knowable MAGAZINE

FROM ANNUAL REVIEWS

SUMMER 2019

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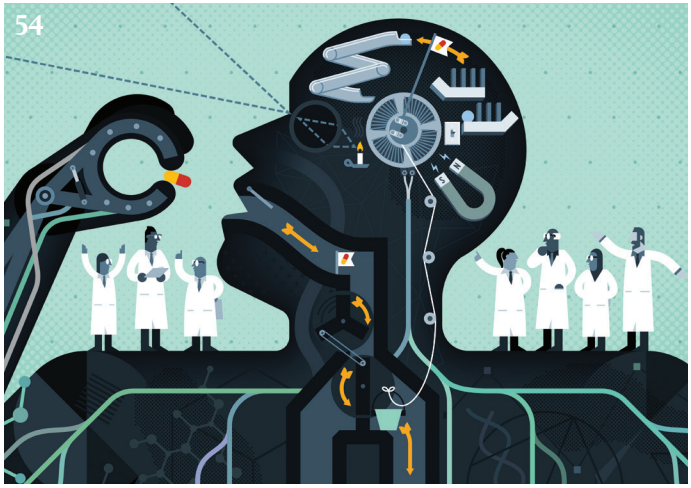

knowable MAGAZINE
FROM ANNUAL REVIEWS

Knowable Magazine is an independent science journalism project published by Annual Reviews, a nonprofit publisher in Palo Alto, California.

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CREDIT: SHAW NIELSEN

Accelerating scientific discovery.

Expanding knowledge.

Advancing the understanding of emerging scientific fields is a cornerstone of our work. Through developing new technologies, supporting imaginative research scientists and creating new collaborations at the frontiers of traditional scientific disciplines, we are expanding knowledge, which is intellectually satisfying and yields practical benefits for society.

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CREDIT: MAKI NARO

Meet *Knowable*, where we make knowledge accessible

How a vision of open science led to a new magazine

What you hold in your hands today is the first print collection of *Knowable Magazine*: a sampling of the content that appears on our website each week and an illustration of our commitment to sound science journalism. By design, *Knowable* is not a science news site, reporting on the latest study. Instead, *Knowable* presents the sum of knowledge and reports on the current state of play, across a breadth of fields. We launched *Knowable Magazine* in late 2017 as a vital exploration of the real-world implications of science as well as a survey of the past, present and future directions of research.

Knowable's origins can be traced back to an unassuming squat brick building on a quiet street in the heart of Silicon Valley. That's the home of the venerable nonprofit publisher Annual Reviews. For more than eight decades, Annual Reviews has built up one of the world's most impressive repositories of scientific knowledge, with some 40,000 expert reviews spanning more than 50 fields. In many ways, Annual Reviews retains its old-school vibe. Rows of colorful bound volumes line its wood-paneled conference room; it produces thoughtful, long-form articles dense with citations; its publishing schedule is based (as its name requires) on a yearly calendar. Founded by scientists, the nonprofit began in 1932 with a single journal focused on biochemistry. It has since expanded to 51 separate titles covering the life, physical and social sciences, as well as medicine. (It's also, of course, now available online.)

For a number of years, Annual Reviews has explored ways to bring this knowledge base into the public realm as part of the open science movement. Audiences outside of academia, outside the United States and even outside of science hunger for reliable information on the progress of science and its relevance to the greater society. The organization's board of directors believed in this need, and staff persuaded two well-known science philanthropies, the Alfred P. Sloan Foundation and Gordon and Betty Moore Foundation, to provide seed funding for a public-facing publication.

Knowable Magazine has grown from those seeds. I believe that science is one of the most powerful ways of knowing, and that (if presented in the right way, in plain English), most people are able to grasp its substance, its significance and its intrigue. So, working with veteran science journalist Rosie Mestel (*Knowable*'s executive editor), the rest of our small staff and a cadre of experienced freelance writers and editors (see Contributors on page 72), we have grown *Knowable* into a fertile garden of the latest scientific knowledge.

Knowable Magazine extends its reach by actively sharing content with other outlets, for free. Our articles have been republished in mainstream publications such as the *Washington Post*, the *Atlantic* and *Scientific American* as well as in specialized newsletters and websites of professional groups, be they healthcare workers or beekeepers. Every article also provides free access to full scientific reviews from Annual Reviews, allowing motivated readers to take a deep dive into the topic.

Our very first article looked at the need to rethink how we talk about placebos (Page 54), a story not just about the fascinating science of the placebo effect, but about the very human issues that make it ethically tricky to harness the effect to help people. As with many *Knowable* articles, it explored the space between what science knows and how that fits into the greater context of our lives and our world. (Two other great examples included here: "Can marriage make you sick?" (on Page 18) and "Nudging grows up and gets a government job" (Page 64).)

That's what *Knowable* is about — exploring what's known, what's not, and why it matters. Our roots remain in academia, but our reach is to the sky, where we are available for all people to share. We are still young, growing and changing. But our origins have set us on a trajectory dedicated to helping people and improving the world we all occupy together — seasoned with a smidgen of wonder and awe. ●

Eva Emerson
Editor-in-Chief
Knowable Magazine
from Annual Reviews

Good to Know

Drink your beets

Athletes seeking a competitive edge have experimented with a wide range of supplements, drugs and drinks — some dangerous, some illegal, most lacking any evidence of effectiveness. But new evidence does support the belief in getting a boost from one beverage: the juice of beets.
knowmag.org/BeetJuice

A second language can boost the brain

For a long time, scientists thought that to learn a language perfectly, you had to do so before adolescence. But newer research finds that's not true: Many people learn languages as adults, and they learn them very well, with lasting benefits. An interview with psycholinguist Mark Antoniou.
knowmag.org/Bilingualism

Coffee declared healthy (for most)

A thorough review of dozens of studies analyzing the health effects of coffee found that it probably reduces the risk of many kinds of cancer and is linked to lower risk of diabetes, cardiovascular disease and Parkinson's. One group that should exercise caution with coffee: pregnant women.
knowmag.org/Coffee

Firestarter

A few embers blown from a wildfire won't usually ignite a house. But a few dozen embers can generate about 40 times the heat you'd feel from the sun on a hot day — about as much as comes from the fire itself and enough to ignite most materials. Most homes that burn in wildfires are sparked by piled embers, often hours after the fire front has passed.
knowmag.org/FirePhysics

Why forgetting may make your mind more efficient

Scientists who study memory say that sometimes failure to remember is not necessarily a sign of a faulty brain. Much of the sensory input that people encounter is not worth remembering. Far from signifying failure, forgetting may be the brain's frontline strategy in processing incoming information.
knowmag.org/Forget

The dating game: When food goes bad

Many foods come with expiration dates on their packaging. But read carefully. "Use by" a certain date suggests possible health risk afterward. But "best before," "best if used by" or "enjoy by" indicate peak quality, not safety. Vast quantities of food are wasted because it's not clear when food really spoils, but new technologies to predict spoilage time accurately may help reduce those wastes.
knowmag.org/FoodGoesBad

Science & Policy

Opioids, addiction and chronic pain

Nearly a third of American adults struggle with chronic pain. But, as neuroscientist Nora Volkow explains, quelling the pain with opioids is problematic, and not only because of the potential for addiction. In some, chronic opioid use can actually worsen pain.
knowmag.org/ChronicPain

Nuclear goes retro

In the search for green sources of energy, some experts have suggested reviving an old idea for an unusual nuclear reactor. "Molten salt reactors" would be fueled by a pot of hot nuclear soup, already liquid, and so not susceptible to catastrophic meltdowns. Such reactors offer economic and safety advantages over existing reactor types, and at least half a dozen start-ups have begun efforts on commercial development.
knowmag.org/NewNuclear

Detecting clandestine nukes

"Now we are in a situation where just about every country

CREDIT: OLEPESHKINA / SHUTTERSTOCK

can probably make nuclear weapons, and just about every country can probably hide it from our technical detection," says policy physicist R. Scott Kemp of the Laboratory for Nuclear Security and Policy at MIT. The challenges of detecting facilities used to generate nuclear weapons material have been magnified by new technologies, he says.
knowmag.org/NukeDetection

Fighting crime with statistics

Analyzing criminal behavior with sophisticated statistical methods could enhance the ability of criminologists to better understand crime and advise policymakers on what to do about it. Statistical tests can also help address concerns about police bias and other law enforcement issues.
knowmag.org/CrimeStats

Genetics extends the long arm of the law

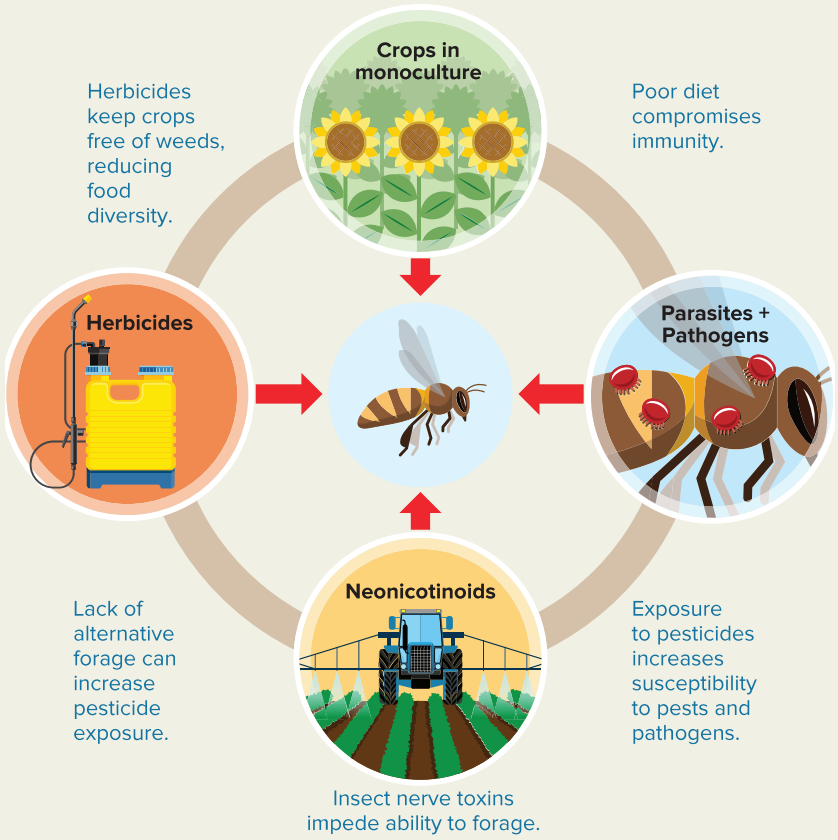
Genealogists analyzing DNA can identify criminal suspects through hereditary links to relatives they have never even met. These new techniques can enable police to solve some perplexing cold cases. But that ability also raises questions and concerns about individual privacy.
knowmag.org/DNAforensics

The financial crisis flared in an era of invisible high risk

Since the Great Recession shocked the economy a little over a decade ago, financial economists have been investigating how to better gauge risks in the financial system. Such studies call into question some of the conventional wisdom about the role of subprime mortgages for low-income consumers in the crash and raise questions about whether new regulatory safeguards will actually be strong enough to prevent another major economic downturn.
knowmag.org/RiskReform

POLLINATORS UNDER PRESSURE

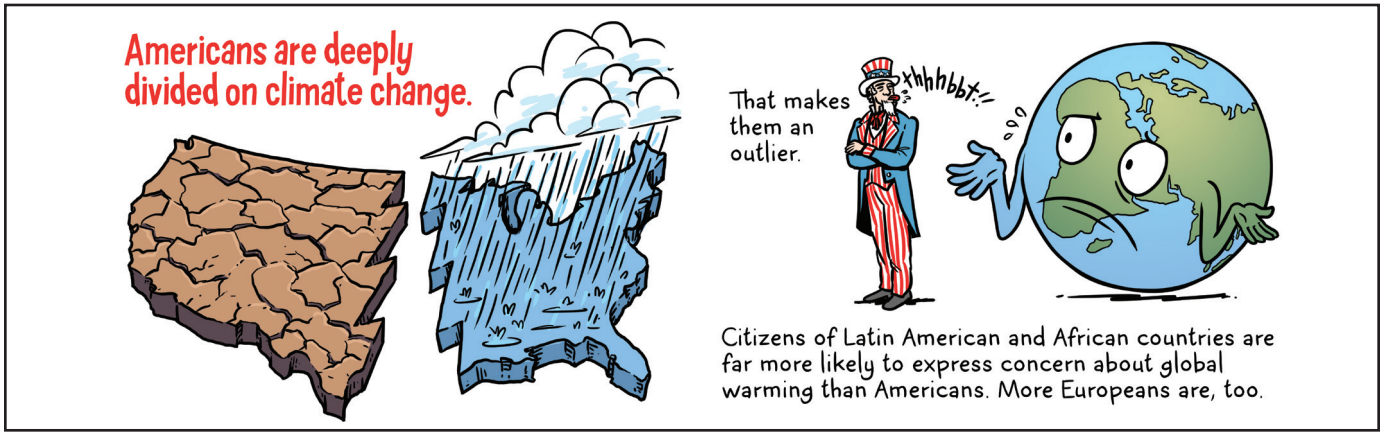
The plummeting number of bees has been blamed on a number of interacting stresses. Read more about the declines and its consequences at knowmag.org/BeeDecline



SOURCE: D. GOULSON *ET AL* / *SCIENCE* 2015, REPORTING BY S. PAIN. CREDIT: 5W INFOGRAPHIC

UNPERSUASIVE: WHY ARGUING ABOUT CLIMATE CHANGE OFTEN DOESN'T WORK

This comic by Andy Warner ran in February 2018 as part of *Knowable*'s Persuasion Special Report and is excerpted here.
Read the full comic at knowmag.org/UnpersuasiveComic



CREDIT: ANDY WARNER

CREDIT: BRIAN STAUFFER

How to ruin cancer's day

BY TAKING ADVANTAGE OF DIFFERING CIRCADIAN RHYTHMS IN HEALTHY CELLS AND TUMORS, RESEARCHERS HOPE TO ADD A POWERFUL NEW TOOL FOR TREATING THE DISEASE

BY ELIE DOLGIN

CHI VAN DANG GENERALLY DECLINES TO discuss the science that made him famous. A leading authority on cancer metabolism, he routinely is asked to speak about how tumors reprogram biochemical pathways to help them slurp up nutrients, and how disrupting these noxious adaptations could be a powerful approach to treating cancer.

Instead, Dang uses his soapbox at every research meeting, every invited lecture and every blue-ribbon panel to advocate for something else entirely: a simple yet radical tweak to how oncologists administer cancer drugs.

The approach, known as chronotherapy, involves timing the delivery of drugs to minimize the side effects of treatment while maximizing its effectiveness. The idea is to synchronize therapy with the body's natural 24-hour rhythms — the circadian clock — striking either when cancer cells are most vulnerable to assault or when healthy cells are least sensitive to toxicity (or, ideally, both).

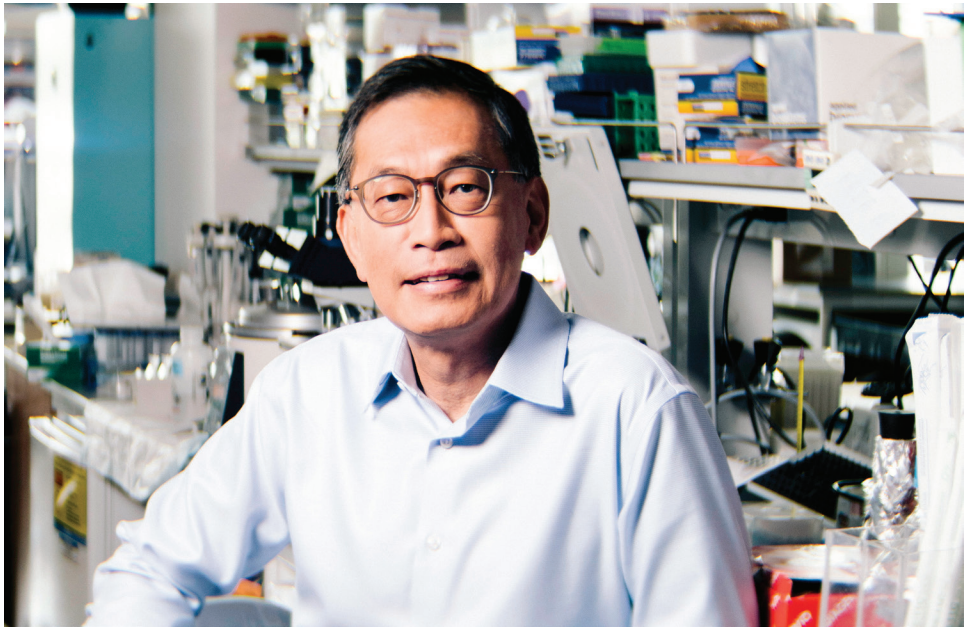
Dang didn't set out to become a global ambassador for this field. But as scientific director of the Ludwig Institute for Cancer Research, a nonprofit that funds hundreds of cancer labs worldwide, and chair of the board of scientific advisers at the US National Cancer Institute, he finds himself in a powerful position to reshape the research agenda — and he believes chronotherapy's time has come.

It is not an entirely new concept. The idea of time-stipulated therapy dates back decades, with some randomized trials in the 1980s and 1990s showing dramatic reductions in toxicities and extended survival times among cancer patients treated in a clock-optimized fashion. But for the most part, "it's just always been on the fringe," says Dang. "There weren't that many card-carrying cancer biologists like me getting into it."

Until now.

The concept of chronotherapy got a major boost in 2017 when the Nobel Prize in Physiology or Medicine went to three biologists who first uncovered the inner workings of our bodies' daily rhythms. Scientists who study the interface of circadian biology and cancer say there's been an uptick in interest in their work since the prize was announced.

But arguably, Dang's own efforts to spread the gospel about the cancer-clock connection and its therapeutic implications have been



Researcher Chi Van Dang is convinced that cancer treatments will be more effective and less toxic if we factor in the body's circadian rhythms.

CREDIT: THE WISTAR INSTITUTE

even more important in revitalizing the field. "It's capturing people's interest," he says — with a growing number of cancer researchers now beginning to explore the ways in which circadian rhythms shape tumor development.

They are finding not only new ways of administering old drugs but also clever tactics for rewiring aberrant clocks. And they are transforming a therapeutic strategy long dismissed as complementary or alternative medicine into a rigorous science.

"Time is an inconvenient truth," Dang says, and one that oncologists and cancer can no longer afford to ignore.

Timing is of the essence

A slender and bespectacled 63-year-old with the confident and unhurried voice of a seasoned physician, Dang cites his father — Chieu Van Dang, Vietnam's first neurosurgeon and former dean of the University of Saigon School of Medicine — as a role model for how he approaches positions of leadership in academic medicine. His father's death from liver cancer in 2004 remains a lasting inspiration to develop better treatments. And family, again, was a driving factor behind a fortuitous career move that prompted Dang's recent zeal for circadian biology.

He had spent nearly 25 years on the faculty at Johns Hopkins University, during which he rose through the ranks to become vice dean for research of the medical school; he figured he'd never leave. But in 2011, after his older brother Bob died of metastatic cancer of the soft tissues, Dang thought to himself: "As a medical oncologist and researcher, I need to do more." So when the University of Pennsylvania approached him with an offer to become director of its cancer center — home to the original discovery that abnormal chromosomes can cause cancer, and where a new generation of lifesaving T cell therapies were being developed — he jumped at the opportunity.

