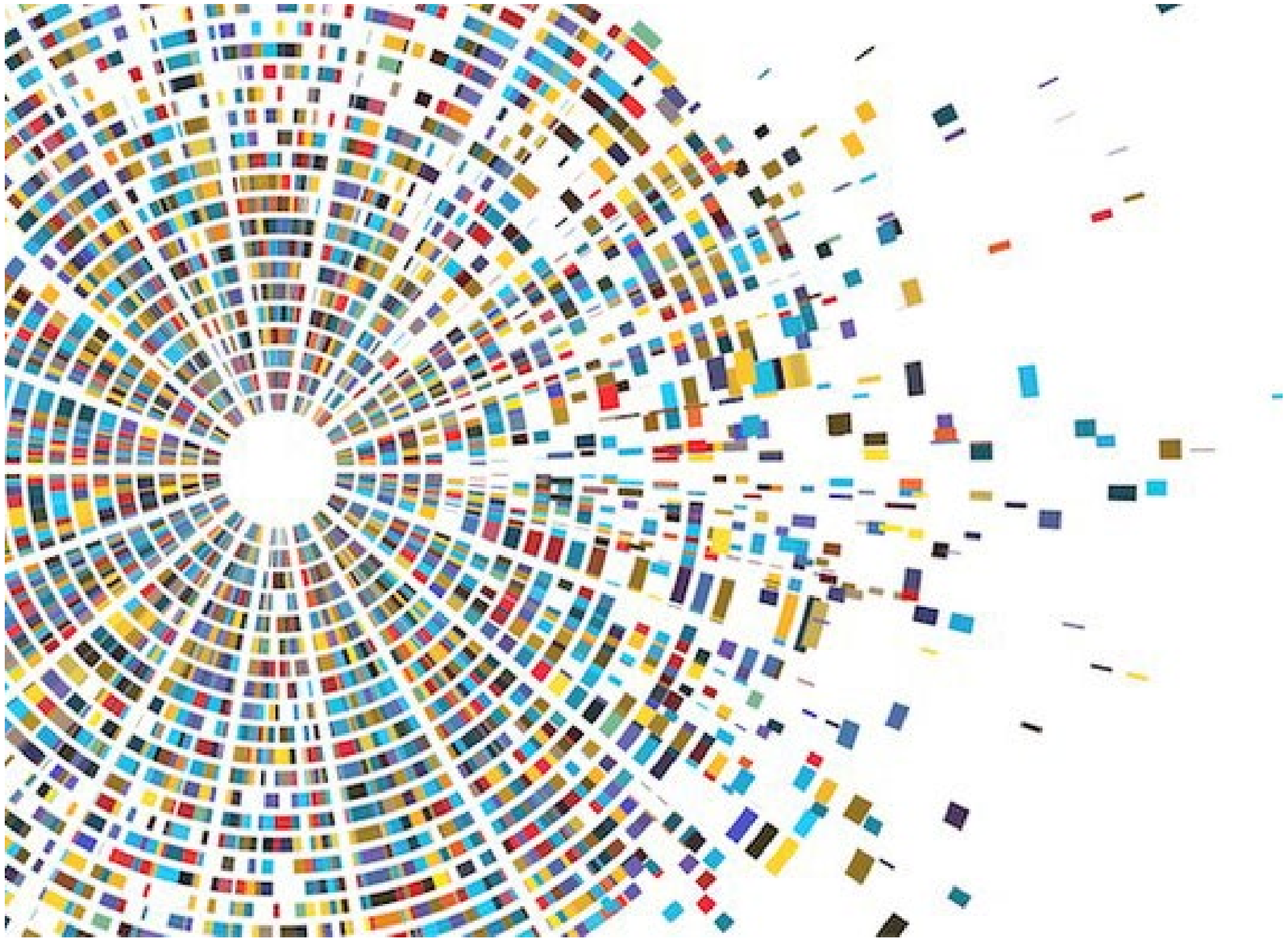
Health and well-being are profoundly social. Ironically, in today's hyperconnected world, we must tackle head-on the growing public health crisis of loneliness if we're to become a healthier nation.

Leo P. Sugrue and **Rahul Desikanis** are assistant professors in the department of radiology and biomedical imaging at the University of California, San Francisco. They are co-directors of the Laboratory for Precision Neuroimaging at U.C.S.F.