> "We still need to identify better biomarkers to personalize chronotherapy."
>
> —FRANCES LÉVI

As luck would have it, Penn also is home to one of the largest assemblages of chronobiology researchers in the country, and Dang soon found himself chatting with — and then collaborating with — clock researchers from across the Philadelphia campus. Those interactions, he says, prompted an academic epiphany: If cancer is a disease of runaway cellular growth, and circadian rhythms are what normally keep the cell cycle in check, then disruption of the internal clock must be, as Dang puts it, a "missing link" of tumor development and growth.

The circadian clock is a complex biological circuit that controls the daily rhythms of sleep, eating habits, body temperature and many other important physiological functions. The body has a master clock in the brain and many secondary clocks in other organs, as well as individual clocks in each and every cell, all controlled by an intricate network of oscillating genes and proteins.

When the various clocks are in sync, the body operates like a well-oiled machine. But when certain clock genes are mutated or thrown out of alignment by chronic jet lag, these systems can get out of whack, creating prime conditions for tumors to grow and spread.

"If I was still in Baltimore, I would probably be working on something else," says Dang (who last year moved his lab again, this time just half a mile away to the Wistar Institute, an independent research center on the Penn campus, where he is a professor in the molecular and cellular oncogenesis program). And by extension, if Dang hadn't started extolling the virtues of this research to officials at the National Cancer Institute, it's unlikely that the agency — the largest funder of cancer research in the world — would ever have lined up behind the idea. It did so last year, putting out a call for grant applications from scientists seeking to better understand how circadian processes affect tumor development and responses of patients to therapy.

Dan Xi, a program director at the NCI, says there's now talk of creating a "human circadian rhythm atlas" to bring systems-level understanding to the study of clock disruption in cancer, immunity, psychiatry and general well-being. "The major challenge for the field is understanding how the function and regulation of clock genes contribute to health and diseases," she says.

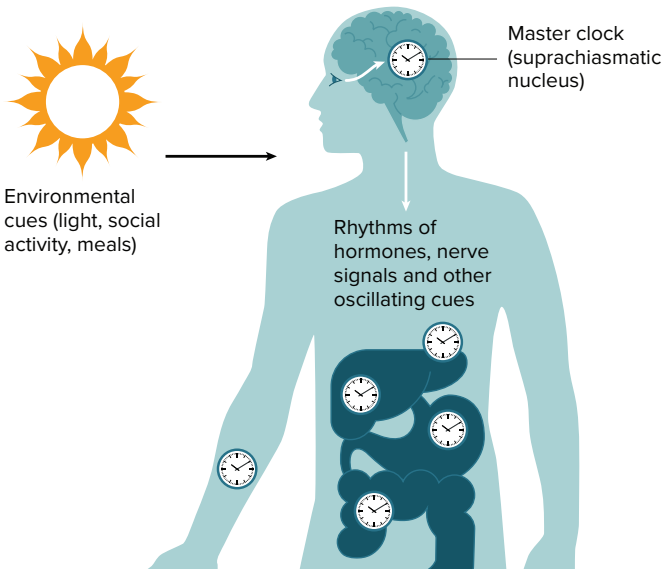
Some of the first hints that a disrupted clock could lead to cancer came in 2001, when two teams of epidemiologists working with independent datasets came to the same conclusion: Women who regularly worked the night shift had an increased chance of developing breast cancer. Later studies established a link between graveyard shifts and cancers of the colon, prostate and

endometrium — which prompted the World Health Organization's International Agency for Research on Cancer in 2007 to designate night-shift work involving circadian disruption as a probable carcinogen.

Researchers now think that nocturnal light, by decreasing the body's natural synthesis of the clock-regulating hormone melatonin, explains such a cancer link, suggesting that taking melatonin pills or modulating ambient lighting could help mitigate the risk among shift workers. But prospectively testing that idea would be difficult given the number of study subjects and years needed to detect a small number of cancers — and as yet, says Steven Hill, a circadian cancer researcher at Tulane University, "there are no published studies or active interventional studies" to that effect.

CLOCKS EVERYWHERE

The body's array of clocks all operate on a nearly 24-hour cycle, neatly aligned with Earth's daily twirl. Set by external signals such as light, a master clock in the brain called the suprachiasmatic nucleus keeps the pace by sending rhythmic messages to clocks in tissues throughout the body. When internal rhythms fall out of sync with external cues, such as in the case of a time-zone jumper, jet lag occurs. When these body clocks falter, people may become more vulnerable to diseases, including cancer.



SOURCE: F. LÉVI *ET AL / AR PHARMACOLOGY AND TOXICOLOGY* 2010; REPORTING BY L. SANDERS

Cancer never sleeps

Logistically — and financially — it is far easier to do such trials for cancer treatment than for cancer prevention, and it's here that many researchers are now focused. In 2018, for example, a team led by circadian biologist Satchidananda Panda at the Salk Institute for Biological Studies in La Jolla, California, described two novel drugs that target key clock components and kill several different types of cancer cells in a laboratory dish, as well as slow the growth of brain tumors in mice.

The drugs, by reawakening the circadian clock in cancer cells, seemed to block biological functions that tumors rely upon, including a garbage cleanup system that helps clear away toxic by-products and a molecular pathway needed for fat synthesis. Importantly, the drugs had this therapeutic effect on tumors without causing any overt toxicity in the mice.

In fact, there are even some data to suggest that resetting the clock in tumors could mitigate the side effects of cancer experienced elsewhere in the body. Cancer biologist Thales Papagiannakopoulos of New York University — his postdoc adviser called him "Chronos," given his Greek roots and academic interests — showed that lung tumor cells secrete a factor that travels through the blood to the liver, where it disrupts normal oscillatory patterns. Such effects, Papagiannakopoulos says, "could explain a lot of the symptoms of having cancer."

For example, the liver is critical for draining blood from several organs, including the spleen, and altered liver rhythms could lead to splenic backups and congestion that shorten the life span of blood cells. This could account for common side effects of cancer, including anemia and leukopenia, the low counts of blood cells experienced by many cancer patients. And if something similar is happening in muscle tissues, circadian dysfunction could underpin cachexia, a devastating loss of body weight

and strength that often afflicts people in the final stages of cancer.

Dang's own therapeutics-related research has focused mainly on showing how a notorious cancer gene named *MYC* is involved in suppressing genes that lie at the very core of the mammalian clock, such as one called *BMAL1*. This perturbs the normal oscillatory cycles of molecular regulation inside the cell, and instead pushes protein synthesis into an aberrant, perpetual state of activity that drives tumor progression. This revealed a potential drug target — one that researchers at Texas Children's Cancer Center have run with. Last year, they reported that a drug that indirectly stimulates *BMAL1* activity could help blunt the growth of neuroblastoma, a cancer of the nerve tissue, both in cell cultures and in mouse models.

Dang, meanwhile, has recently turned his attention to a class of drugs that target NAMPT, an enzyme involved in both cancer metabolism and circadian feedback loops. Around 10 to 20 years ago, a handful of NAMPT inhibitors entered clinical testing. But they all caused such low platelet counts in recipients that they never progressed past early trials.

Now, working with mouse models of lymphoma, Dang's team has found that administering these drugs at either 10 a.m. or 6 p.m. caused the same degree of tumor regression — with a key difference. Only at 6 p.m., when NAMPT expression was at its natural zenith in the liver, did the treatment cause low platelet counts in the mice. Inhibiting NAMPT at 10 a.m. caused no such problems whatsoever.

The work has led Dang to think that chronotherapy could help salvage this promising class of new cancer drugs. "We may be interfering with liver function simply by giving those drugs at the wrong time," he says.

Peaks and valleys

Another drug that doctors may currently be administering suboptimally is streptozocin, a chemotherapeutic agent that's routinely used to treat a rare form of pancreatic cancer. In a paper published in 2017, Penn sleep medicine doctor Ron Anafi took reams of gene-activity data from both cancerous and healthy liver tissue, and then developed an algorithm that models all the molecular rhythms.

His analysis showed that activity levels of a gene called *SLC2A2*, which encodes a glucose transporter protein that shuttles streptozocin, cycled in a daily fashion in normal liver cells. With John Hogenesch, a chronobiologist at Cincinnati Children's Hospital Medical Center, he then showed that administering streptozocin to mice at the nadir of *SLC2A2* expression, when levels of streptozocin's gatekeeper protein are low, minimized drug toxicity.

Anafi and Hogenesch hope to eventually test this time-optimized treatment schedule for streptozocin in patients with pancreatic tumors. At the moment, though, there is only one chronotherapy trial running in the United States (unlike in Europe and Asia, where these kinds of studies are more common). It's happening at the Washington University School of Medicine in St. Louis, where neuro-oncologist Jian Campian and her colleagues have enrolled 30 people with brain cancer and given them a standard chemotherapy drug called temozolomide either at 8 a.m. or 8 p.m.

So far, says Campian, it looks as if the side effects of the drug are far worse when people take their pills in the morning. It's too early to say anything conclusive, although animal studies from Campian's collaborators, Erik Herzog and Joshua Rubin, suggest that the drug should work best when activity of the core clock regulator *BMAL1* is highest in the tumor cells.

That would imply that the 8 p.m. dosing strategy will work better than the 8 a.m. one, at least on average. But, as Herzog points out, "people are different from each other." We have something called a chronotype that, at its most basic level, determines whether someone is a morning person or an evening person, and that will probably affect individual responses to drugs like temozolomide.

Ideally, says Herzog, the timing of treatments would be finely tuned to a patient's unique chronotype, and thus to the peaks and crests of their internal molecular activity. "This might end up being the ultimate personalized medicine," he says.

But measuring something like *BMAL1* activity in a tumor is no small task. It's invasive (one has to obtain the tumor samples), expensive and unfeasible to do routinely, in real time and for many patients. In search of an easier way, a research team at Northwestern University has a 30-person pilot study looking for genomic indicators of clock status in blood and saliva.

Yet most clock researchers have settled on tracking cruder measures like skin temperature and wrist actigraphy to get a rough estimate of whether the body is in its activity or rest phase. Those are imperfect proxies, acknowledges Francis Lévi, a chronotherapy expert at the University

of Warwick in the United Kingdom. "We still need to identify better biomarkers to personalize chronotherapy."

Even if there were an ideal biomarker, there's still the problem of the medical system being designed around a standard working day. It's not built to administer drugs at off hours — and there's little financial incentive for change. So rather than bend the system to the needs of the patient, it might be easier to bend the circadian clock to the needs of the system. This may be possible simply by time-shifting eating, sleeping, exercise habits or ambient lighting to get a patient's biological rhythms in sync with the business hours of a chemo ward.

Or perhaps the tumor's clock itself could be reprogrammed. In a study published in 2017, Silke Kiessling, a circadian biologist who conducted the work as a postdoc at McGill University in Canada, showed that injecting tumors in mice with a steroid drug called dexamethasone reset genes like *BMAL1* and induced rhythmicity in the cancer cells. Conceivably, that means a patient could take a shot of steroid a few hours before treatment so that, no matter when therapy is scheduled, that patient gets the benefit of chronotherapy without the inconvenience.

ASSOCIATED ANNUAL REVIEWS CONTENT

Circadian Clock's Cancer Connections

Z.E. Walton *et al* /
Annual Review of Cancer Biology

"This could be applicable for any kind of cancer you can reach with a needle," says Kiessling, now at the Technical University of Munich in Germany. She is also thinking about making an aerosolized formulation to extend the strategy to lung cancer. "I'm more than confident that this could work, even in humans."

Bedtime routine

For now, most of the human data come from anecdotal reports like those of Joe Kuna, who was diagnosed with metastatic colon cancer in 2014 and given two to five years to live. Four years on, the 61-year-old has beaten back a tennis-ball-size tumor in his colon and 15 lesions in his liver. Kuna, who runs a family-owned bowling alley in Johnsburg, Illinois, opted to undergo chronotherapy at the nearby Block Center for Integrative Cancer Treatment.

For the better part of two years after his diagnosis, Kuna would arrive at the center every other Tuesday, usually some time between 1 p.m. and 3:30 p.m., for his dose of oxaliplatin. Since different anticancer drugs kill cells in different ways, "each drug has a window of time" when it works best, says oncologist Keith Block, medical director of the clinic in Skokie, Illinois — and oxaliplatin, according to Block, seems to work best in the afternoon.

Kuna would sit in the cubicle with the palm tree painted on the wall and eat his tuna fish sandwich while the intravenous medication dripped into his veins through a port implanted over his right nipple.

Another one of the drugs in Kuna's chemotherapeutic cocktail, fluorouracil, is considered more of a nighttime agent — which meant Kuna had to take home a special pump, about the size of a paperback novel, that he could carry around in a fanny pack or leave on the mattress next to him in bed. The pump was programmed to kick in at 10 p.m., initially as a slow trickle. The flow would ramp up until 4 a.m. before dialing back down again and finishing up at 10 in the morning.

If you ask Kuna, this unusual drug regimen, plus the diet he followed and supplements he took as directed by the clinic, is the reason he's alive today. "I truly believe it's why I'm still here," he says. And although a scan from January 2018 revealed two new cancerous spots in his liver, Kuna is confident that, with surgery and more chronotherapy, he could be cancer-free once more. Doctors removed the tumors in April of last year.

But there's no proof, without controlled trials, that the therapy as Kuna received it made a difference. Notably, of the other patients whom Kuna befriended at the Block Center, none is alive today. Most chronotherapy strategies now in place are based on a limited understanding of clock biology — which frustrates experts like Dang.

"We really want to provide the mechanistic basis of why you treat at a certain time of day," Dang says, "and not just rely on trial and error."

It's defining why those little tweaks to common drug regimens improve patient outcomes that captures Dang's imagination as he stares out the window of the Amtrak train on his semiweekly commute from Philadelphia, where he lives and runs his lab, to New York, for his office job at the Ludwig. Just as a small career move reshaped his own research agenda, "it could be," he says, "that simple adjustments make a big difference for patients." ●

E-cigarettes: A win or loss for public health?

They're less toxic than traditional cigarettes but still addictive and not without their own health risks. Researchers disagree on whether vaping can help or harm efforts to reduce tobacco use.

BY VIVIANE CALLIER

CREDIT: VAPING360.COM

IN 2003, CHINESE PHARMACIST HON LIK created the first commercially successful electronic cigarette. Motivated by the death of his father, a heavy smoker who died of lung cancer, Lik wanted to separate nicotine delivery from the carcinogens in cigarettes. Instead of burning tobacco, his device vaporized a nicotine-containing liquid, creating smoke-like vapor that could be inhaled.

In 2006, e-cigarettes were introduced in Europe and the US. In 2016, more than 2 million US middle and high school students had used e-cigarettes in a 30-day period, and about 10 million US adults were current users. Because e-cigarettes don't burn tobacco, but simply heat a liquid until it vaporizes, users refer to "vaping" rather than smoking. There is a widespread perception that e-cigarettes are less damaging to health than conventional cigarettes. But are they?

Early on, before studies of e-cigarettes' potential harm, some scientists and advocates adhered to the "precautionary principle" — that is, "until we have more science, we don't know what to do about this and we ought to be very careful because it's got nicotine in it and we don't know what harm the aerosol has," says clinical health psychologist David Abrams of the New York University College of Global Public Health. That, he believes, is no longer the case today.

Research on the safety of e-cigarettes has grown substantially in recent years, but two very different interpretations have emerged among the scientists who study e-cigarette use.

Some researchers argue that e-cigarettes are an obvious win for public health. "The e-cigarette is just the beginning of a proof of principle of what I regard as a potential disruptive technology that literally could

> "I think we all agree that no nicotine-containing products should be sold or marketed directly to kids under the age 21."
>
> —DAVID ABRAMS

Since electronic cigarettes were first introduced in the United States and Europe in 2006, a wide variety have come to market. Many questions remain about their long-term health risks.

CREDIT: © 2017 CALIFORNIA DEPARTMENT OF PUBLIC HEALTH

make cigarettes obsolete and save lives," by helping smokers quit, says Abrams. Yet studies suggest that e-cigarettes may be depressing quitting rates and creating a gateway to traditional cigarettes, especially among youth. "We would be way better off if they didn't exist," says tobacco control scientist Stanton Glantz of the University of California, San Francisco.

Fewer carcinogens doesn't mean safe

Because an e-cigarette doesn't deliver the tar and carcinogens that traditional cigarettes do, users largely believe that it is a much safer nicotine delivery product. Studies show that e-cigarettes release fewer harmful chemicals, such as hydrogen cyanide and carbon monoxide, than found in tobacco smoke. So e-cigarettes may be a more effective way to reduce tobacco use — and prevent lung cancer — than current quitting aids. "The scientific evidence supports that they can be a reduced-harm product that could save millions of lives more rapidly than the current status quo," says Abrams.

But other studies show that aerosols produced by e-cigarettes contain ultrafine particles that cause cardiovascular disease, Glantz says. His work shows that daily e-cigarette use nearly doubles the risk of heart attacks (conventional cigarettes nearly triples the risk). The ultrafine particles also cause lung inflammation, leading to increased risk of respiratory infections and severe asthma.

E-cigarettes are "actually looking like they're worse than cigarettes in terms of effects on the lungs and it's hard to believe anything could be worse than a cigarette," says Glantz.

Overall, e-cigarettes may well be less harmful than cigarettes, as many e-cigarette makers claim, but there are no long-term studies of that issue. E-cigarettes haven't been on the market long enough for that kind of research, explains Erika Westling, a public health researcher at Oregon Research Institute. Still, many argue that e-cigarettes offer a reasonable pathway to getting people to quit smoking. But that, too, is contentious.

E-cigarettes don't snuff out smoking

In a pilot trial published in 2017 in *Cancer Epidemiology, Biomarkers & Prevention*, 68 adult smokers were randomized to receive e-cigarettes or no aid. Those with the option to use e-cigarettes made more attempts to quit and decreased conventional smoking relative to the control group. At the end of the four-month trial, 27.3 percent of control participants had made an attempt to quit compared with 40 percent of those receiving low-dose e-cigarettes and 47.6 percent of those receiving high-dose e-cigarettes.

E-cigarettes could be useful in helping adults quit smoking, concludes Matthew Carpenter, an addiction scientist at the Medical University of South Carolina who led the trial. He's now planning a larger one to see if the findings can be replicated.

Population studies show a different picture. In a meta-analysis of 20 studies, Glantz and UCSF colleague Sara Kalkhoran found the odds of quitting cigarettes were

28 percent lower for smokers who used e-cigarettes than for those who did not. In the real world, many e-cigarette users take them up with an intention to quit tobacco. But others use them with a different aim, perhaps to get a nicotine fix in areas with smoking restrictions. “Importantly, most adults who use e-cigarettes continue to smoke conventional cigarettes (referred to as dual users),” Glantz and David Bareham of Lincolnshire Community Health Services in the UK wrote in the 2018 *Annual Review of Public Health*. “In 2014 in the United States, 93 percent of e-cigarette users continued to smoke cigarettes, 83 percent in France, and 60 percent in the United Kingdom.”

In a study of young adults, Westling found that a large portion of smokers who add e-cigarettes and become dual users aren’t more likely to quit. Because e-cigarettes are convenient and relatively discreet, users might actually increase their habit, worsening their addiction, Westling says.

Smokers who have a plan for tapering their nicotine levels can use e-cigarettes as a cessation tool, “but if they don’t have that plan in place and haven’t really thought it through, adding e-cigarettes can really just increase their level of nicotine dependence, unfortunately,” Westling says. “You can’t really just add e-cigarettes in and think that that’s going to take care of the problem.”

From vaping to cigarettes

Critics have complained that e-cigarettes are aggressively marketed to youth. The packaging can be attractive, and e-liquids come in thousands of flavors, including bubble gum and cinnamon red hots. “A lot of these kids think that it’s just flavored water, so no big deal,” says Westling.

But once they become addicted to nicotine, it’s notoriously difficult to stop. Public health researcher Jessica Barrington-Trimis and her colleagues have shown that adolescents who vape are more likely to start smoking cigarettes, too. The University of Southern California researchers found that 40.4 percent of high schoolers who used e-cigarettes took up cigarettes. Only 10.5 percent of high schoolers who never used e-cigarettes did so.

Abrams contends that adolescents with risk-taking behavior are likely to try a variety of things, including e-cigarettes, traditional cigarettes, marijuana and alcohol. When controlling for these other factors, the gateway effect of e-cigarettes disappears, he argues.

The bottom line

Until scientists have more data, collected over more time, it’s likely that the opposing views on the public health implications of e-cigarettes will continue.

Most public health researchers do concur, though, that e-cigarettes shouldn’t be allowed in places where smoking isn’t allowed, or sold to young people. “I think we all agree that no nicotine-containing products should be sold or marketed directly to kids under the age 21,” Abrams says. “There’s no reason on Earth to have either alcohol or marijuana or nicotine accessible to minors.” ●

ASSOCIATED ANNUAL REVIEWS CONTENT

The Debate About Electronic Cigarettes: Harm Minimization or the Precautionary Principle

L. W. Green *et al* / *Annual Review of Public Health*

Q&A

with psychologists Janice Kiecolt-Glaser (left) and Stephanie Wilson

Can marriage make you sick?

In general, it promotes health. But it might not if your relationship is troubled or your partner is ill. Here's why, and what can be done.

By Ricki Rusting

IS HOSTILITY IN YOUR marriage stressing or depressing you? Does your partner have a chronic disorder? Then watch out. Though married people generally have better health than others, partners in these two situations can face an increased risk of obesity and cardiovascular disease.

Janice K. Kiecolt-Glaser, director of the Institute for Behavioral Medicine Research at Ohio State University in Columbus, and Stephanie J. Wilson, a postdoctoral researcher in her lab, study and explain here the health effects of intimate relationships.

This interview has been edited for length and clarity.

Is it true that, overall, being married is good for you?

JKG: A bunch of studies show that marriage, on average, is beneficial for rates of disease, recovery from surgery, cancer risk — most of the things you can look at.

The effects of being single are similar in magnitude to the health risks of smoking, high blood pressure, obesity or a sedentary lifestyle.

SW: A recent analysis showed that the effect of a quality marriage on physical health was about equivalent to that of daily exercise or a healthy diet.

Now the flip side. Studies show that a person's risks for obesity, diabetes and metabolic syndrome rise dramatically if their partner has the condition — doubling in the case of obesity, for example. What explains this "contagion"?

JKG: If your partner has less healthy behaviors, it gives you license, and perhaps subtle social pressure, to adopt them as well.

Being stressed by ongoing marital discord also aligns with poor health. What are common effects?

JKG: Cardiovascular disease has been well described, hypertension has been described — the whole metabolic syndrome group of diseases. Marital discord doubles the risk for metabolic syndrome.

SW: A lot of the chronic illnesses that develop at higher rates in couples who are unhappy may be caused in part by inflammation.

Also, marital distress and depression are strong fellow travelers. An unhappy marriage is really, really fertile ground for depression, and depression has very well-documented health consequences.

It sounds as if most roads lead through inflammation.

JKG: It's one of the central pathways we know the most about these days, although there are certainly others. Inflammation is associated with a variety of different diseases.

Behaviors also change as a result of marital stress. How do they link to ill health?

JKG: Most of us don't tend to eat more broccoli when we're stressed, or all the things our mothers told us to do: eat healthily, exercise, drink moderately. Those are all behaviors that, with stress, get worse.

Can these effects contribute to inflammation?

JKG: When you are eating a high-fat, unhealthy diet, it's inflammation-producing. Drinking heavily, smoking, sedentary behavior are all associated with inflammation. Depressive symptoms have inflammatory consequences, too.

How does one show that marital discord affects physiology?

JKG: In the earlier studies in our lab, we would bring couples in and put a catheter in their arm and ask them to discuss a disagreement, and we could watch stress hormones in the blood respond to the quality of the disagreement. When people were more nasty or hostile, we would see much larger increases in stress hormones.

CREDIT: JAMES PROVOST

What behaviors do you look for, specifically?

JKG: Bad marriages often have the same kinds of symptoms. One classic signature is the demand-withdraw pattern, where one person will be saying they want a change and the other person doesn't want to discuss it. Another signature is negative escalation: One person says something negative, the other person responds in kind, and it goes up and up and up.

Do you see gender differences in responses to marital distress?

JKG: There is a large psychological literature showing that women remember both positive and negative events in much more detail than men; women ruminate or think about those relationship events much more than men. So it would be surprising if there were not greater health effects for women.

At the other end of the spectrum, having a really good relationship can put a person at risk for health problems if the partner is ill. What goes on there?

JKG: Some of the best evidence comes from the extreme case of spouses caring for partners with Alzheimer's disease. Years ago, we showed that the spouses' immune systems were less likely to respond to vaccination as they should; spouses healed wounds more slowly; they had higher levels of inflammation. There is now good evidence across less-dramatic illnesses that a spouse's illness matters.

Elderly couples in a happy marriage face a greater health risk than younger people do when a partner is ill. Why?

JKG: Older couples have longer, more intense relationships. Also, the older someone is, the more vulnerable they are physiologically. Stress for someone in their 20s is not likely to make them sick or have huge health effects, but we know that when someone is 65 or 70, noticeable declines in the immune response begin, and age-related increases in inflammation.

SW: In general, as people age, there is a decrease in the size of the social network. Psychological weight is placed on the marital relationship.

Is there a good way to protect health when couples have marital problems?

JKG: There is some evidence that marital problems are going to be most responsive to marital therapy (as opposed to individual therapy). It can address the utility, or lack of utility, of the way couples are thinking about particular problems.

SW: And it can encourage making an effort to take the other person's perspective and to approach problems as a team. We only have a few studies to look to. But they've shown that if the therapy is effective at reducing marital problems, we see a reduction in stress hormone reactivity.

To limit marital tension when one partner is ill, the advice to a spouse seems to be "be supportive." But how do you do that without seeming to be a nag or too critical?

SW: Supporting the person in their independence — essentially saying, "I believe in you; this is a challenge, but you can do this" — can build a partner's self-confidence. Being empathic has also been shown to be effective — listening actively when the partner wants to share, and being generally loving and warm.

In your own relationships, have you used anything you've learned from the research?

JKG: Yes — the idea that you pay attention to your relationship; that it matters how you talk about it and think about it. And it matters that you take good care of yourself, as well as attending to your partner, when your partner is ill.

My husband has Alzheimer's disease. When he was first diagnosed with mild cognitive impairment, I saw the train coming down the tracks. Our lives were very much intertwined. He was my primary research collaborator and we had a really good relationship and a closeness.

So I tried to make sure that I had my own life aside from the marriage, in terms of friendships — and I tried very hard to take care of my own health. I knew all too well what happened when people didn't take care of themselves.

Don't breakups cause anxiety, depression and stress too? And loneliness. Which is worse for health — staying in a non-ideal relationship or going it alone?

SW: The evidence is mixed. One study found that singles had lower resting blood pressure than unhappily married people. But a study of people with rheumatoid arthritis found that singles and the unhappily married were in an equal amount of pain. In both cases, happily married people fared best.

As for divorce, most people cope well and recover quickly post-marriage, but a consistent minority (10–15 percent) struggle and face heightened health risks.

And as for loneliness, it is possible to feel lonely in a marriage. In the unmarried, surrounding oneself with other friends and family seems to be especially important. ●

The human factor in clean water

THERE ARE MANY CHEAP AND EFFECTIVE WAYS TO PROVIDE SAFE WATER TO THE WORLD'S POOR REGIONS. BUT PROJECTS OFTEN FAIL DUE TO INADEQUATE PLANNING, MAINTENANCE OR PERSUASIVE POWER.

BY LINDZI WESSEL

OPPOSITE PAGE CREDIT: GRANT ROONEY PREMIUM / ALAMY STOCK PHOTO
THIS PAGE SOURCE: PROGRESS ON DRINKING WATER, SANITATION AND HYGIENE / WHO & UNICEF, 2017. MAP FROM NATURAL EARTH / WIKIMEDIA COMMONS

FOR MORE THAN 2 billion people, safe drinking water isn't a given. Not for them a clean, reliable supply of treated water splurting out on demand from a kitchen tap — instead, they often face long treks to wells, rivers, pools of rainwater or faucets that yield water laced with disease-transmitting feces and other contaminants.

More than 500,000 deaths a year from diarrhea are linked to this very basic lack, and public health officials, philanthropic groups and researchers have worked to move the needle on the problem for decades.

So enthusiasm soared in the early 2000s for a new and compellingly simple approach. Instead of waiting for governments to act, or for projects that progressed at a snail's pace, what if villages and households were empowered to clean water themselves? A slew of cheap and easy technologies were available for the job.

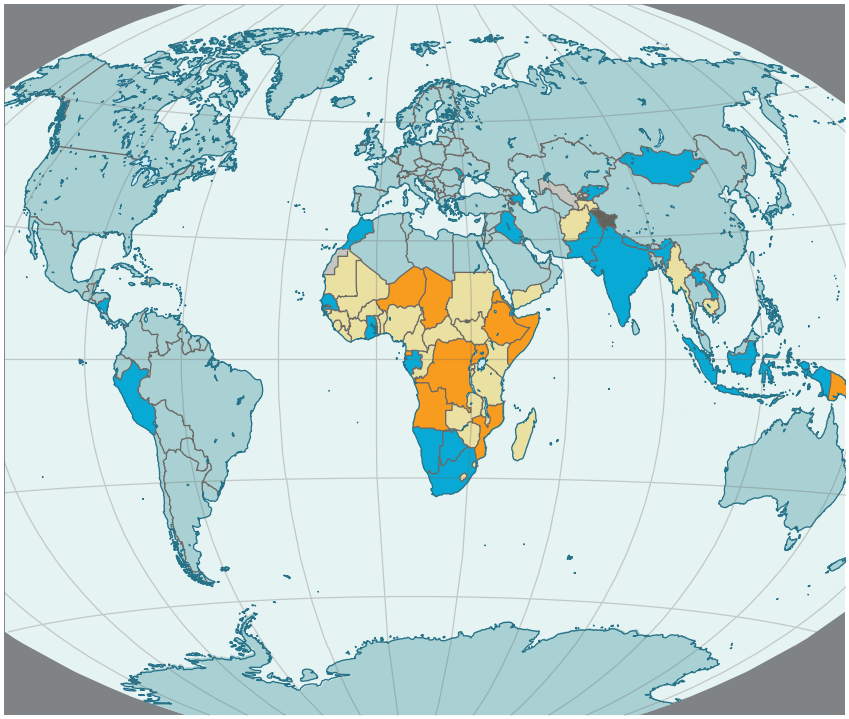
From Ghana to Afghanistan to Bangladesh, development workers leaped to action. They fitted hand pumps to boreholes in rural communities. They held workshops explaining how a few hours of sunlight could purify water held in plastic bottles. Households received ceramic filters that fit on tables, or larger sand filters cemented outside their doors. Volunteers promoted water-boiling, handed out bottles of chlorine and educated people about threats lurking in even the clearest-looking untreated water.

"Household water treatment was seen as potentially this huge revolutionary new model," says Joseph Brown, a public health engineer at Georgia Tech who spent much of his early career designing portable filters. "You could just deliver these devices, and everybody would start using them."

WORLDWIDE WATER AVAILABILITY IN 2015

Percent of population with access to a protected or treated water source within a 30-minute round trip

● < 50% ● 50–75% ● 76–90% ● 91–100% ● Insufficient data ● Not applicable



The bad news

Then, in 2009, came the bucket of cold water. A newly published review argued that there was little solid evidence that household water treatment in poor rural regions was working: Placebo-controlled trials in Ghana, Gambia and Brazil found no effect on incidence of diarrhea. Brown recalls that he was giving a talk at the World Bank in Washington, DC, about the benefits of treating water at the household level when, even as he spoke, someone in the audience was circulating copies of the paper.

It was "really the first skeptical paper that had come out around household water treatment — specifically to say that this method for providing safe water is totally bonkers," Brown says.

More criticism followed. People targeted for interventions didn't seem to value treatments and weren't willing to pay for them. They used treatment tools incorrectly or inconsistently, and

A girl in Kenya chlorinates her water. Chlorine dispensers placed next to water collection points save time and effort for people who already must make long treks to get water. Mixing happens during the walk back.

CREDIT: THOMAS CHUPEIN FOR J-PAL

usage dropped sharply over time. In a trial that taught members of poor communities in Dhaka, Bangladesh, about water safety and supplied 600 households with two free months' worth of water-treatment products, the devices went largely unused. On site visits, when asked if they had treated their water in the last day, more than 70 percent said no. "Adoption among the global poor is very low," wrote the study authors, "and little evidence exists on why."

For public health workers and researchers, it was a huge conundrum. They knew the technologies *could* make water safe — the methods worked well in laboratory settings — so what was stopping these simple solutions from taking hold in the real world, with the people who needed them most? That puzzle has spurred a sea change in research around clean water development. Where once investigators asked what tools were best to gift to communities, they now ask why those "gifts" may have no impact. Questions of engineering and chemistry have given way to quite different questions about policy, maintenance — and the realities of human behavior.

"There's no technology that eliminates the need for implementing well," says Millie Adam, director of international partnerships at the Canadian charity Centre for Affordable Water and Sanitation Technology (CAWST). "There's many organizations that have tried to find the silver bullet that you can just drop in, do it, and then check that community off the list and walk away. I don't think that solution exists."

From lab to field

In 2015, member states of the United Nations set a package of development goals including universal safe water by 2030, with the ideal being safe, piped water delivered to homes and communities. The world is nowhere near on track. Most researchers, public health officials and development workers agree that household water treatment options can be crucial as interim solutions in emergencies or where no other resources are available — but experts are still divided on the role household water treatment should play in filling the gaps long-term.

An abundance of cheap solutions can mimic the process that water goes through at a modern large-scale municipal utility. Chlorination, filtering and disinfection by heating water in the sun can kill or remove more than 90 percent of microbial pathogens in laboratory settings,

while boiling, when done properly, kills 100 percent of the microbes causing diarrheal diseases.

But lab success doesn't necessarily translate to field victory, and there are many reasons why.

Durability is one of them. A 2009 study that evaluated use of ceramic filters in 13 villages in rural Cambodia found that filter use declined at a rate of 2 percent each month, due mostly to breakage of spigots, containers and ceramic filter elements. Four years out, filtering had practically ceased. And a 2016 study of ceramic candle filters in a village in South Africa found that the filters stopped working properly months earlier than expected due to higher-than-expected levels of use. Eight months after distribution, people were still using the filters, but none produced water free from contamination.

A lack of long-term planning and follow-up has also contributed to the failures. As noted in a March 2009 briefing of the International Institute for Environment and Development, an estimated 50,000 African boreholes and wells, dug to tap safe sources of groundwater, were no longer working due to lack of plans and funds for basic upkeep. "Rather than construct a thousand wells, I'd rather construct 800 wells and put aside a chunk of money for maintenance," says Michael Kremer, a developmental economist at Harvard University.

Purification, with imperfections

Long-term planning matters even for the simplest modes of water treatment. Boiling, the most common purification method, is used by around 20 percent of households in low- and middle-income countries. But not all boiling is equal. Whereas electric boilers can be safe and efficient, using other forms of fuel can be costly and even dangerous. Collection or purchase of fuel is a burden, and household air pollution from burning solid fuels such as wood, charcoal and animal dung causes more than 3.5 million premature deaths annually.

Chlorine is favored as one of the cheapest options for water treatment — 1,000 liters of water can be treated at a cost of only 10 cents. But households without taps must store water for extended periods, so chlorine levels must be high to protect against recontamination, imbuing water with an acrid smell and taste. Chlorine is also less effective in cloudy or muddy water. And even though it's cheap, users must still mix the appropriate amount with the water and wait for the chemical to take effect.

In circumstances where people are poor and already overworked, these small extra steps can doom a process that needs to be done right to work, says Isha Ray, an economist specializing in water and development at the University of California, Berkeley, where she co-heads the Berkeley Water Center. Ray doubts that she herself would do much better if she were in the same position. In fact, she says, research suggests she wouldn't.

> "In the US you have a municipal system, and there are all sorts of regulatory bodies.... We forget that we rely on these systems, and we go into low-income countries and we think the infrastructure is going to be enough."
>
> —CHRISTIE CHATTERLEY

"One thing we know from the social sciences is people are not all the time driven only and exclusively by health considerations," she says. "Every single person I know has a gym membership they don't use, including myself." How then, she asks, is it practical to expect a person with fewer resources and

more daily chores to take on the additional burden of treating water? Lugging and treating water can be a "painful chore that has to be repeated every day," she says, one that typically falls to women. "And that means her body is acting as infrastructure, covering for a piece of pipe."

And anything short of perfection may reap few returns, according to a 2012 modeling study coauthored by Brown. It found that skipping treatment of high-risk water just 10 percent of the time would result in a 96 percent drop in the potential health benefits.

Keeping it simple

So it would make sense that the most effective approach would be to make water treatment as automatic as possible, eliminating extra steps. Behavioral research is starting to confirm this.

In a study in Kenya that ran from 2007 to 2011, chlorine dispensers were placed right next to pipes providing continuous water flow where villagers went daily to fill up their jugs. After filling a container, all the villager had to do was place it under a chlorine dispenser and turn a knob. The walk home took care of mixing. That convenience seemed to pay off: Three and a half years later, 51 percent of village participants had adequate levels of chlorine in their water, compared with only 6 percent of people in similar villages. Those people received only promotional messaging about the value of chlorine, then had to go pick it up themselves.

Kremer, who worked on the project, says he's excited about efforts to go one step further and design completely automatic chlorine dispensers that apply the right amount of chlorine as water is collected at taps. Removing extra steps also applies to payments, he says: People will pay for access to water, but often not the cleanliness of water. Thus, bundling the costs together should be more effective than adding a separate fee on top.

The right kind of information may be powerful, too. In a 2018 study, researchers gave poor families in rural India water-safety education and the means to get readings on water quality in their own households, either through self-administered test kits or lab reports. After a month, participants who received such information reported boiling their water more consistently than participants who just received water safety education, and their water also had a bigger drop in *E. coli* levels.

Brown, one of the lead authors, thinks direct feedback like this might help people get involved in tackling their water issues. "Most water that's unsafe looks and smells perfectly fine. The challenge is making this invisible problem visible," he says.

Dry facts, but no easy answers

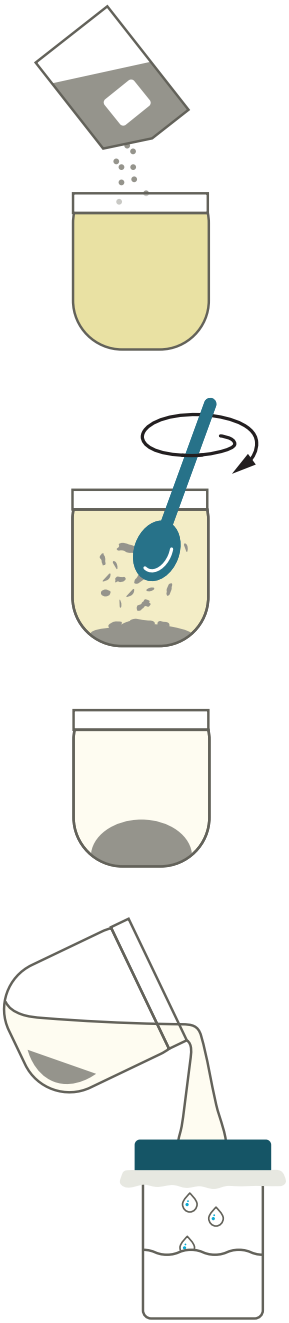
Researchers are investigating other factors that might improve water treatment efforts. Some studies, with mixed results, have examined whether establishing leadership roles for women — who are often responsible for a household's water supply — could improve long-term adherence to water treatment. And researchers who worry that offering free water treatment might undervalue the service in participants' eyes have suggested that vouchers for chlorine and other treatments might help convey that value without precluding treatment for those who can't pay. Other questions linger about how to educate people on safe water storage and use: Often, community leaders are more persuasive than foreign development workers, and the nuances of local marketing can be crucial.