THE BODY

How Well Can a Genetic Test Predict Your Future Health?

A physician-scientist with crippling ALS says a so-called polygenic score could someday help patients like him alter the course of even the most terrible diseases



TETIANA LEZUNOVA GETTY IMAGES

If a crystal ball could reveal your personal risk for developing heart disease or breast cancer or Alzheimer's disease, would you pay to take a look? Would you believe what it predicted and would you be willing to change your behavior to prevent or reduce the risk of this disease taking over your body? These may sound like abstract philosophical questions—but for us they are not.

Two years ago, as I (Desikanis) completed my final year of training as an M.D.-Ph.D. neuroscientist and neuroradiologist, and spent my afternoons rushing back and forth between the hospital and the lab, I was oblivious to the fact that I had a high risk of dying soon. A year later, I was diagnosed with amyotrophic lateral sclerosis, or ALS—the same disease that killed Lou Gehrig and Stephen Hawking. If I had any hint that I would develop ALS, which has locked me inside my body as though inside a cell, unable to move or breathe normally on my own, I can tell you without hesitation that I would have done anything and everything to stop or slow the devastation this disease has visited on my life. If only I could have glimpsed into my future …

Today, thanks to the mapping of the human

genome and subsequent efforts to make sense of the resulting blueprint of As and Ts, Gs and Cs, we are close to being able to predict your future health from your DNA. Using advanced computer models, scientists are adding together the influence of the hundreds, even thousands, of DNA variants associated with a given disease into what is called a polygenic score.

The influence that each genetic variant exerts on a person's disease risk may be tiny, but by distilling all of this complex genetic information into a single number that quantifies an individual person's particular genetic risk of disease, polygenic scores pack powerful risk prediction into a single number. The hope is that your personalized polygenic score could help you prevent disease, live longer and plan for your future.

Can a genetic test really predict your health? Do you want to know today that you are at high risk of a disease whose onset may be three decades from now? And if the genetic test comes out positive for a terminal disease that has no cure, what would you do? These are the kinds of tough questions that we need to start discussing as we enter this new age of genomic medicine.

As we embark on this discussion, the most important thing to know is that polygenic scores are not diagnostic tests. Even doctors and other health professionals get this wrong. Polygenic scores measure your risk for developing a disease, not whether you do or don't have the disease, or even whether you will ever get that disease. Given your combination of genetic risk factors, these scores estimate the probability that you will develop a particular disease over time.

Using advanced computer models, scientists are adding together the influence of the hundreds, even thousands, of DNA variants associated with a given disease into what is called a polygenic score.

Like the probability of rain in next week's weather forecast, polygenic scores have inherent uncertainty. Appreciating this uncertainty is key because the uncertainty in polygenic scores leaves room for action. We know that for many complex diseases behavior is just as important as genes in setting the stage for what is to come. If disease onset isn't solely determined by genes, then lifestyle or therapeutic interventions can prevent or modify the trajectory of disease.

Polygenic scores will need to undergo rigorous evaluation by the medical community before being incorporated into clinical practice. However, companies are already offering these tests direct to consumers. Myriad Genetics has launched a commercial polygenic test that estimates breast cancer risk for women. HealthLytix and Dash Genomics have developed a polygenic test for Alzheimer's disease available to anyone who already has their DNA data from Ancestry.com or 23andMe—upload your data and for $99 an app on your smartphone will tell you when you are at greatest risk for developing dementia.

These easy to understand scores are being hailed as a breakthrough technology. But how might these scores actually help you? First, polygenic risk can inform treatment decisions and lifestyle modifications. For example, aggressively lowering cholesterol in individuals with a high polygenic score for heart disease may lead to a much greater reduction in the risk of a heart attack than doing so in people with a low polygenic score.

Polygenic scores may also influence disease-screening strategies. Recently, it was shown that a polygenic score can predict risk for aggressive prostate cancer, suggesting that it could identify men who would benefit most from PSA screening. Finally, knowledge of polygenic risk can be useful in planning for the future. For example, although we don't yet have effective treatment for dementia, knowing that you are at high risk for Alzheimer's disease can help you make informed decisions about changing your behavior—keeping heart and brain healthy through diet and exercise, and, of course, paying more attention to your future finances and plans for long-term care.

In our laboratory at the University of California, San Francisco, we are experimenting with and developing molecular pathway-specific polygenic scores. We have found that different molecular processes appear to underlie and drive brain diseases like Alzheimer's and ALS in different patients. The implication is that a subset of people

with Alzheimer's may be genetically susceptible to immune dysfunction, whereas another group of Alzheimer's patients may have genetic abnormalities that make them susceptible to cardiovascular disease. We are building an online platform for people at risk for or living with Alzheimer's and ALS: upload your DNA, and the Web site will send you a cardiovascular and immune polygenic report card that you can take to your doctor.

Today we have unprecedented access to information. Our genetic data will soon be added to the global libraries of digital information to which we have almost instant access, and the use of genetic risk scores will soon become commonplace in our lives. As a society, we need to understand what this genetic knowledge does and does not mean and become comfortable with the prognostic uncertainty inherent in these genetic risk scores. As an individual, you should know that your polygenic risk profile has the potential to tell you which interventions are likely to have the biggest positive impact on your long-term health.

Armed with knowledge about the capabilities and limitations of polygenic scores, you can make informed decisions and choose exactly how a genetic test will shape your future.

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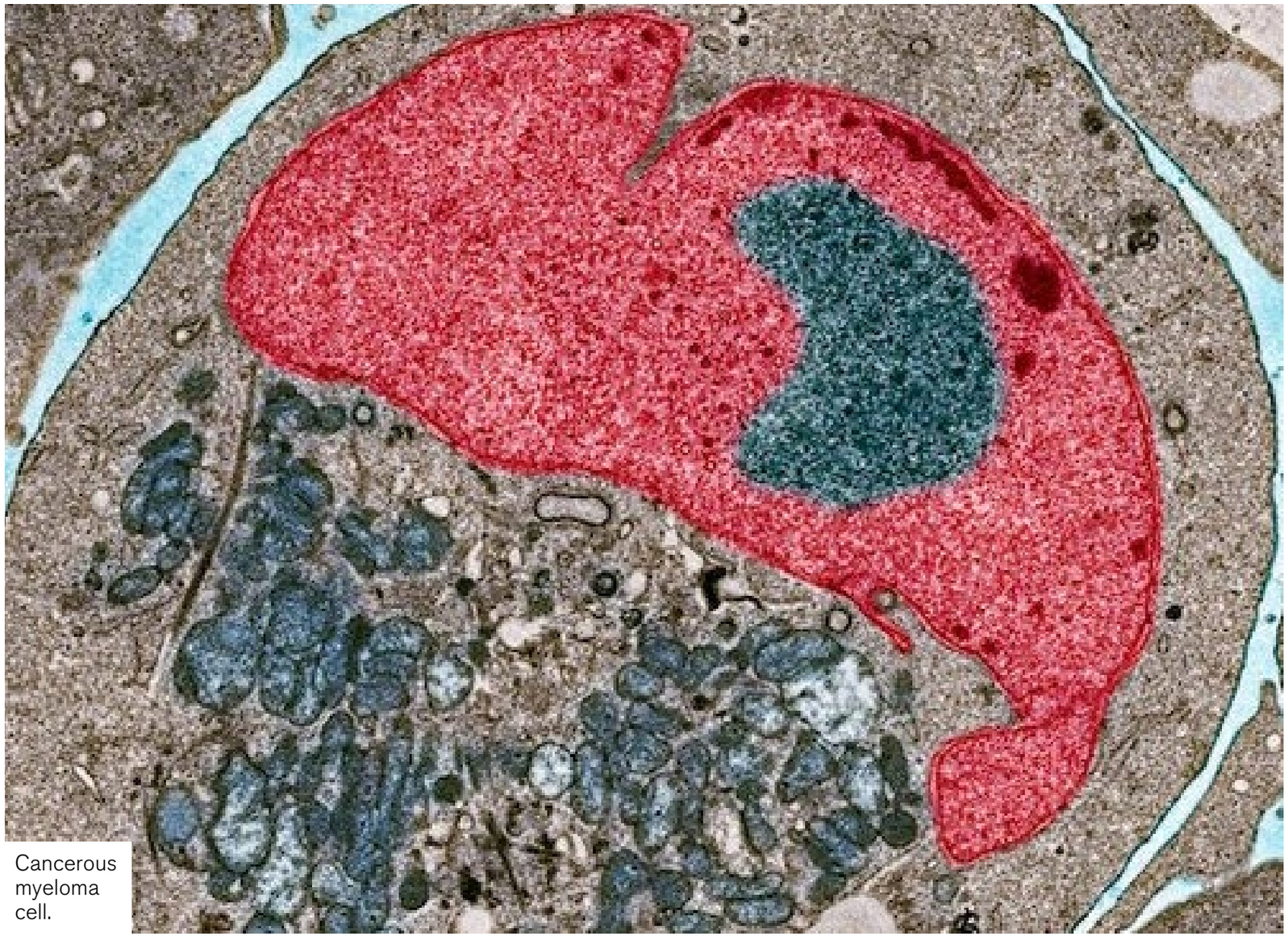
MEDICINE