The solution for one community may well be unsuitable for another. Romain Villiers, global water, sanitation and hygiene advisor for CAWST, spends months learning about a community before recommending a water treatment project. Sometimes, two settings can feel

ASSOCIATED ANNUAL REVIEWS CONTENT

Safe Drinking Water for Low-Income Regions

S. Amrose *et al* / *Annual Review of Environment and Resources*



SOURCE: CDC

Floating particles in cloudy water can clog filters. But chemicals called coagulants and flocculants can clump the particles so they drop out of the water. Some can help remove heavy metals like arsenic.

"like working on different planets," he says, making it daunting to predict what will work. Even gold-standard controlled trials — ones comparing people who received an intervention to ones who didn't — won't tell you if results will generalize to other communities.

For that reason, some global health researchers are experimenting with statistical analyses across interventions in different communities. By assigning scores to factors such as financial management and community cooperation and comparing them across interventions, they hope to tease out common drivers of success.

A 2014 study used such a method to evaluate sanitation and hygiene programs across 16 schools in rural Bangladesh. The study found that schools continuing to have working toilets usually had higher financial contributions from local governments or communities than schools where toilets ended up broken, unclean and unusable. In the rarer cases where toilets remained functional without higher financial support, schools had concrete maintenance plans and a "local champion" — typically a teacher or project field officer — who oversaw regular cleaning and upkeep.

In a similar vein, a 2018 study sought to identify common features of successful drinking water systems by analyzing shared characteristics of 20 cases across the globe. Though the researchers couldn't consider all the factors they were interested in, they did identify good financial management and community involvement in project decisions as two critical ingredients.

The importance of those two factors makes sense to Christie Chatterley, an environmental engineer at Fort Lewis College in Colorado who worked on the Bangladesh sanitation study and spent her early career working on sanitation, water and energy projects for low- and middle-income countries. One was a community water-treatment system in Rwanda that combined a settling tank, sand-based filtration and solar-powered ultraviolet disinfection.

That technology should have worked, she says: "Everyone thought, 'It has to — it's designed so perfectly!'" Except it didn't. Missing was adequate attention to less sexy but critical questions of long-term maintenance, monitoring and funding.

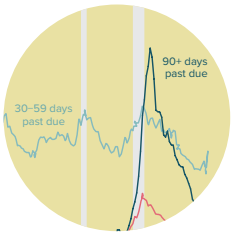
"In the US you have a municipal system, and there are all sorts of regulatory bodies, and we have water meters, and we have people checking on things and making sure the treatment is adequate," Chatterley says. "We forget that we rely on these systems, and we go into low-income countries and we think the infrastructure is going to be enough."

These days, Chatterley focuses on water policy and "systems building" — industry-speak for helping communities establish the support, planning and resources they need to keep a project going. It may not be a glitzy term but there is no getting around it, she says. It's why the projects that are likely to last take so long to set up.

Creating the supply chains, financial management, monitoring systems and other pieces needed to keep a project going is slow work. But building these systems may be the most important part of meeting the United Nations goal of getting safe water to everyone in just over a decade.

"You would think with all the resources and knowledge in the world, we would be able to figure it out by 2030," Chatterley says. "But when you look at the reality of things, then it does feel really daunting." ●

Q&A



with economist Antoinette Schoar

A ‘subprime’ crisis in housing? Think again.

Economist Antoinette Schoar and colleagues found that middle-class homebuyers had more to do with 2008’s real estate crash than the less-wealthy consumers usually blamed

By Eryn Brown

THINGS HADN’T BEEN THIS bad for the American economy since the Great Depression: 2008 was a disastrous year.

Facing a hot housing market, lower-income would-be homeowners had taken out risky, deceptively marketed “subprime” mortgages. When real estate boiled over and home values plummeted, these borrowers defaulted on their loans, dragging the entire economy down with them.

Or so the story goes.

MIT Sloan School of Management economist Antoinette Schoar studies the decisions people make about their money, from picking credit cards to investing for retirement. Housing is one of the biggest such decisions. It’s hard to pin down, Schoar says, but for many homeowners, their house represents more than half their wealth. Writing in the 2018 *Annual Review of Financial Economics*, she and coauthors Manuel Adelino and Felipe Severino take a deeper look at how consumer homebuying decisions contributed to the 2008 collapse.

Schoar and her colleagues reach a few surprising conclusions. First, shoddy lending practices, long blamed for sparking the ill-fated housing boom, were probably symptoms, rather than causes, of a larger problem of overoptimism. The team also says that calling the housing crash a “subprime crisis” — a problem that emerged primarily from the subprime mortgage loan market catering to less-wealthy consumers with relatively low credit scores — doesn’t make a whole lot of sense.

But the recession has definitely had an effect on homeownership. Census data show that 69 percent of Americans owned houses before the crisis, Schoar notes. After, that number fell to 55 percent. *Knowable Magazine* asked Schoar about her takeaways on 2008 a decade after the crisis, as well as her thoughts about the future. This interview has been edited for length and clarity.

Where were you in 2007, when the problem that became the financial crisis was beginning to emerge? Were you following what was happening in the housing market?

Yes. I was at MIT, studying the intersection of behavioral economics and consumer finance. I’m interested in the gamut of individual financial choices households make, and how they make them. A year or two before the financial crisis, I had started becoming interested in the housing segment. It was clear that behavioral issues were playing a big role in what was going on.

What kinds of behavioral issues?

Specifically, the way people were thinking about house prices, which had been going up for a very long time — in the United States, for almost a decade, in certain areas at least.

House prices were very high relative to people’s incomes, and relative to historic levels. It was interesting to me to see consumers becoming actually more bullish in such an environment. The data should have made them more concerned. Historically, house prices always revert to the mean — once they go up a lot, they have always dropped back down.

I was getting so worried that in the late spring of 2008, I sold my house in Boston! That turned out to be a good decision. But I was not expecting a Great Recession. I didn’t anticipate that bank failures would accompany the housing crash and that it would have such a dire impact on the economy.

You made two findings that contradict the usual narrative about the crash. One was that exuberance about housing prices, rather than bad banking practices, got the ball rolling.

Yes. Consumers, homeowners and borrowers seem to have had very optimistic and overinflated

CREDIT: MICHAEL MORGANSTERN; *KNOWABLE MAGAZINE*; JAMES PROVOST

views of how much house prices could still increase. They were willing to bet on the housing market, and to buy above and beyond what they might have normally, placing themselves at great financial risk.

People often say that banks' lax lending practices fueled this consumer optimism. But our research suggested that the housing market exuberance went hand in hand with it. Everyone, including the banks, got caught up in it.

The problem with the banks was less a misalignment of incentives or deliberate mis-selling of loans to people who couldn't afford it, and more, if you want, stupidity. It was this belief that house prices could only go up, and so it didn't matter whether the person who was buying a particular house might lose his or her job and default on their payments. The bank would be holding valuable collateral and everything would be fine.

So banks who made bad loans are not to blame?

That's absolutely not the idea to take away from our research! Buyers can get overoptimistic and can misunderstand housing dynamics, but it's financial institutions' job to know more than the consumer. The fact that banks were overoptimistic in making these mortgages doesn't absolve them of anything.

Your second surprising insight was that the housing crash was mostly caused by middle-class homebuyers — not by less-wealthy buyers with subprime mortgages, who are often blamed.

Right. Many economists studying the crisis looked at it through the lens that had been touted in the press: this idea that the subprime segment caused everything. We thought that seemed too narrow an understanding of what had been going on. Maybe because we were living in Boston, a city where similar effects were going on in middle-class or upper-middle-class neighborhoods.

If you actually look at the size of the subprime market in the US, it is very small. These are mortgages of people who are poorer, have much lower income and can only take very small mortgages. The typical middle-class person in the US has a mortgage of around $230,000. The typical subprime loan is below $70,000.

Most mortgage dollars lent in the US economy go to the middle class and the upper middle class. When those segments have problems, *that's* when the banking system and the rest of the financial system is impacted.

What could government do to prevent this from happening again in the housing market?

It's very important for regulators, and in particular the Federal Reserve, to take into account that during times of exuberant expectations, a lot of individual banks may make bad decisions at the same time. If my competitor gives an ill-advised loan, if I don't match it I'll miss out on getting business. It's a race to the bottom.

Regulators need to put safeguards in place to prevent this from happening.

Did changes like the 2010 Dodd-Frank Act help accomplish that? Are regulators on top of the situation today?

Dodd-Frank and many of the regulations the Fed implemented post-2008 were very helpful and definitely move us in the right direction. But in my opinion, housing is the one market where regulation has failed, in many ways.

For instance, Fannie Mae and Freddie Mac, which buy and securitize pools of mortgages and sell them to investors, are still government-controlled and underwritten. Over the last 10 years, traditional banks have reduced their participation in mortgage origination and mortgage lending, because regulation has made it costlier for them. Half of mortgages are originated by nontraditional lenders like Quicken Loans and H&R Block, who make loans and then sell them to Fannie and Freddie.

These are new players in the mortgage market, and we don't know how good they are at screening borrowers. If there's a crash today, the banks will be less affected, because they're not holding such a large chunk of mortgages, but Fannie and Freddie — which are public institutions — will suffer. And if they default, they default on the government, and that means all of us.

How are you feeling about the state of the housing market today?

I'm starting to get nervous, I have to say. I don't think housing will cause a banking crisis again, because the big banks are much less exposed to housing.

But I worry that if we have another downturn in the housing market, which might not be so unrealistic, that now it potentially will have a drawn-out, almost hidden, but creeping effect. Because the government will be bailing out underwater mortgages, and it might divert a lot of resources from other things that are really important, like education. ●

Awesome ears: The weird world of insect hearing

EVOLUTION MADE INSECT EARS MANY TIMES OVER, RESULTING IN A DAZZLING VARIETY OF FORMS FOUND ALL OVER THE BODY. BIOLOGISTS ARE DIGGING DEEP INTO SOME OF THOSE EARS TO FIGURE OUT HOW AND WHY THEY CAME TO BE.

BY STEPHANIE PAIN

IN A SMALL WINDOWLESS ROOM ON A sweltering summer's day, I find myself face-to-face with an entomological rock star. I'm at the University of Lincoln in eastern England, inside an insectary, a room lined with tanks and jars containing plastic plants and dozing insects. Before I know it, I'm being introduced to a vibrant-green katydid from Colombia.

"Meet *Copiphora gorgonensis*," says Fernando Montealegre-Z, discoverer of this six-legged celebrity. This katydid's name is familiar: It's been splashed across the world alongside photos of the insect's golden face and miniature unicorn's horn. Its renown rests not on its looks, though, but on its hearing. Montealegre-Z's meticulous studies of the magnificent insect revealed that it has ears uncannily like ours, with entomological versions of eardrums, ossicles and cochleas to help it pick up and analyze sounds.

Katydids — there are thousands of species — have the smallest ears of any animal, one on each front leg just below the "knee." But their small size and seemingly strange location belie the sophisticated structure and impressive capabilities of these organs: to detect the ultrasonic clicks of hunting bats, pick out the signature songs of prospective mates, and home in on dinner. One Australian katydid has capitalized on its auditory prowess to capture prey in a very devious way: It lures male cicadas within striking distance by mimicking the female part of the cicada mating duet — a trick requiring it to recognize complex patterns of sound and precisely when to chip in.

Awesome? Absolutely. Unexpected? That, too. I'd never given much thought to insect ears until now. Insect eyes and antennae stand out, but ears? Even the eagle-eyed could be forgiven for wondering if insects have them. Yet obviously, some must hear: The summer air is filled with the trills, chirps and clicks of lovelorn crickets and grasshoppers, cicadas and katydids, all trying to attract a mate.

Curiosity piqued, I call neurobiologist Martin Göpfert at the University of Göttingen in Germany, who studies hearing in the fruit fly *Drosophila melanogaster*. Amazing though katydid ears are, he tells me, they're just one of many insects with astonishing capabilities: Evolution has made many attempts at shaping ears, resulting in a huge diversity of structures. Most are hard to spot, and in many cases insects produce and sense sounds so far beyond our own range that we overlooked their abilities entirely. But new tools and technologies are bringing more examples to light.

> "Insects only hear what they need to hear. And evolution provided what was necessary."
>
> —MARTIN GÖPFERT

Sensory biologists, acoustics experts and geneticists are working together to pin down how they all work, how and when they evolved, and why. And thanks to some of this newfound knowledge, and an assortment of fossil insects, there's even the tantalizing prospect of being able to eavesdrop on the ancient past, adding a new dimension to our understanding of the life and times of some long-vanished animals.

When insects first appeared some 400 million years ago, they were deaf, Göpfert says. These ancestral insects went on to diversify into more than 900,000 species, and while most remain as deaf as their ancestors, some gained the means to hear. Of the 30 major insect orders, nine (at last count) include some that hear, and hearing has evolved more than once in some orders — at least six times among butterflies and moths. The 350,000 species of that most dazzlingly diverse group, the beetles, are almost all deaf, yet the few that have ears acquired them through two separate lines of evolution. All told, insect ears arose more than 20 separate times, a surefire recipe for variety.

Ear, there and everywhere

Location is the most obvious difference between one insect's ears and another's: There are ears on antennae (mosquitoes and fruit flies), forelegs (crickets and katydids), wings (lacewings), abdomen (cicadas, grasshoppers and locusts) and on what passes for a "neck" (parasitic flies). Among moths and butterflies, ears crop up practically anywhere, even on mouthparts. The bladder grasshopper has an abundance of ears with six pairs along the sides of its abdomen. Praying mantises have a single, "cyclopean" ear in the middle of their chest.

This anywhere-goes approach might seem a little weird but there's a simple explanation: In every case where an insect ear evolved, the starting point was an existing sensory organ: a stretch detector that monitors tiny vibrations when neighboring body segments move. Those detectors occur throughout the insect body but evolution typically only modified a single pair — apparently, almost any pair — to perceive the airborne vibrations generated by sound.

From there on, each new attempt to forge ears went even further in its own direction as other structures were co-opted and

OPPOSITE PAGE CREDIT: ANTON SOROKIN / ALAMY STOCK PHOTO

reconfigured to capture, amplify and filter sound, extract the relevant information and convey it to the nervous system. In mosquitoes and fruit flies, sound causes fine antennal hairs to quiver. Most other hearing insects have "eardrums": thin, membranous patches of exoskeleton that vibrate when sound waves hit. Some eardrums are backed by air-filled acoustic chambers, others by fluid-filled ones. The number and arrangement of sensory cells that detect and decode those vibrations — and the neurons that send the signals to the brain — also vary from ear to ear. So while some moth ears function with just one or two neurons (making moths the most rapid responders), a male mosquito's ear has around 15,000 (making it exquisitely sensitive).

Some ears are relatively simple; others have extra bells and whistles linked to their lifestyle. Take the parasitic fly *Ormia ochracea*, which deposits its larvae on a particular species of cricket after identifying and locating it from its characteristic call. The fly's ears sit side by side on its "neck" and are theoretically too close together to pinpoint its target. Yet they take the prize for accurate location, thanks to an elastic band connecting the eardrums so they rock up and down like a seesaw, ensuring sound hits one ear fractionally later than the other.

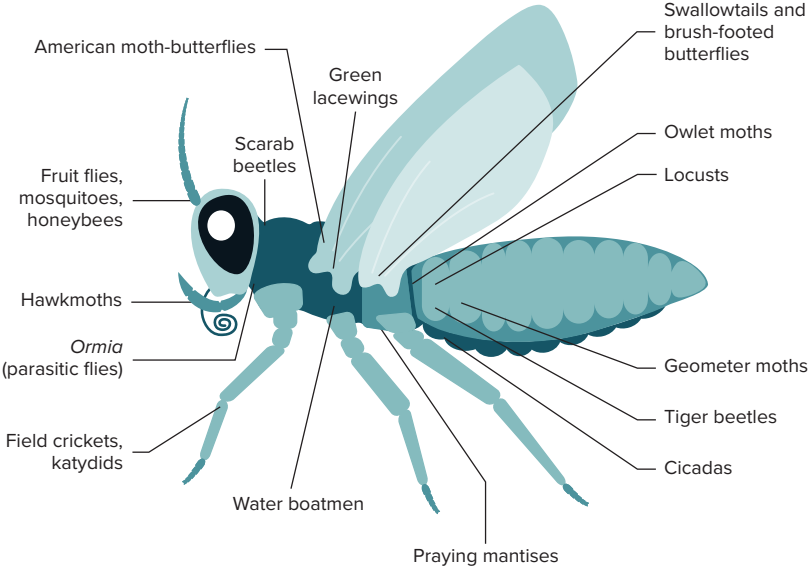
Katydid ears, as so neatly demonstrated by Montealegre-Z and his colleagues, are unique both in their complexity and their similarity to a mammal's. Using a micro-CT scanner, the scientists reconstructed the insect's entire hearing system, discovering two previously unknown organs in the process. The first is a small, hard plate behind the eardrums; the second, a fluid-filled tube containing a line of sensory cells. Through painstaking investigation that included shining lasers at the eardrum and recording the light bouncing back, the team showed that the small plate transmits vibrations in the insect's eardrum to the fluid in the tube — the same role played by the bones in our middle ear. The signal then travels in a wave along the tube and over sensory cells tuned to different frequencies — making this organ a miniature, uncoiled version of our own, snail-shaped cochlea.

The team has now gone on to show why female katydids are so good at finding a mate in the dark, even though their ears are close together (not so close as those of the parasitic *Ormia*, but near enough to make pinpointing sound a sizable challenge). Our own ears lie on either side of our (large) heads and are far enough apart for a sound to reach them at different-enough times and loudness for the brain to compute and locate the source.

Katydids solved the problem (again, in a unique way) by enlarging a breathing tube that runs from a pore in the side of the chest to the knee; sound reaches the eardrums both from outside the body and from the inside via the tube. Montealegre-Z and his colleagues showed that sound travels this inner, back route more slowly — so each sound hits the eardrum twice, but at slightly different times, dramatically improving the insect's ability to locate the source.

HERE AN EAR, THERE AN EAR, EVERYWHERE AN EAR

Where hearing organs reside on various insects



Hearing has evolved at least 20 times in insects, leading to ears in an astonishing number of different locations, as shown on this image of a generalized insect.

CREDIT: REPORTING BY S. PAIN

The katydid's remarkable ears haven't yet given up all their secrets, and Montealegre-Z's team is now trying to pin down how the receptors in the insect version of the cochlea pick out different frequencies. The star of this study is *Phlugis poecila*, a "crystal" katydid named for its transparent outer cuticle, a feature that allows the team to record and measure processes as they happen. "We'll be able to watch hearing at work and see processes never seen before," Montealegre-Z says.

If how insects hear varies enormously, so does what they hear. Mosquito ears are good for maybe a meter; the many-eared bladder grasshopper can hear from a kilometer or more away. Cricket ears detect low frequencies; mantis and moth ears are tuned to ultrasound, way beyond anything humans (or their dogs) can hear. Still other ears, such as a katydid's, have broadband hearing. "Insects only hear what they need to hear," says Göpfert. "And evolution provided what was necessary."