A New Way to Fight Cancer

Metabolic therapy is showing promise in robbing malignant cells of their primary energy source



Cancerous myeloma cell.

STEVE GSCHMEISSNER *GETTY IMAGES*

On any given day, there are often more than 100 news articles focused on cancer, many of which speak to new and promising studies or breakthroughs in a research lab. The desperation for better treatment options is palpable. And it is no wonder, since one in three people will be diagnosed with cancer in their lifetime. While cancer research and treatments have made great strides, cancer is still far too common, which raises the question: What is missing?

Traditional cancer treatments such as chemotherapy, radiation and immunotherapy have grown by leaps and bounds, but they each have their limitations. Chemotherapy can be very effective and is still the standard of care, but it shuts down the immune system in the process and recurrence is often likely, among many other concerns. Most types of radiation cannot reach all parts of the body and therefore cannot be used for cancers that have spread. Finally, the medical community is increasingly hopeful about advances made in immunotherapy, but it is still only 20 to 30 percent effective in some cancers and completely ineffective in others.

There is another type of cancer treatment, however, known as cell metabolic therapy, which has been researched and discussed for decades without producing viable treatment options. Cell metabolic therapy targets the mitochondria—energy producers—of cancer cells, shutting down their

growth and preventing them from spreading. If we remove the energy source that these cells use to power their attack on the body, we can stop the disease dead in its tracks.

There are many reasons why cell metabolic therapy has failed in previous decades, but recent data are demonstrating that it is finally turning a corner.

The mitochondria regulate the metabolism of most cells in the body, giving them energy they need to perform. In the last decade, our understanding of the role that mitochondria play in cancer growth has developed exponentially. Scientists used to think that mitochondria were dispensable because they did not seem to be active in tumor cells. However, we now understand that the opposite is true.

Cellular metabolism is the set of chemical reactions that occur in living organisms in order to maintain life, involving a complex sequence of controlled biochemical reactions known as metabolic pathways. Back in the 1920s, Otto Warburg observed that thin slices of tumors consume more glucose than normal cells and convert most of the glucose to lactic acid. This "Warburg effect" is the foundation of one of the earliest concepts of cancer, which holds that at the root of tumor formation and growth is a fundamental disturbance of cellular metabolic activity.

Today, we understand that the metabolic transformation from a healthy cell to a cancer cell involves mitochondria, not only for generating energy but also for producing biosynthetic intermediates, the building blocks used to support new cell growth and proliferation. Therefore, by targeting the mitochondria of cancerous cells, we can diminish their ability to grow—hitting cancer where it hurts the most.

Developing a treatment that can do this effectively is not so simple, however. While many labs have tried to create therapies that target cancer cell mitochondria, most have failed. Often, the challenge has been selectively targeting the mitochondria of cancer cells while sparing those of healthy cells. Another challenge is that cancer cells quickly find ways to get around the therapy-induced suppression of metabolic pathways. For decades, the field of cancer cell metabolic therapy has remained a deserted island.

But all of that is changing. In fact, we are seeing a renewed interest with researchers exploring the metabolic emergence of cancer cells to facilitate the discovery and development of new therapies. Metformin and hydroxychloroquine, for example, are two widely used FDA-approved drugs that have been repurposed as anticancer drugs, for cancer therapy. Metformin typically is used as a first-line agent for diabetes treatment. Its anticancer effect is due in part to the way it diminishes mitochondrial metabolic functions.

Currently, there are multiple trials using metformin, including a large phase III clinical trial in breast cancer. Hydroxychloroquine is an antimalaria drug. Studies have shown that hydroxychloroquine can decrease tumor growth by cutting off the fuels that promote mitochondrial function. There are multiple phase I and II trials testing the efficacy of hydroxychloroquine.