But what drove evolution to turn stretch receptors into ears in the first place, and so bring sound to the insect world? That's a question still on many entomologists' minds. A reasonable guide is how insects use their ears today, but it's only a guide, since an ear originally acquired for one purpose might easily have shifted over the eons to serve another. One thing's certain: As biologists investigate more insect groups in greater detail, some long-held notions may bite the dust.

An ear for danger

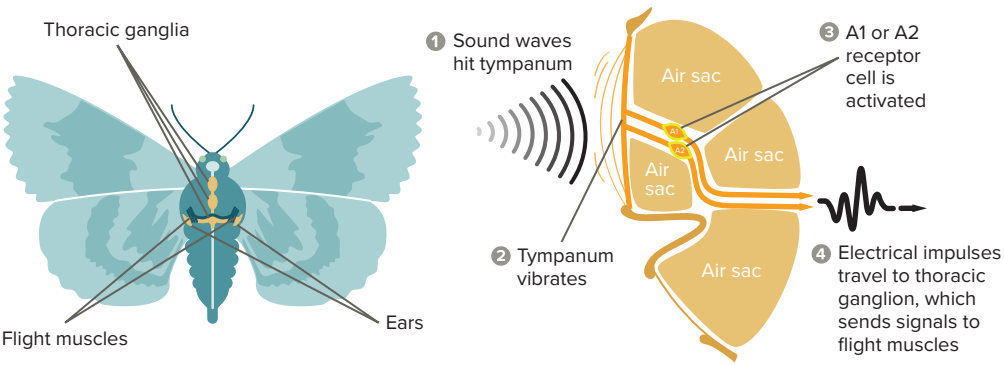
In modern insects, one of the primary functions of ears is to hear the approach of a predator in time to take action and avoid it. For night-flying insects, the greatest threat comes from insectivorous bats that detect and track prey with ultrasonic sonar, and so their hearing is tuned to the frequencies of the bats' echolocating clicks. The insects then respond with characteristic moves to escape the sonar beam: sharp turns, loop-the-loops, air-to-ground power dives. Certain tiger moths even jam the bat sonar with clicks of their own. Experiments have shown that bat-detecting ears dramatically improve an insect's prospects of surviving attack: In one study, mantises escaped 76 percent of bat attacks, but that number fell to 34 percent when they were deafened.

If predation is a powerful driver of evolution, so, too, is sex. And sound is an efficient way for an insect to identify itself to prospective mates: Sound travels well, works in the dark and provides the means to develop signature songs and private communications that no one else can hear.

So, successful sex or survival? Which lies behind whose ears?

In some cases, researchers are reasonably sure. Cicadas seem to have evolved hearing for mating purposes: Only singing species have ears and they are sensitive only to their own low-pitched songs. For moths, bats were the trigger. Lepidoptera have been around some 150 million years, yet no moths had ears before

HOW INSECTS HEAR: THE OWLET MOTH EXAMPLE



Owlet moths have very simple ears, one on each side of the thorax. The tympanum vibrates in response to sound, such as the ultrasonic clicks of a hunting bat. There are two receptor cells. One receptor — A1, the main bat detector — can sense bats from 30 meters away. The moth alters its flight to reduce the incoming signal, which indicates it's moving away from the bat. The other receptor, A2, is an emergency system that fires when the bat is closer, prompting the moth to execute erratic maneuvers in a last-ditch effort to avoid the bat. Signals travel to a ganglion in the thorax, which sends instructions directly to flight muscles — enabling superfast responses.

CREDIT: GRAPHICS RESEARCH BY S. PAIN, B. DRAXLER

echolocating bats arrived on the scene about 60 million years ago. And many of the eared moths are sensitive only to the frequencies employed by their local bats — strong evidence that the ears evolved as bat detectors.

What, though, to make of the mantis and its cyclopean ear? Today, mantises seem to use their ears exclusively as bat detectors. But entomologists have abundant data on the varied anatomy of mantis ears and an accurate DNA-based mantis family tree, from which they trace the original mantis ear. It belonged to a species that lived 120 million years ago, earlier than those sonar-guided bats. There's growing evidence that predators other than bats might have spurred the evolution of their ears and those of some other insects — perhaps reptiles, or birds, or early mammals. Animals moving through the undergrowth, pattering over rocks or landing on a leafy branch make noises that include audible and ultrasonic elements.

Flying birds, which have existed for 150 million years, are increasingly seen as contenders. Canadian biologists recorded sounds generated by the beating wings of chickadees and eastern phoebes as they moved in on insect prey, and found that the wing beats included a wide range of frequencies that insects can detect, from low-pitched sounds audible to cicadas, butterflies and grasshoppers, to ultrasonic sounds picked out by moths and mantises.

Modern katydids use their ears both in communication and as bat detectors. But the katydid sound-producing apparatus can be traced back to an early type of ancestor that lived 250 million years ago, well before bats did. So the prevailing theory up till now has been that the ears' initial function was to enable katydids to hear one another, and later on, those ears were co-opted to serve as bat detectors. This led to the extension of their hearing from the audible range (below 20 kHz) to the ultrasonic (beyond the reach of human ears). That allowed evolution of the more complex, higher-pitched songs that katydids exhibit today. Today, only a minority of katydids sing in the audible range, while about 70 percent have ultrasonic songs. A few have extraordinarily high-pitched songs. The record holder is *Supersonus aequoreus*, which calls at an astonishing 150 kHz.

To verify that story, scientists needed to take a close look at the fossil record to infer what katydids could hear in the distant past. The fossilized ears are not themselves very informative: They are rare and their structure hard to make out. But there's another way of getting at hearing: from the detailed anatomy of the sound-producing file-and-scraper apparatus on fossilized katydid wings. "Those structures are much larger and clearer, and we can use them to re-create the sound they made very accurately," says Montealegre-Z — and from that, infer what katydids must have heard.

Blast from the past

In 2012, Montealegre-Z and fellow bioacoustics expert Daniel Robert at the University of Bristol made headlines when they used this approach to reconstruct the song of a katydid from Jurassic times, a sound unheard for 165 million years. What made that possible was the discovery of a Chinese fossil katydid with almost perfectly preserved wings. *Archaboilus musicus*, as the extinct insect has been named, would have "sung" musical songs at frequencies around 6.4 kHz, sounding more like a cricket than a modern katydid. That fits nicely with the story that katydids first evolved hearing to communicate.

Since then, though, further studies suggest the theory might need an overhaul. It seems that some ancient katydids used ultrasound long before bats existed, says Montealegre-Z. Katydids also hear a wider range of frequencies than needed just to hear themselves. This indicates that their ears first evolved not for singing but, like mantises, for self-preservation. "I think their ears evolved to hear predators," he says. "Predators make a diversity of sounds and so ears must be able to pick them out."

Besides helping to unravel the history of insect hearing, these studies promise more: the opportunity to eavesdrop on the ancient insect behavior. They've also made me impatient for summer.

In summer, the air over the Sussex Downs is alive with a symphony of insect sound as grasshoppers and katydids chirp, buzz and click in their quest for love. If I strain my ears to the limit, I might be able to pick out the sewing-machine rattle of a great green katydid or the soft hissing song of a conehead, and if I'm very lucky, perhaps even the rapid-fire clicks of the wart-biter, the UK's rarest katydid. But how much more will I be missing? I'd give a lot to have ears that can pick out the songs and sounds scientists are piecing together, but that insects alone can hear. ●

ASSOCIATED ANNUAL REVIEWS CONTENT

Hearing in Insects

M.C. Göpfert *et al* / *Annual Review of Entomology*

What makes a tree a tree?

Despite numerous studies and 30-plus genomes under their belts, scientists are still struggling to nail down the defining traits of these tall, long-lived, woody plants

BY RACHEL EHRENBERG

CREDIT: CHAO YEN

SEVERAL YEARS AGO, AFTER THANKSGIVING dinner at my parents' house in Vermont, lightning struck a backyard maple tree. There was a ferocious crack and the darkness outside the kitchen windows briefly turned day-bright. It wasn't until spring that we knew for certain the tree was dead.

This maple was a youngster, its trunk the diameter of a salad plate. Were its life not cut short by catastrophe, the tree might have lived 300 years. But death by disaster is surprisingly common in trees. Sometimes it results from a tragic human blunder, as with the 3,500-year-old Florida bald cypress that was killed in 2012 by an intentionally lit fire. More often, calamity strikes via extreme weather — drought, wind, fire or ice. Of course, trees also are susceptible to pests and disease; adversaries like wood-decaying fungi can significantly shorten a tree's life. But the ones that manage to evade such foes can live for an incredibly long time.

In describing what makes a tree a tree, long life is right up there with wood and height. While many plants have a predictably limited life span (what scientists call "programmed senescence"), trees don't, and many persist for centuries. In fact, that trait — indefinite growth — could be science's tidiest demarcation of treeness, even more than woodiness. Yet it's helpful only to a point. We think we know what trees are, but they slip through the fingers when we try to define them.

Trees don't cluster into one clear group: They emerge in multiple lineages and have adopted multiple strategies to become what they are. Take longevity. A classic example of the Methuselah-ness of trees is the current record-holder, a 5,067-year-old great bristlecone pine that grows high in the White Mountains of California. (That tree was centuries old when the first pyramids were built in Egypt.) Scientists speculate that the hardy bristlecones owe their endurance largely to location: They avoid fires that sweep through lower elevations and pests that can't stomach the harsh terrain of the subalpine zone. The giant sequoias, a short way down

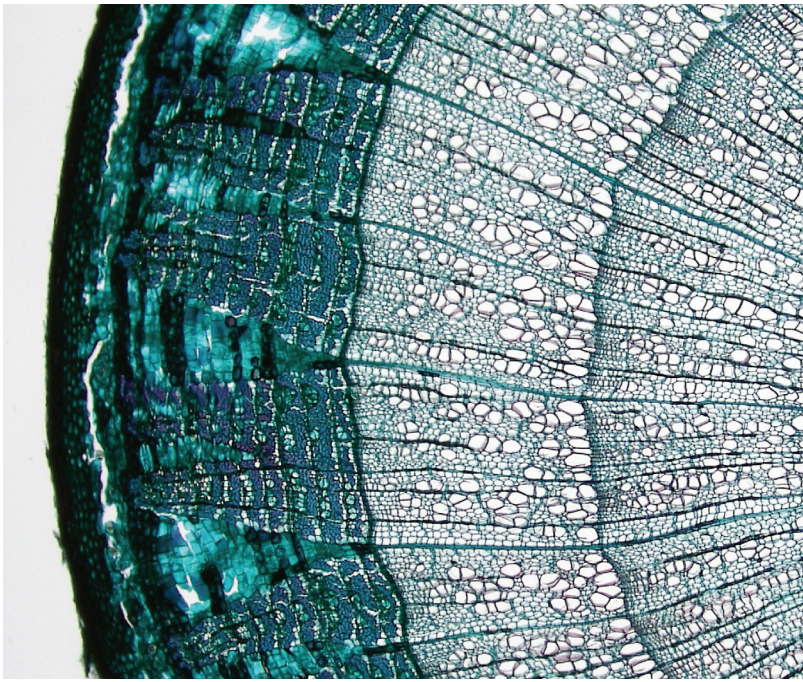
> "There does not seem to be some profound unique biology that distinguishes a tree from a herbaceous plant."
>
> —DAVID NEALE

the mountains from the bristlecones, take an entirely different longevity tack. These beasts — their trunks can be more than 30 feet across — live thousands of years, fighting fire and pestilence with thick, resistant bark and plentiful in-house repellent compounds.

Some 400 miles to the east, a spindly wisp of a tree has both the bristlecones and the sequoias beat when it comes to life span — through another strategy altogether. The quaking aspen (*Populus tremuloides*) — a tree you can wrap your arms around that rarely grows taller than 50 feet — excels at sending up new shoots from its base. This results in giant stands of "trees" that are, in fact, one genetic individual connected beneath the ground. A Utah colony of quaking aspen is estimated to be 80,000 years old. Neanderthals were around back then.

Once you add clones to the mix, trees quickly lose their claim on old age. King's holly (*Lomatia tasmanica*) is a shiny green shrub native to Tasmania. (Shrubs, technically speaking, aren't trees because they don't have a central, dominant stem.) There is only one population of king's holly in the world, and scientists think it's entirely clonal: Although it does occasionally flower, its fruit has never been seen. Recent radiocarbon dating suggests that it (they?) is at least 43,000 years old. Up there too is a scrubby ring of creosote bush out in the Mojave Desert of California, called "King Clone," with an estimated age of 11,700 years. Longevity is wholly unsatisfying in a search for a unified "treeness of trees," as forester Ronald Lanner terms it in a 2002 essay in *Ageing Research Reviews*.

Geneticist Andrew Groover of the US Forest Service Pacific Southwest Research Station in Davis, California, also spends a lot of time thinking about trees. He is quick to acknowledge that defining them is problematic. "Visit your favorite plant nursery and you will find plants categorized by their appearance and function, including a group categorized as 'trees,'" he wrote in a paper titled "What genes make a tree a tree?" in *Trends in Plant Science* in 2005. "This categorization is intuitive and practical but contrived."



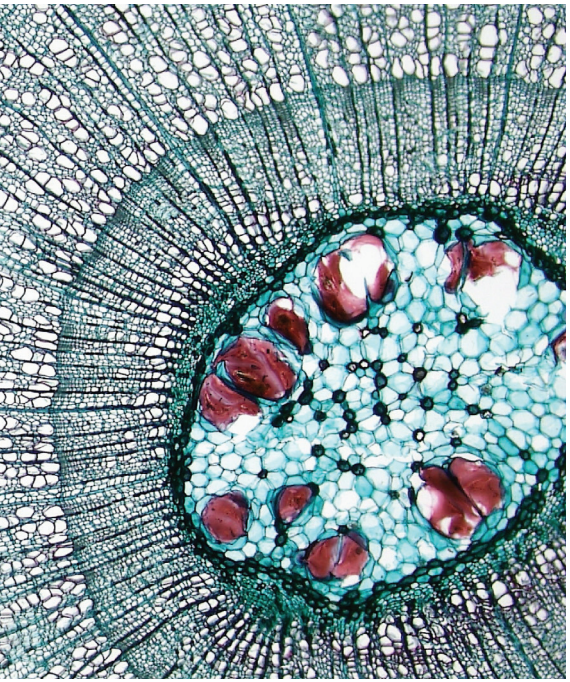
Part of what makes a tree a tree is the ability to make wood, a process that originates with the band of cells called the vascular cambium, seen here between the bark (blue, outer cells) and wood (whitish middle bands of cells).

CREDIT: BERKSHIRE COMMUNITY COLLEGE BIOSCIENCE IMAGE LIBRARY

Groover points to wood, surely a defining feature of trees. "True" trees make wood through "secondary growth," which allows trees to grow out (thicken), in addition to growing up. Secondary growth emerges from a ring of specialized cells that encircle the stem. Called the vascular cambium, these cells divide in two directions: toward the outside of the tree, yielding bark, and toward the center of the tree, yielding wood. Year after year, this wood is deposited in new inner rings of growth that are doped with cellulose and the long, rigid polymer called lignin. After this cellular stiffening, the wood cells are killed and dismantled, for the most part, until nothing but their rigid walls remain.

In plants that exist today, secondary growth probably had a single evolutionary origin, although the now-diminutive club mosses and horsetails invented their own version some 300 million years ago, enabling the extinct *Lepidodendron*, for example, to grow more than 100 feet tall. But secondary growth doesn't automatically lead to treeness: Despite that single origin, woodiness pops up scattershot across the plant family tree. Some groups of plants have lost the ability to form wood; woodiness has reappeared in lineages where it had vanished. It seems to evolve fairly quickly after plants colonize islands. Hawaii, for example, has woody violets, and the Canary Islands have dandelion trees.

The very concept of woodiness is quite flexible, belying its literal robustness — think of the stiff stems of garden salvia or lavender.



It's not a matter of present or absent, but a matter of degree. "Non-woody herbs and large woody trees can be thought to represent two ends of a continuum, and the degree of woodiness expressed by a given plant can be influenced by environmental conditions," Groover and a colleague wrote in a 2010 review in *New Phytologist*. "Indeed, the terms 'herbaceous' and 'woody,' while practical, do not acknowledge the vast anatomical variation and degrees of woodiness among plants variously assigned to these classes."

Molecular biology offers some insights into why the ability to make wood reappears so often in plant evolution. Genes involved in regulating the growing shoot — the upward, "primary" growth of trees and non-trees alike — are also active during the secondary growth that yields wood. This suggests that these already existing and essential shoot-growth genes were co-opted during the evolution of woodiness. And it might explain why the ability to become woody is maintained in non-woody plants and why it's relatively easy for evolution to dial woodiness back up.

Still, you don't need wood to be a tree. Monocots, an enormous group of plants that lost the ability to undergo secondary growth, have several arborescent members that aren't "true" trees but sure look like them. Bananas grow tall with what appears to be a trunk but is really a "pseudostem" mass of tightly packed, overlapping leaf bases or sheaths. The true stem of a banana plant emerges only when it's time to flower, pushing itself up and out through the leaf sheaths. Yet banana trees can be more than 10 feet tall.

Given all this, perhaps it's not surprising that a recent analysis of tree genomes tells us little about the defining features of trees. Geneticist David Neale of UC Davis and colleagues pored over results from the 41 genomes (including grape) that have been sequenced, beginning with black cottonwood in 2006. Their analysis, published in 2017 in the *Annual Review of Plant Biology*, did find that trees making edible fruits often have an outsized number of genes devoted to making and transporting sugars, compared with non-edible-fruit trees. Then again, so do grapes and tomatoes. Several trees, including spruce, apple and some eucalyptus, have expanded genetic toolkits for dealing with environmental stresses such as drought or cold. But so do many herbaceous plants, including spinach and *Arabidopsis*, that weedy little lab rat of the plant world that is about as un-treelike as you can get.

So far, there is no standout gene or set of genes that confers treeness, or any particular genome feature. Complexity? Nope: Full-on, whole-genome duplication (a proxy for complexity) is prevalent throughout the plant kingdom. Genome size? Nope: Both the largest and smallest plant genomes belong to herbaceous species (*Paris japonica* and *Genlisea tuberosa* — the former a showy little white-flowered herb, the latter a tiny, carnivorous thing that traps and eats protozoans).

Neale confirms that tree-ness is probably more about what genes are turned on than what genes are present. "From the perspective of the genome, they basically have all the same stuff as herbaceous plants," he says. "Trees are big, they're woody, they can get water from the ground to up high. But there does not seem to be some profound unique biology that distinguishes a tree from a herbaceous plant."

Notwithstanding the difficulty in defining them, being a tree has undeniable advantages. Trees can exploit the upper reaches where they soak up sunlight and disperse pollen and seeds with less interference than their ground-dwelling kin. So maybe it's time to start thinking of *tree* as a verb, rather than a noun — tree-ing, or tree-ifying. It's a strategy, a way of being, like swimming or flying, even though to our eyes it's happening in very slow motion. Tree-ing with no finish in sight — until an ax, or a pest, or a bolt of Thanksgiving lightning strikes it down. ●

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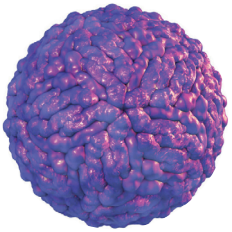
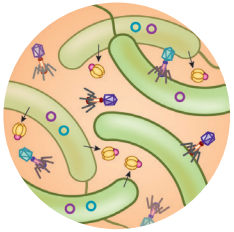
Novel Insights into Tree Biology and Genome Evolution as Revealed Through Genomics

D. B. Neale *et al* /
Annual Review of Plant Biology

Q&A





with viral ecologist Marilyn Roossinck

Why viruses deserve a better reputation

Sure they cause disease, but the microbes can be a help as well. Witness long-lasting pepper seeds, drought-resistant crop plants and even our own placentas.

By Amber Dance

WE'VE KNOWN FOR A LONG time that viruses aren't all bad. Many just hitchhike through living organisms without causing any problems. And some are beneficial, even necessary, for life on Earth. We wouldn't be here without them, says Marilyn Roossinck of Pennsylvania State University.

Roossinck loves viruses so much she wrote the book *Virus: An Illustrated Guide to 101 Incredible Microbes* (Princeton University Press, 2016). She also coauthored the article "Symbiosis: Viruses as Intimate Partners," in the 2017 *Annual Review of Virology*.

And the association *is* intimate. Viruses can only survive by entering and copying themselves inside a living cell. They use the machinery of the host cell to replicate their genetic material and produce more viral particles.

More than 200 kinds of viruses are known to infect people, and scientists estimate that a few hundred thousand infect other mammals. Add in those that infect plants, bacteria and other organisms, and viruses are big players in the biosphere. Overall, scientists propose there are 10^{31} individual viruses on the planet — that's 10 nonillion of them.

Knowable Magazine caught up with Roossinck to ask about how viruses benefit plants and people, and to discuss the plant viruses she's most excited about right now.

Why do you, personally, study viruses?

I fell in love with viruses when I was an undergraduate student, taking a microbiology course. A virus of bacteria called lambda was the first virus I met, and it looked so cool, like a little spaceship. I was amazed at the intricacy of their relationships with their hosts and I made a decision, at that moment, that I was going to be a virologist. I still love them. They're just amazing.

What do we know about viral numbers and diversity on Earth?

Viruses are the most abundant and diverse beings on the planet, and they're found everywhere. We probably still know only a small fraction of the viruses that exist, but we're learning more every day. We keep accumulating more and more virus-like genetic sequences from what are called metagenomics studies — where scientists are just sampling everything in an environment.

What we are really lacking is an understanding of what any of these things we've sequenced do, or how they might be related to each other. Often, we don't even know what their host is.

Do we know how many viruses a person hosts at a given time?

That's a tough question to answer these days. Scientists are finding lots and lots of viruses in metagenomics studies of the human gut, and a lot of these viruses are probably infecting the bacteria in the gut, rather than the person's cells. I wouldn't like to put a number on it, but when people ask I usually say, "a bazillion." We don't know. There's a lot.

And do we know how many viruses are bad, good or neutral for their host?

I like to say 1 percent are pathogens, which harm their host, but I think that's probably a very high estimate. That's based on early studies with simian [ape and monkey] viruses, which were studied a lot during early days in molecular virology. There were 80-something of these simian viruses they discovered and they were numbered SV1, SV2, et cetera. Of those, SV40 is the only one that's had very much study done, and that's because it turned out to be a pathogen, causing tumors in mice. None of the rest of them had any effect on the host they were tested in. That's where I get my "about 1 percent."

CREDIT: KATERYNA KON / SHUTTERSTOCK; *ANNUAL REVIEW OF VIROLOGY* 2017; JAMES PROVOST

You were originally inspired by bacterial viruses, but in your research today, do you have a favorite virus?

I would say, more like a favorite class of viruses. For the last few years I've become really fascinated with what are called "persistent plant viruses." This is largely because when I was doing virus discovery work, we found they were the most common type of viruses in wild plants. They're also very common in crops, but nobody had studied them very much.

These are viruses that have infected their hosts for, probably, thousands of years. They're passed, through the seed, into the next generation, and then they infect every single cell in the host. They don't pass between adult plants, so far as we know.

They're usually found in pretty low numbers, and we don't know very much about what they do. In some cases, we know they benefit the plant. For example, white clover cryptic virus affects nodulation in legumes. Legumes normally form nodules of bacteria, in their roots, to help them take up nitrogen from the atmosphere. But doing so is costly for the plant. In virus-infected legumes, when there's enough nitrogen in the soil, then they don't form nodules, and that's a benefit to the plant.

We've been studying another one called pepper cryptic virus. It's a very hard thing to prove, but it seems like virus-infected seeds have a lot longer longevity than uninfected ones. After a couple of years, the uninfected seeds don't germinate, whereas the infected cells last for many years.

What are some other ways viruses benefit their hosts?

Many plant viruses confer drought tolerance or cold tolerance to plants. We don't always know how this works but, for example, elevated sugar is very common in virus-infected plants. More sugar would allow the plant cells to retain more water, protecting them from drought. And you know, things that are really sweet freeze slowly, so extra sugar would make plants cold-resistant. And in animals, actually in mice, herpes viruses confer resistance against bubonic plague. That's because the herpes virus, dormant in the mouse, turns up the mouse's immune system and makes it better able to fight the plague.

Similarly, in people, hepatitis G virus may offer some protection against AIDS. Hepatitis G, now called pegivirus or GB virus C, is quite common in humans, and isn't known to cause any disease. But it does affect the immune system in a variety of ways. If people are infected with hepatitis G first, and then HIV, it takes longer for the HIV to progress to AIDS.

Some viruses even become an integral part of their host, with their genes incorporated into the host's DNA. Can you give some examples of that?

We call that symbiogenesis. "Symbiogenesis" has been used to refer to things like the mitochondria or chloroplasts, that were of bacterial origin and then were involved in the evolution of eukaryotic life. But the more genomes we sequence, the more we find viruses. And not just retroviruses, which we know integrate into host genomes during their normal life cycle, but all kinds of RNA viruses, small DNA viruses. There are lots of things that viruses could do in a host genome. For example, they might turn genes on or off.

I think the very first example of symbiogenesis that was studied by scientists has to do with the breakdown of starches by our saliva. Most of us did this little experiment in elementary school: You chew bread until it turns sweet. That's because an enzyme called amylase, in our saliva, breaks the starch down into sugars. A more obvious place for amylase is in the gut, to break down food. The reason it's made in the salivary glands too is because viral genetic material integrated in front of the amylase gene, and turns it on in salivary glands.

The most dramatic example of symbiogenesis is in the evolution of the mammalian placenta. A protein called syncytin fuses cells together to make a placenta, and it evolved from a virus protein. So the gene for this protein integrated into the mammalian genome during the evolution of the placenta.

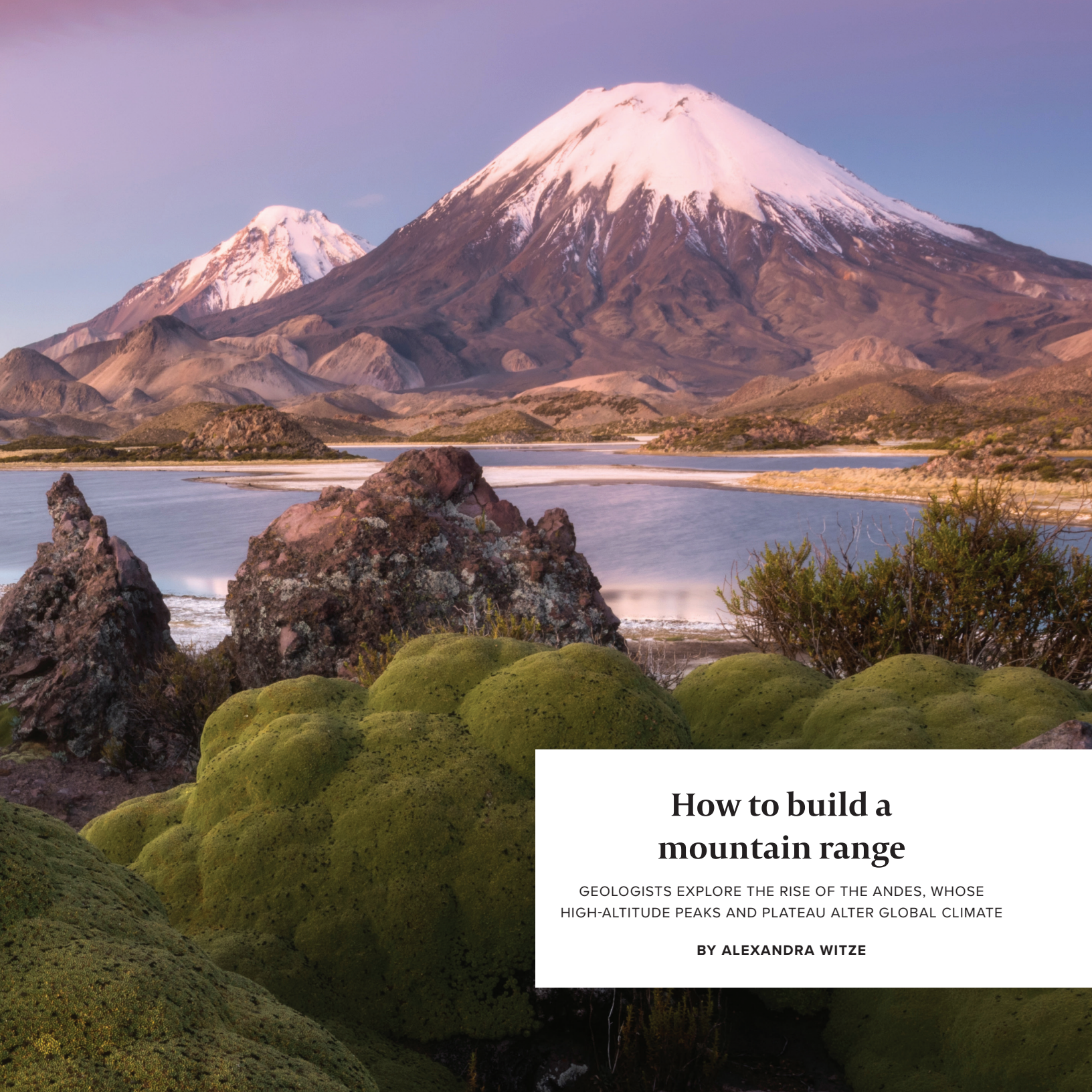
What else is in the future for virology?

I would say that in the future, we're going to find a lot of things that we can use viruses for, as beneficial agents. For example, some work is going on right now to use viruses to get rid of bacteria that are infecting crop plants.

But the biggest obstacle, I would say, is that people are still a little afraid of viruses. If you say to somebody, "Why don't you ingest some hepatitis G virus because it would protect you from AIDS?" — you know, probably nobody's going to do it. Even among some virologists, that bias against viruses is still a hurdle.

You have written that viruses are central to life. Can you imagine a virus-free world?

There wouldn't be a world. I think that viruses are probably remnants of the original life form. It's high time they got the credit they're due. ●



How to build a mountain range

GEOLOGISTS EXPLORE THE RISE OF THE ANDES, WHOSE HIGH-ALTITUDE PEAKS AND PLATEAU ALTER GLOBAL CLIMATE

BY ALEXANDRA WITZE

THERE'S ONLY ONE PLACE ON the planet where you can see flamingos roaming salt flats, vicuñas grazing in herds and condors soaring overhead, all as hot springs bubble beneath towering volcanoes. It's the Altiplano of South America — a nearly 1,000-kilometer-long, otherworldly plateau that stretches from southern Peru through Bolivia and into Chile and Argentina.

At an average of 3,800 meters above sea level, the Altiplano is the high-altitude heart of the Andes Mountains. To the plateau's east and its west, chains of mountains soar some 6 kilometers high, rocky backbones that snake along the western edge of the South American continent. The sheer volume of elevated ground makes it especially fascinating to those who study the Earth's deep dynamics: How did so much land soar so high into the air? And how did that rise change the planet?

Researchers do know how the story began: around 200 million years ago, when one enormous plate of Earth's crust began diving beneath another. Around 45 million years ago, the process sped up, and the plate on top began crumpling skyward to form the Andes. But the details of how it happened have remained unclear.

Now, new clues are emerging from the rocks that form the Altiplano. For millions of years, the plateau has been filling with sediment that washes down from the nearby ranges. That makes it a geological time capsule containing a record of the mountains' past. "The Altiplano basin has this amazing climate archive that goes back tens of millions of years," says Carmala Garzione, a geologist at the University of Rochester in New York. "You can literally march through time as you walk through these strata."

By probing those layers of sediment, Garzione and her colleagues have found that parts of the Altiplano didn't gain their great height until 5 million to 10 million years ago. That means the Andes did not rise gradually over the last 45 million years, but lurched skyward in dramatic pulses. Cold, dense rock beneath the Altiplano would have weighed it down like an anchor. When blobs of that rock dripped off its underbelly into the deeper Earth, the Altiplano became more buoyant, like a bobber on a fishing line, and rose higher.

Scientists' interest goes beyond the origin story. Being so close to the sky means the mountains also exert a heavy influence on atmospheric circulation, which alters weather and climate. And the Altiplano's time capsule captures those changes.

As the Andes grew to their current height, they shaped the climates and history of South America. They trapped water on the eastern side of the ranges, allowing the great Amazon River system to develop and flourish. On the west, the Atacama Desert is one of the driest places on Earth.

"From our perspective as humans looking at mountains, it's why we are interested," says geologist Nadine McQuarrie of the University of Pittsburgh. "How do these mountains, these really big impressive features we can see and experience, alter the world?"

"How do these mountains, these really big impressive features we can see and experience, alter the world?"

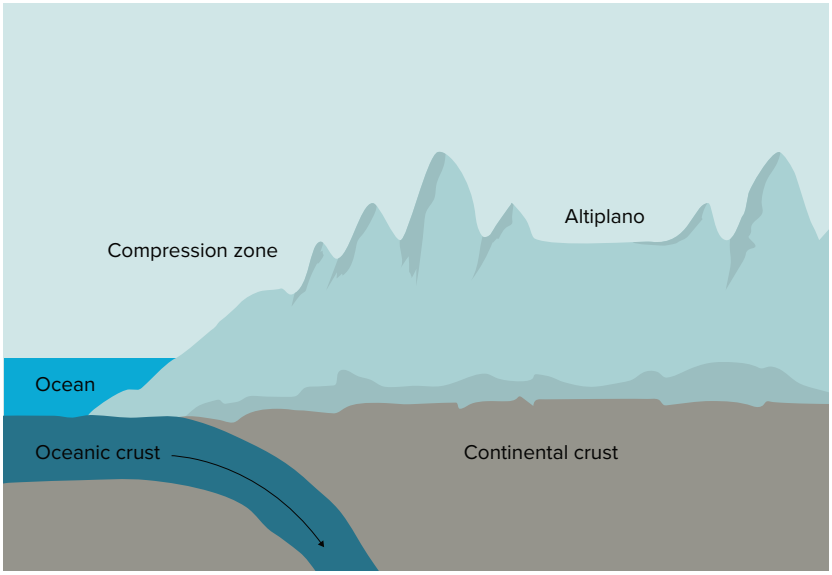
—NADINE MCQUARRIE

Rising Earth

The Andes are one of the best places to study geology in action. The Nazca oceanic plate slides eastward and dives beneath the South American continental plate. As the plates come together, the continental plate becomes riddled with faults. Like a car smashing into a brick wall, it crumples, shortening and becoming thicker. The thickening crust continues to push the Andes into the air;

OPPOSITE PAGE CREDIT: DANIEL KORDAN

A cross-section of the Andes shows how the immense mountain range formed as the oceanic plate dove under the continental plate, squeezing and lifting the land to the east.



their highest peak, Aconcagua in Argentina, reaches nearly 7 kilometers above sea level.

To understand the history of the Andes, researchers look deep beneath their feet. Among other tools, they use a network of seismometers to measure the location and magnitude of earthquakes occurring where the plates meet. Those measurements reveal the varying depth of the plate boundary and the geometry of the crust below.

In 2010 a University of Arizona-led team also peppered the northern part of the Altiplano with 50 additional seismometers for two years, showing more clearly how the crust was thickening in that region.

Part of the crust wasn't behaving as expected. Earth is layered with brittle rocks on top, a region called the lithosphere, which includes all of the crust and a little bit of the underlying mantle. Beneath that, starting at roughly 100 kilometers deep, is the asthenosphere, where mantle rocks are warm enough to flow like hot taffy.

In the Altiplano, researchers expected to see cold rocks near the bottom of the lithosphere, at about 45 to 70 kilometers beneath the Andes. But the seismic waves showed that there were hot rocks there. Garzione thinks that relatively cold, high-density rocks called eclogite detached as a blob and sank into the Earth. "It's kind of like a lava lamp, but in this case it's a one-way lava lamp," she says.

Once that eclogite blob dropped off, the overlying lithosphere bobbed higher, raising the plateau. Garzione and her colleagues, including McQuarrie, describe the scenario in the 2017 *Annual Review of Earth and Planetary Sciences*.

They cross-check this story through geology. As sediment washed off the high Andes into the Altiplano, it built up into rock layers, producing an unprecedented environmental archive of the past. "It's an excellent place to do the climate studies you need to do," says Garzione.

The Altiplano rocks contain clues to the heights of different parts of the plateau at various points in its past. Some clues rely on the fact that temperatures generally get cooler the higher you go — think of driving up a mountain to escape the summer heat. Those temperature differences are reflected in the differing amounts of heavy and light forms of elements such as oxygen and carbon in the rocks. By measuring the chemical ratios in rocks of a certain age, scientists can figure out how high the Altiplano was at that time.

In some places they found it was moving upward in bursts

SOURCE: SCIENCESTRUCK.COM

ASSOCIATED ANNUAL REVIEWS CONTENT

Tectonic Evolution of the Central Andean Plateau and Implications for the Growth of Plateaus

C.N. Garzione *et al* / *Annual Review of Earth and Planetary Sciences*

as rapid as half a kilometer or more every million years. “For a geologist that’s very fast,” says Garzione. The Altiplano could have rocketed up so quickly only if something heavy, like an eclogite anchor, dropped off its bottom, she says.

The process might even happen in cycles; after a cold blob drops off, another forms in its place and eventually detaches as well. In at least one place beneath the eastern Andes, a combination of evidence suggests, one blob probably detached between 22 million and 17 million years ago, and a second one between 10 million and 5 million years ago.

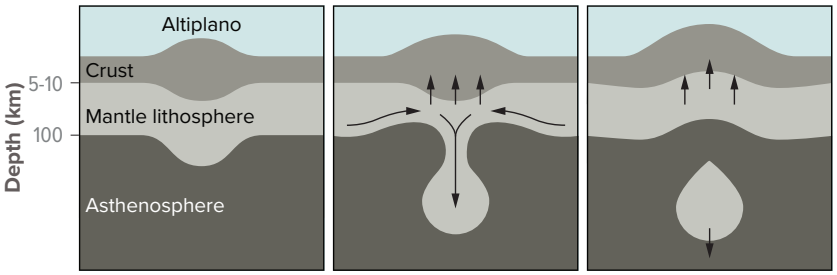
A second mechanism could be at work. Beneath the mountain ranges bordering the Altiplano, to the west and the east of the plateau, the lithosphere is relatively thick. Heat from the asthenosphere can warm the lithosphere, heating rocks so they flow like molasses from beneath the neighboring mountain ranges to beneath the Altiplano. This “crustal flow” could have helped the Altiplano thrust so rapidly upward during some periods.

For now, there’s no way to tell whether the eclogite-anchor or the crustal-flow idea is more important. Some combination of the two may have ultimately pushed the Altiplano skyward, Garzione says. When the eclogite anchor drops off, that detachment may cause hot rocks from the asthenosphere to well upward in the region, allowing the crustal flow to get going and the molasses to begin flowing.

What scientists learn in the Andes can illuminate the Tibetan plateau, which began forming about 50 million years ago when the Indian crustal plate rammed into Eurasia. Now at an average of 5 kilometers high, the plateau modifies weather and climate patterns such as the Asian monsoon. Unlike the Altiplano, the Tibetan plateau does not contain a detailed sedimentary record — and so the studies in the Andes can help scientists better understand the broad geological patterns that could have also shaped Tibet.