There are also newer drugs, developed in the past decade, that diminish mitochondrial function.

One example is devimistat, a clinical-stage drug that is being evaluated in phase I, II and III trials. In a phase I trial, devimistat used in combination with a chemotherapy regimen known as FOLFIRINOX increased survival in pancreatic cancer patients. Devimistat inhibits enzymes in the mitochondria, thus preventing mitochondria from producing macromolecules for growth. Another clinical-stage drug is CB-839, which inhibits an enzyme that provides fuel to mitochondria. CB-839 is in phase I and II clinical trials.

Cancer metabolism is becoming an exciting and promising area for the development of drugs to treat the disease, especially with promising recent research showing that cell metabolic therapy can selectively target the mitochondria of cancer cells. By better understanding cancer-specific metabolic processes, researchers can find new drugs to revolutionize cancer treatment and explore this new alternative to traditional treatments.

Targeting cancer metabolism represents an opportunity to develop novel, selective and broadly applicable drugs to treat a multiplicity of cancer types. An exciting area that is being explored is how metabolic therapy might enhance the efficacy of existing therapies, including immunotherapy. Within the next decade, the field of therapy targeting cancer metabolism may join the mainstream cancer treatments.

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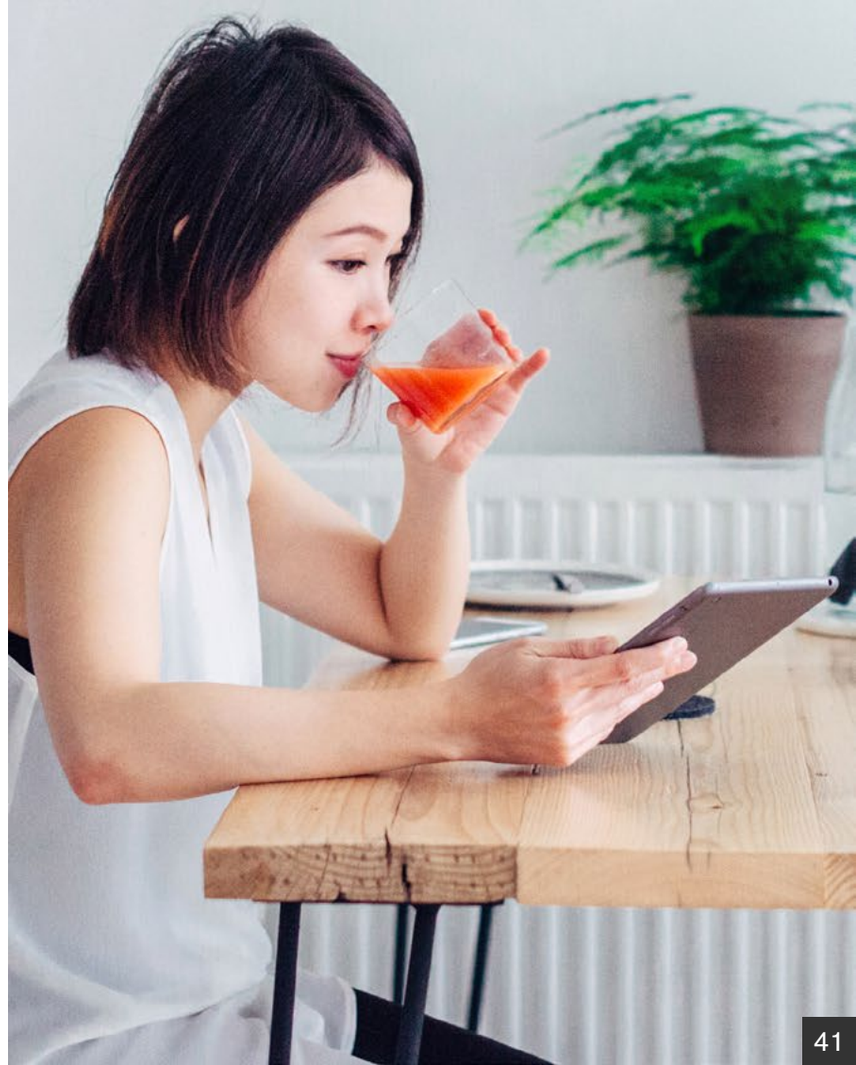

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