Meanwhile, the American West holds clues to the Altiplano’s future. Geologists think there was once a high-elevation plateau there similar to the Altiplano, but starting around 30 million years ago it began to collapse as the crust beneath it spread apart. Today it is the lower but still spectacular landscape of the Basin and Range of the southwestern United States and northern Mexico. One day the Altiplano may look like this as well.

So understanding the rise of the Andes helps geologists understand the stability of mountain ranges over time, says McQuarrie. One day, they will begin to collapse and sink. But for now the heights of the Altiplano are a rare way for scientists to explore the depths of the planet, she says. “That’s where you can get insight into the deep processes that are going on in the Earth.” ●



Relatively cold and dense rocks push from the lithosphere into the deeper asthenosphere.

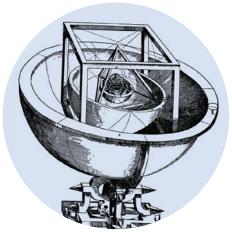
A blob of the high-density rocks detaches and drips into the deep Earth.

In response, the overlying lithosphere rises up, lifting the Altiplano to greater heights.

Evidence suggests that the Altiplano rose in pulses — speedy for geologic phenomena. One explanation for these pulses involves the dripping of dense rock called eclogite from the lower crust, buoying the land above.

SOURCE: K. CANTNER (AMERICAN GEOSCIENCES INSTITUTE) / *EARTH MAGAZINE*

Q&A



with theoretical physicist John Donoghue

Making sense of many universes

The idea of a multiverse — multiple realms of space differing in basic properties of physics — bugs some scientists. Others find it a real possibility that should not be ignored.

By Tom Siegfried

ALMOST ANYBODY WHO HAS ever thought deeply about the universe sooner or later wonders if there is more than one of them. Whether a multiplicity of universes — known as a multiverse — actually exists has been a contentious issue since ancient times. Greek philosophers who believed in atoms, such as Democritus, proposed the existence of an infinite number of universes. But Aristotle disagreed, insisting that there could be only one.

Today a similar debate rages over whether multiple universes exist. In recent decades, advances in cosmology have implied (but not proved) the existence of a multiverse. In particular, a theory called inflation suggests that in the instant after the Big Bang, space inflated rapidly for a brief time and then expanded more slowly, creating the vast bubble of space in which the Earth, sun, Milky Way galaxy and billions of other galaxies reside today. If this inflationary cosmology theory is correct, similar big bangs occurred many times, creating numerous other bubbles of space like our universe.

Properties such as the mass of basic particles and the strength of fundamental forces may differ from bubble to bubble. In that case, the popular goal pursued by many physicists of finding a single theory that prescribes all of nature's properties may be in vain. Instead, a multiverse may offer various locales, some more hospitable to life than others. Our universe must be a bubble with the right combination of features to create an environment suitable for life, a requirement known as the anthropic principle.

But many scientists object to the idea of the multiverse and the anthropic reasoning it enables. Some even contend that studying the multiverse doesn't count as science. One physicist who does affirm that the multiverse is a proper subject for scientific investigation is John Donoghue of the University of Massachusetts, Amherst.

As Donoghue points out in the 2016 *Annual Review of Nuclear and Particle Science*, the Standard Model of Particle Physics — the theory describing the behavior of all of nature's basic particles and forces — does not specify all of the universe's properties. Many important features of nature, such as the masses of the particles and strengths of the forces, cannot be calculated from the theory's equations. Instead they must be measured. It's possible that in other bubbles, or even in distant realms within our bubble but beyond the reach of our telescopes, those properties might be different.

Maybe some future theory will show why nature is the way it is, Donoghue says, but maybe reality does encompass multiple possibilities. The true theory describing nature might permit many stable "ground states," corresponding to the different cosmic bubbles or distant realms of space with different physical features. A multiverse of realms with different ground states would support the view that the universe's habitability can be explained by the anthropic principle — we live in the realm where conditions are suitable — and not by a single theory that specifies the same properties everywhere.

Knowable Magazine quizzed Donoghue about the meaning of the multiverse, the issues surrounding anthropic reasoning and the argument that the idea of a multiverse is not scientific. His answers have been edited for brevity and clarity.

Can you explain just what you mean by multiverse?

For me, at least, the multiverse is the idea that physically out there, beyond where we can see, there are portions of the universe that have different properties than we see locally. We know the universe is bigger than we can see. We don't know how much bigger. So the question is, is it the same everywhere as you go out or is it different?

CREDIT: IDA VIGGIANI; PUBLIC DOMAIN; JAMES PROVOST

If there is a multiverse, is the key point not just the existence of different realms, but that they differ in their properties in important ways?

If it's just the same all the way out, then the multiverse is not relevant. The standard expectation is that aside from random details — like here's a galaxy, there's a galaxy, here's empty space — that it's more or less uniform everywhere in the greater universe. And that would happen if you have a theory like the Standard Model where there's basically just one possible way that the model looks. It looks the same everywhere. It couldn't be different.

Isn't that what most physicists would hope for?

Probably literally everyone's hope is that we would someday find a theory and all of a sudden everything would become clear — there would be one unique possibility, it would be tied up, there would be no choice but this was the theory. Everyone would love that.

But the Standard Model does not actually specify all the numbers describing the properties of nature, right?

The structure of the Standard Model is fixed by a symmetry principle. That's the beautiful part. But within that structure there's freedom to choose various quantities like the masses of the particles and the charges, and these are the parameters of the theory. These are numbers that are not predicted by the theory. We've gone out and we've measured them. We would like eventually that those are predicted by some other theory. But that's the question, whether they are predicted or whether they are in some sense random choices in a multiverse.

The example I use in the paper is the distance from the Earth to the sun. If you were studying the solar system, you'd see various regularities and a symmetry, a spherically symmetrical force. The fact that the force goes like 1 over the radius squared is a consequence of the underlying theory. So you might say, well, I want to predict the radius of the Earth. And Kepler tried to do this and came up with a very nice geometric construction, which almost worked. But now we know that this is not something fundamental — it's an accident of the history. The same laws that give our solar system with one Earth-to-sun distance will somewhere else give a different solar system with a different distance for the planets. They're not predictable. So the physics question for us then is, are the parameters like the mass of the electron something that's fundamentally predictable from some more fundamental theory, or is it the accident of history in our patch of the universe?

How does the possibility of a multiverse affect how we interpret the numbers in the Standard Model?

We've come to understand how the Standard Model produces the world. So then you could actually ask the scientific question: What if the numbers in the Standard Model were slightly different? Like the mass of the electron or the charge on the electron. One of the surprises is, if you make very modest changes in these parameters, then the world changes dramatically. Why does the electron have the mass it does? We don't know. If you make it three times bigger, then all the atoms disappear, so the world is a very, very different place. The electrons get captured onto protons and the protons turn into neutrons, and so you end up with a very strange universe that's very different from ours. You would not have any chance of having life in such a universe.

Are there other changes in the Standard Model numbers that would have such dramatic effects?

My own contribution here is about the Higgs field [the field that is responsible for the Higgs boson]. It has a much smaller value than its expected range within the Standard Model. But if you change it by a bit, then atoms don't form and nuclei don't form — again, the world changes dramatically. My collaborators and I were the ones that pointed that out. There's some maybe six or seven of these constraints — parameters of the Standard Model that have to be just so in order to satisfy the need for atoms, the need for stars, planets, et cetera. So about six combinations of the parameters are constrained anthropically.

By "anthropically," you mean that these parameters are constrained to narrow values in order to have a universe where life can exist. That is an old idea known as the anthropic principle, which has historically been unpopular with many physicists.

Yes, I think almost anybody would prefer to have a well-developed theory that doesn't have to invoke any anthropic reasoning. But nevertheless it's possible that these types of theories occur. To not consider them would also be unscientific. So you're forced into looking at them because we have examples where it would occur.

Historically there's a lot of resistance to anthropic reasoning, because at least the popular explanations of it seem to get causality backwards. It was sort of saying that we [our existence]

determine the parameters of the universe, and that didn't feel right. The modern version of it, with the multiverse, is more physical in the sense that if you do have these differing domains with different parameters, we would only find ourselves in one that allows atoms and nuclei. So the causality is right. The parameters are such that we can be here. The modern view is more physical.

If there is a multiverse, then doesn't that change some of the goals of physics, such as the search for a unified theory of everything, and require some sort of anthropic reasoning?

What we can know may depend on things that may end up being out of our reach to explore. The idea that we should be searching for a unified theory that explains all of nature may in fact be the wrong motivation. It's certainly true that multiverse theories raise the possibility that we will never be able to answer these questions. And that's disturbing.

Does that mean the multiverse changes some of the questions that physicists should be asking?

We certainly still should be trying to answer "how" questions about how does the W boson decay or the Higgs boson, how does it decay, to try to get our best description of nature. And we have to realize we may not be able to get the ultimate theory because we may not be able to probe enough of the universe to answer certain questions. That's a discouraging feature. I have to admit when I first heard of anthropic reasoning in physics my stomach sank. It kills some of thethings that you'd like to do.

Don't some people even argue that though a multiverse would seem to justify anthropic reasoning, that approach should still be regarded as not scientific?

It's one of the things that bothers me about the discussion. Just because you feel bad about the multiverse, and just because some aspects of it are beyond reach for testing, doesn't mean that it's wrong. So if it's worth considering, and looking within the class of multiverse theories to see what it is that we could know, how does it change our motivations? How does it change the questions that we ask? And to say that the multiverse is not science is itself not science. You're not allowing a particular physical type of theory, a possible physical theory, that you're throwing out on nonscientific grounds. But it does raise long-term issues about how much we could understand about the ultimate theory when we can just look locally. It's science, it's sometimes a frustrating bit of science, but we have to see what ideas become fruitful and what happens.

An important part of investigating the multiverse is finding a theory that includes multiple "ground states." What does that mean?

The ground state is the state that you get when you take all the energy out of a system. Normally if you take away all the particles, that's your ground state — all the background fields, the things that permeate space. The ground state is described by the Standard Model. Its ground state tells you exactly what particles will look like when you put them back in; they will have certain masses and certain charges.

You could imagine that there are theories which have more than one ground state, and if you put particles in this state they look one way and if you put particles in another state they look another way — they might have different masses. The multiverse corresponds to the hypothesis that there are very many ground states, lots and lots of them, and in the bigger universe they are realized in different parts of the universe.

Even if a theory of particles and forces can accommodate multiple ground states, don't you need a method of creating those ground states?

Two features have to happen. You have to have the possibility of multiple ground states, and then you have to have a mechanism to produce them. In our present theories, producing them is easier, because inflationary cosmology has the ability to do this. Finding theories that have enough ground states is a more difficult requirement. But that's a science question. Is there one, is there two, is there a lot?

Superstring theory encompasses multiple ground states, described as the "string landscape." Is that an example of the kind of theory that might imply a multiverse?

The string landscape is one of the ways we know that this [multiple ground states] is a physical possibility. You can start counting the number of states in string theory, and you get a very enormous number, 10 to the 500. So we have at least one theory that has this property of having a very large number of ground states. And there could be more. People have tried cooking up other theories that have that possibility also. So it is a physical possibility.

Don't critics say that neither string theory nor inflationary cosmology has been definitely established?

That's true of all theories beyond the Standard Model. None of them are established yet. So we can't really say with any confidence that there is a multiverse. It's a physical possibility. It may be wrong. But it still may be right. ●

GRAPHIC: THE PERVASIVE INFLUENCE OF ARTIFICIAL LIGHT AT NIGHT

The scale and scope of disruption to wildlife has surprised ecologists who study the effects of electric lights at night. Here are a few selected findings that illustrate the enormous variety of impacts. Read the full article at knowmag.org/NightLight

Going hungry
Florida's Santa Rosa beach mouse (*Peromyscus polionotus leucocephalus*) forages under the cover of dark. A bright moon — or artificial light — prevents it.

Fatal attraction
A recent estimate puts the number of birds killed at lit communications towers in the United States and Canada at 6.8 million each year.

Wrong scent
Light causes female cabbage moths (*Mamestra brassicae*) to give off faulty sex pheromones, producing less and using the wrong recipe.

Communication error
The male eastern firefly (*Photinus pyralis*) flashes its tail-lights to attract a mate, but under artificial light females don't flash back as often as they do in the dark, so males can't find them.

Crop failure
Bright floodlights from an Ohio prison prevent normal development of soybeans (*Glycine max*) in a nearby field.

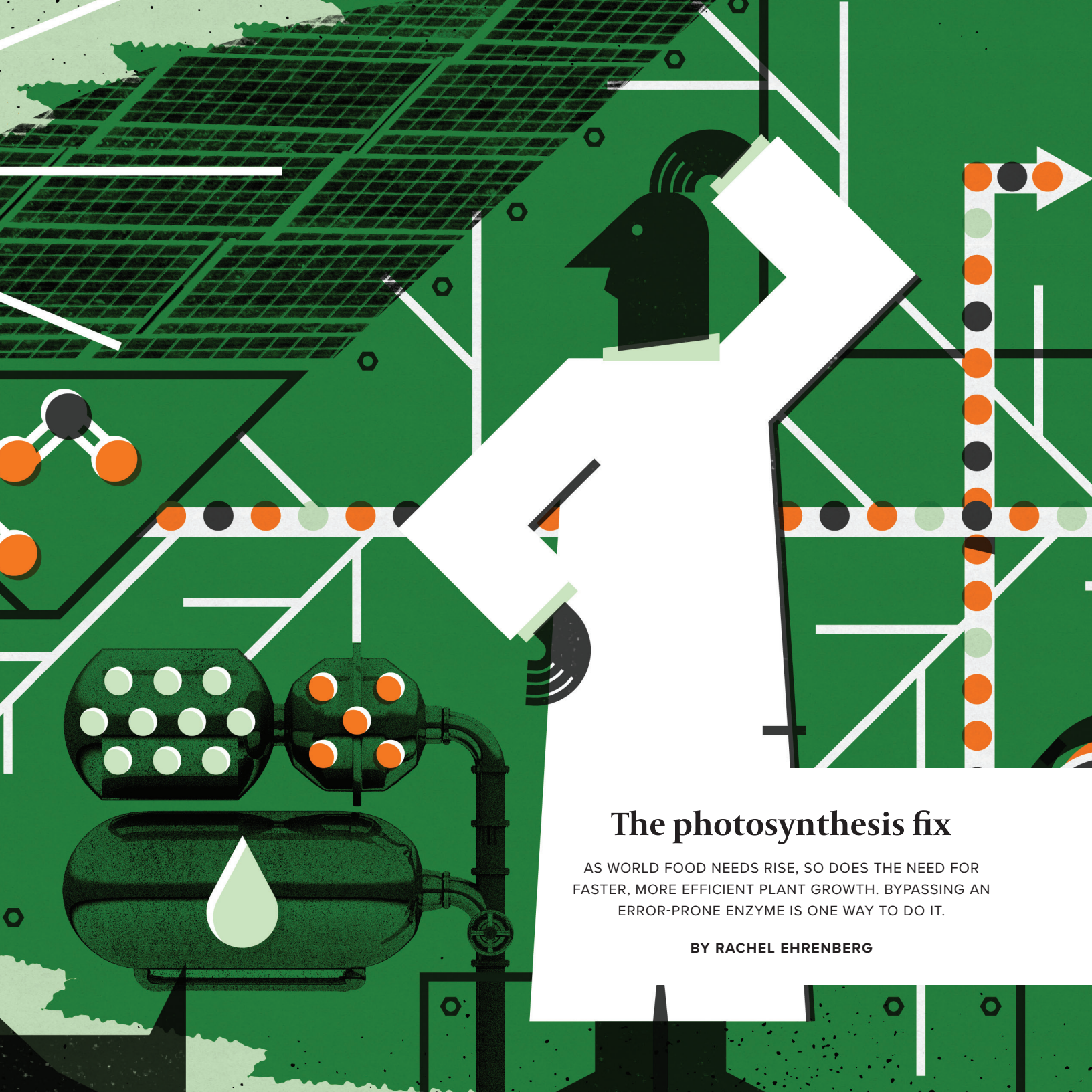
Speed dating
Increased light makes female Tungara frogs (*Engystomops pustulosus*) less selective in their choice of mate — the risk of predation is lower if they rush to reproduce.

Delayed departure
Light from buildings and bridges along the Cedar River in Renton, Wash., delays the migration of sockeye salmon fry (*Oncorhynchus nerka*) heading for the Pacific.

Compass jammed
Nocturnal dung beetles (*Scarabaeus satyrus*) navigate by the Milky Way and polarized light from the Moon. Too much light sends them round in circles.

Missing microbes
Light causes a loss of diversity in microbial communities in freshwater sediments. Photosynthesizers — diatoms and cyanobacteria — proliferate at the expense of other organisms.

SOURCE: REPORTING BY STEPHANIE PAIN; ILLUSTRATION BY MESA SCHUMACHER



The photosynthesis fix

AS WORLD FOOD NEEDS RISE, SO DOES THE NEED FOR FASTER, MORE EFFICIENT PLANT GROWTH. BYPASSING AN ERROR-PRONE ENZYME IS ONE WAY TO DO IT.

BY RACHEL EHRENBERG

IN A DIMLY LIT BASEMENT at the University of Illinois at Urbana–Champaign, not far from a nurtured, sunlit plot of corn at the center of campus, there's a torture chamber for plants. It looks pretty innocuous: a plywood box the size of a small coffee table, with air sifting in through a tube and out from a fist-size hole in the lid. The box has two tiers. The top holds tiny, nine-day-old tobacco seedlings, no bigger than your thumbnail. The bottom is layered with soda lime, a granular, Kitty Litter–like material. It's the same stuff they use in submarines to scrub carbon dioxide from the air.

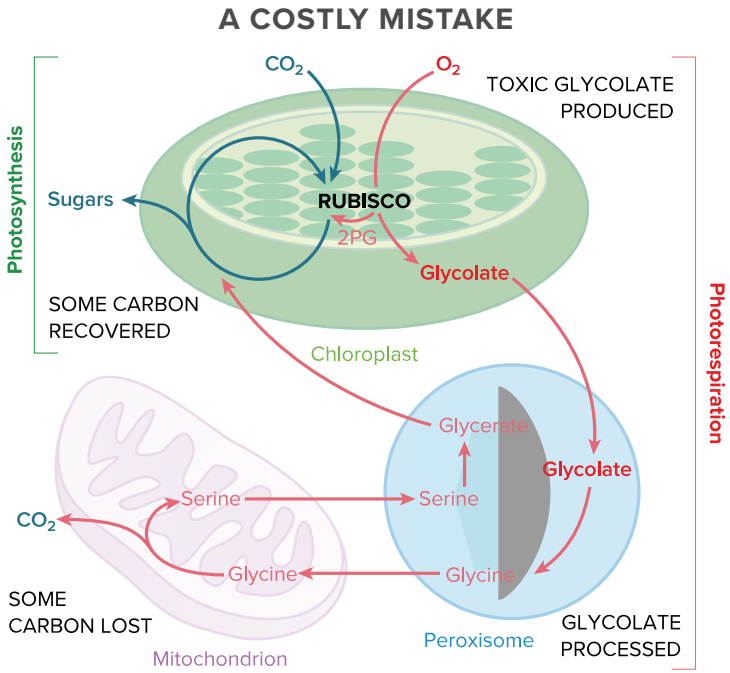
For someone in a submarine, getting rid of carbon dioxide is lifesaving. For the little plants in the box, it is a death sentence — unless, that is, they've inherited a protective genetic tweak. If a seedling can sweat it out for 24 hours and emerge with its chloroplasts unruffled, the UI scientists know they've got something special.

Plants need just three basic ingredients — sun, water and carbon dioxide in the air — to create the sugars that ultimately sustain most of life on Earth. Photosynthesis makes the world go round: It provides the oxygen we breathe, the food we eat and the fuel we burn. But though it is a marvel, it is also stupefyingly inefficient. From a given amount of sunshine, most plants convert less than 5 percent of that light energy into biomass, and under some environmental conditions, as little as 1 percent.

And yet that very inefficiency is giving scientists hope, because it offers room for improvement and a way to provide for humankind's future. If plants could photosynthesize better, the extra growth might help feed the nearly 10 billion people that the United Nations estimates will populate the planet by 2050. And it could help offset other anticipated challenges: global dietary shifts toward meat and dairy, an uptick in demand for biofuels that leaves less land available to grow food, and a hotter landscape that will meddle with many crops' photosynthesizing skills.

"There is much uncertainty about how we will get to the yield increases we need in the future," says agricultural scientist Tony Fischer of the Commonwealth Scientific and Industrial Research Organization in Australia. "We need to be trying every tool in the toolbox."

Part of the solution may lie with a little seedling gasping for air, right now, in the box in that Illinois basement.



In photosynthesis, plants make sugars using CO_2 (left) from air. But the enzyme rubisco, which adds CO_2 to the photosynthesis assembly line, is sloppy and sometimes adds oxygen (right). This generates a toxic compound, glycolate, and kicks off a process called photorespiration. Glycolate is dismantled and some carbon is recovered to build sugars. But the process uses energy and some carbon is lost.

The limits of good breeding

Traditional crop-improvement tools have already led to extraordinary leaps in yield. Starting as far back as the 1920s, plant breeders created plants that not only grew faster, allowing for more plantings per season, but also produced more calories for eating. Those gains, part of a larger agricultural initiative known as the Green Revolution, were partly achieved by selecting for two traits: plants with leaves that would intercept as much light as possible and plants that would funnel as much biomass as possible into the edible seeds. Today's premier varieties of soybeans capture nearly 90 percent of available sunshine and pack as much as 60 percent of their biomass into the bean; wheat and rice also saw hefty boosts in yield.

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THIS PAGE, REPORTING BY R. EHRENBERG, ILLUSTRATION BY E. HUNTER

But the gains are approaching a ceiling — a plant can't be nothing but seed, after all. Where might crop scientists turn? The inefficiencies of photosynthesis are an obvious choice, says Don Ort, a plant biologist at the Urbana–Champaign campus. The Green Revolution didn't tackle this feature. Conventional plant breeding harnesses natural variation, seeking out individual plants with traits of interest: slightly larger seeds than their neighbors, for example, or significantly shorter stems. But that strategy doesn't work for photosynthesis, Ort says. Most plants' photosynthetic machinery chugs along at pretty much the same rate — there isn't a spectrum of lousy to superstar to select from.

Still, research that would lay the groundwork for confronting those inefficiencies was under way at the University of Illinois decades ago. In 1965, the United States Department of Agriculture hired William Ogren to work at the campus and look into improving soybean photosynthesis. The mild-mannered chemist would end up doing groundbreaking research that set off some fiery years in plant biology and saw more than one academic meeting devolve into shouting matches.

Ogren — and much of the plant physiology community — was intrigued by what appeared to be a major glitch in photosynthesis. Under certain circumstances, plants produced a toxic compound called glycolate. Plants make it, but because it's toxic they then have to dismantle it. Making and then cleaning up glycolate — a process called photorespiration — is a major waste; it leads to chemical reactions that release valuable carbon back into the air. So what caused the plants to make the glycolate in the first place? Ogren and his postdoctoral researcher George Bowes discovered the culprit: the enzyme in charge of one of the first steps of photosynthesis. Known today as rubisco (for ribulose-1,5-bisphosphate carboxylase/oxygenase), this enzyme's job is to grab carbon dioxide that enters the leaf and tack it onto another molecule in the assembly line. It turned out that the inept enzyme will happily grab oxygen instead, sending it along in carbon dioxide's place. And when rubisco passes oxygen into the photosynthesis assembly line, glycolate results, gumming up the works.

Rubisco's mistake is costly. Estimates suggest that photorespiration can reduce the efficiency of photosynthesis by more than 40 percent. "If you designed that, it would be considered an engineering failure," says biochemist Sabeeha Merchant of the University of California, Los Angeles.

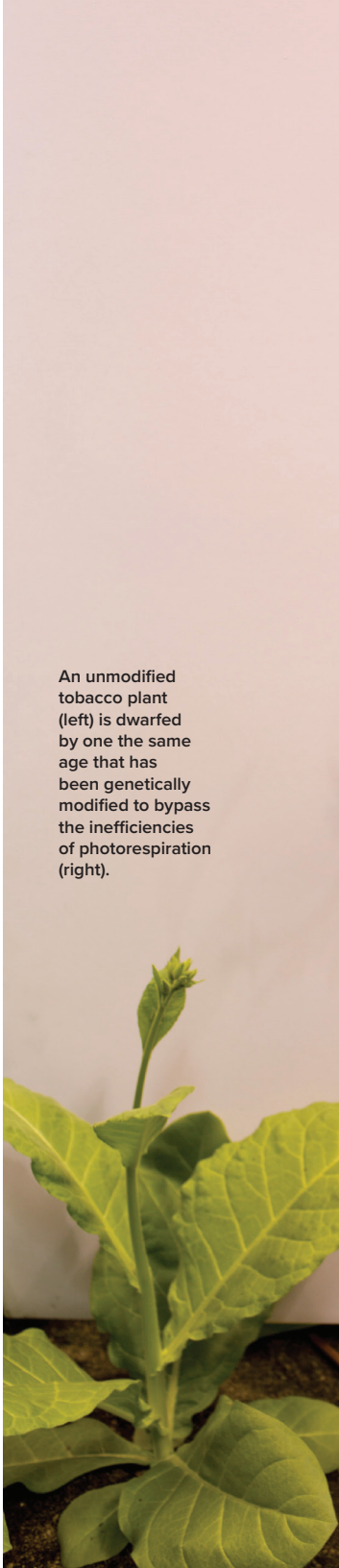
Yet rubisco's sloppiness today is rooted in its ancient origins and stunning past success. It is ubiquitous — possibly the most abundant protein on Earth. Plants, algae and light-harvesting bacteria all depend on it for turning inorganic carbon into usable organic matter. It is responsible for more than 99 percent of global primary production, that remarkable process whereby biomass emerges from thin air.

Billions of years ago, when rubisco began doing its job, there was barely any oxygen in the air. It didn't matter if the enzyme picked up the occasional oxygen molecule — there wasn't much of the stuff around. Rubisco's life work, photosynthesis, changed that. Over the eons, it pumped more and more oxygen into the atmosphere. Today, atmospheric oxygen is roughly 500 times more abundant than CO_2. That oxygen is rubisco's Achilles's heel. Though precise numbers vary depending on environment, broad-brush calculations suggest that for every five carbon dioxides, rubisco grabs two oxygen molecules. And rubisco could not evolve later on to fix its biochemical promiscuity: Scientists surmise that its evolutionary journey had boxed it in, such that minor mutations would knock out its function altogether.

ASSOCIATED ANNUAL REVIEWS CONTENT

The Costs of Photorespiration to Food Production Now and in the Future

B.J. Walker *et al* / *Annual Review of Plant Biology*



An unmodified tobacco plant (left) is dwarfed by one the same age that has been genetically modified to bypass the inefficiencies of photorespiration (right).

CREDIT: CLAIRE BENJAMIN / UNIVERSITY OF ILLINOIS

"When we think about plants, we forget that they've been around for so long," says Amanda Cavanagh, a University of Illinois postdoc, as we descend in an elevator toward an underground tunnel that serves double duty as a campus tornado shelter and a quick shortcut between buildings. "Their machinery can't cope with the current high-oxygen environment, the environment they shaped. It's a problem for the plant, and it's a problem for the food system."

A genetic bypass

I'm in the tunnel with Cavanagh and Paul South, a molecular biologist with the US Department of Agriculture, headed to the tobacco seedling torture chamber. The tunnel is well-lit and clean, though South gleefully points out a budding stalagmite on the floor, the result of a slow drip through a ceiling crack. Somewhere above us, a few hundred yards of dirt away, is the greenhouse where Ogren grew his soybeans decades earlier.

Six-day-old seedlings sprout perkily in a tray next to the torture chamber, unaware of their future. The box is a crucial first test after months of genetic tinkering by South. If his efforts are successful, some of those baby tobacco plants won't mind the dangerously low levels of carbon dioxide they're being subjected to. They contain a genetic workaround, a bypass that will compensate for rubisco's cursed affinity for oxygen. Their photosynthesis machinery will keep humming even as neighbor seedlings without the bypass ultimately wilt and die, their chlorophyll ravaged by the toxic product of rubisco's mistake.

Photorespiration is a convoluted process, akin to trekking through three different buildings to get waste to the curb. The glycolate is modified piecemeal. It is made in the chloroplast, then transits through two other cellular compartments, the peroxisome and the mitochondrion. Some of its carbon is recycled along the way and sent back to the chloroplast to make sugars, but the effort still adds up to loss. The idea behind the scientists' bypass is to modify the plant's genetic material and so recycle glycolate immediately — right in the chloroplast — recovering all the carbon and saving energy. "Photorespiration takes the country roads," says South. "The bypass is like installing a freeway."

The idea has a proven track record. A decade ago, for example, researchers led by plant biologist Christoph Peterhänsel, then at RWTH Aachen University in Germany, successfully created a photorespiration bypass in the weedy mustard *Arabadopsis*, the plant-biology equivalent of the lab rat. Their approach, reported in *Nature Biotechnology* in 2007, borrowed genes from the bacterium *Escherichia coli* to streamline

In a 2016 field experiment, an infrared gas analyzer measures carbon dioxide intake — and thus photosynthesis rate — of plants genetically engineered to bypass photorespiration.

CREDIT: CLAIRE BENJAMIN / UNIVERSITY OF ILLINOIS

the glycolate cleanup. The plants responded, growing faster and producing more shoots and roots than their ordinary counterparts.

Another approach, led by plant biochemist Veronica Maurino of Heinrich Heine University in Germany, used genes from both plants and *E. coli*. Published in 2012 in *Frontiers in Plant Science*, that work also led to enthusiastic growth. But these past efforts didn't use the tools available to today's genetic engineers, which make it possible to insert several desirable genes in a row, and to include bits of DNA that can dial up or down the activity of the inserted genes.

Also in the years since, researchers have discovered two more proteins to play with. Their job is to ferry glycolate out of the chloroplast, allowing the by-product to escape. The Illinois scientists have tools to inactivate these, in what's now a full-court anti-photorespiration press.

The Illinois work also adds a grand computational twist. Rather than deciding which precise genes to modify and how, South has used computer programming to generate 24 potential designs that mix and match the bypass machinery. They cover an array of alterations: new arrangements of already tested bypass genes; genes snipped from different sources such as algae; and sundry DNA switches to turn various genes on and off (or dial photorespiration back up if it turns out to be more important than scientists assume).

The end result of all this shuffling is 140 genetically distinct tobacco plant lines with distinct bypass designs. Each will undergo a battery of tests, including greenhouse and field trials. Maurino, whose early bypass research helped fuel the current work, is confident in the approach. "Their results seem very promising," she says. "I'm very excited to hear more."

The researchers may not end up with one "best" solution — in fact, they don't want to, because real-world environments vary greatly. Working with several bypass designs will allow them to identify versions that would excel in, say, drought conditions, nitrogen-poor soils or very hot temperatures. That would be the mark of success: ramped up photosynthesis in a true crop plant, grown the way a farmer might grow it. The current work modifies a cigar variety of tobacco called Petit Havana, but soybean, potato, and cowpea — a staple in sub-Saharan Africa — are all on the horizon.

Green machines?

Early results are encouraging. I'm taken to one of the lab greenhouses and the bypass plants are easy to pick out, with flowering shoots that stretch above the fledgling greenery of their ordinary neighbors. In field trials conducted in 2016, tobacco plants with a bypass had 18 to 20 percent more biomass — the added heft in leaves and stems — than ones that hadn't been tinkered with. They also flowered earlier, which could enable two plantings a year, Cavanagh explains. She is testing the plants to see how different versions of the bypass handle different environmental conditions, taking advantage of a unique university field station where you can manipulate temperature and gas concentrations in plants grown outdoors. She notes that people often assume that the higher carbon dioxide levels of the future will be better for plants, but this isn't necessarily the case (see sidebar on Page 51).

Researchers aren't putting all their seeds in one basket, though. The bypass project is just one prong in a larger international initiative called RIPE (Realizing Improved Photosynthetic Efficiency), headquartered at

the Illinois campus and with collaborators at the University of California, Berkeley; Louisiana State University; and institutions in Australia, the United Kingdom and China. RIPE is targeting weak links and bottlenecks all along the roughly 160 steps of photosynthesis, supported by $25 million from the Bill and Melinda Gates Foundation and $20 million more from the Foundation for Food and Agricultural Research and the UK's Department for International Development. The ultimate goal is to increase the output of staple food crops.

There's an urgent need to push this work along, says University of Illinois crop physiologist Steve Long, director of RIPE. Revving up the various sluggish spots in the photosynthesis pathway and bringing them all together through a mix of genetic engineering, computer modeling and conventional plant breeding will be a long, slow process. And though it might be hard for Americans to conceive of a world short of calories, the forecasted population increases, combined with global warming and their heavy toll on the environment may mean more expensive food in many parts of the world. "Whatever we invent today is not going to be available for 20 years or more, so we need to be looking now at what are the best technologies we can put on the shelf," Long says.

Dealing with rubisco's shortcomings is one major focus. In addition to the bypass project, researchers at RIPE and elsewhere are working on ways to swathe rubisco with CO_2 so it doesn't encounter oxygen to begin with, and scouring algae and wild plants for versions of rubisco that stay on task, ignoring oxygen.

The team is also tackling aspects of photosynthesis that aren't the fault of rubisco but of inefficient use of light. When sunlight gets too strong, plants shed the extra energy as heat, to avoid damage. This light-quenching mode can take minutes to hours to turn off, even after clouds have moved in — a major waste. To fix the problem, Long and his RIPE colleagues added genes to tobacco plants to speed the bounce-back. The strategy, reported in *Science* in 2016, upped the amount of biomass in plants by 14 to 20 percent.

Other scientists outside of RIPE are tackling the photosynthesis problem by trying to mimic a strategy that has evolved numerous times in the natural world. Roughly 3 percent of land plants use a different enzyme, one that ignores oxygen, to snatch up CO_2. These "C4" plants, which include crabgrass, sugarcane and corn, have a very different anatomical structure that keeps rubisco away from oxygen. (Rubisco still has jobs later on in the photosynthesis assembly line.) Such plants have very low levels of photorespiration. Inspired by this, a team led by plant developmental geneticist Jane Langdale at the University of Oxford in England are trying to engineer a C4 version of rice. The project, funded by the Gates foundation, is complex, but in a solid step toward that goal, the scientists reported in 2017 in *Current Biology* that they'd engineered anatomical tweaks to bring rice closer to C4 anatomy.

Of course, science won't be enough to feed the world of the future, says Fischer of the Commonwealth research organization. It's also going to take policy changes and basic infrastructure improvements, such as roads and electricity, in developing parts of the world. "All of these have to be fixed as farmers embrace new technologies, and that means huge changes in public and private investment and in governance," Fischer says.

Those are gargantuan challenges. But in the hopes they will be met, researchers are doggedly torturing one generation of plants at a time and seeing what bears fruit. ●

IS MORE CO_2 GOOD FOR PLANTS?

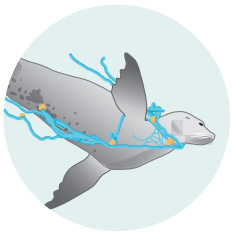
Plants need carbon dioxide to grow, and CO_2 levels are rising. Still, a CO_2-rich world won't necessarily bode well for plants. The uptick in temperature that comes with the uptick in atmospheric CO_2 poses several problems:

Rubisco, an already sloppy photosynthesis enzyme, gets sloppier at higher temperatures. That suggests it will make more errors, mistakenly grabbing oxygen instead of CO_2, as the climate warms.

Many plants close their pores in hotter weather to prevent water loss. This means oxygen builds up inside the leaves, which translates into lower photosynthesis rates.

While some experiments find that crops grow bigger when exposed to higher CO_2 concentrations, those plants typically don't pack as hefty a nutritive punch. They are lower in essentials such as iron and zinc.

Q&A



with environmental engineer Jenna Jambeck

The pileup of plastic debris is more than ugly ocean litter

A solid-waste specialist offers ways to halt the plague of pollutants choking the seas

By Kenneth R. Weiss

HOW MUCH PLASTIC DEBRIS ends up in the world's oceans every year? That's a question that preoccupied University of Georgia's Jenna Jambeck for years until she worked out the math with colleagues in 2015 and published the findings in *Science*. Bottom line: The tonnage translates to the equivalent of five grocery bags full of plastic lined up on every foot of coastline around the globe.

Jambeck coauthored "Plastic as a Persistent Marine Pollutant," a 2017 review on how marine plastics work their way into the food web, in *Annual Review of Environment and Resources*. It argues for a "Global Convention on Plastic Pollution," similar to other international conventions to tackle persistent organic pollutants. This interview has been edited for length and clarity.

How does all this plastic debris end up in the ocean?

The commonly quoted statistic is that the majority, about 80 percent, comes from land. It gets washed by runoff or blown by wind into the ocean or into waterways that lead to the ocean. The rest, about 20 percent, comes from catastrophic events or maritime sources, much of it fishing gear. In my work, I focus on municipal solid waste and poor design of trash receptacles, collection vehicles and landfills, especially in rapidly developing economies where waste management is lagging. Deliberately tossing litter or open dumping and burning trash is a part of human nature and how we've historically managed waste. But some cultures still do it.

That wasn't a problem for the oceans until plastics came on board. If you throw out metal or glass or burn paper, that's one thing. But plastics are persistent synthetic polymers that can last for centuries. The steep, steep increase of production of plastics, 620 percent in the last 40 years, has completely changed our waste stream.

Is the plastic problem growing or shrinking?

Right now, it's still on the growth curve because of population growth and increase of plastic use.

If there's so much in the ocean, why don't we see more of it? Doesn't it float?

Some floats and some sinks. It depends on the density of the polymer. Beverage bottles are denser than seawater and would sink, unless the cap is on. Capped bottles are filled with air and people tend to see them floating. Polyethylene, such as milk jugs, and polypropylene, which is used to make food packaging and wrappers, are the most common types of packaging that floats. Over time, the materials fragment into smaller and smaller pieces. Their density can change as they get colonized by bacteria and algae and then they can drift to the seafloor like marine snow.

We know that the ocean can spit plastic back on beaches. And there is plastic flying above our heads in the stomachs of seabirds. But we hypothesize that most of it probably ends up at the bottom of the ocean, potentially ground into smaller and smaller bits.

Why should we be concerned?

We've all seen heartbreaking pictures of entangled marine life, struggling to get free. We find plastic bags in the stomachs of sea turtles, plastic straws stuck in their nostrils. Plastics don't biodegrade in the ocean, but fragment over time into microplastics, about the size of pencil erasers. And now we are finding microbeads, the size of the tip of a pencil, or even smaller. They replaced walnut shells or pumice as abrasives in toothpaste and exfoliating agents in body cleansers. And now, there's a hot new area of environmental research tracking microfibers from synthetic fabrics, like fleece, often made of polyethylene. When you

CREDIT: KENNETH R. WEISS; G. MAHONEY & E. JEWETT-HALL / *KNOWABLE*; JAMES PROVOST

wash these garments, little pieces of these fibers wash out with the wastewater and can end up in the ocean. We're just learning how all these fragments might come back to haunt us.

Can you offer an example of how plastic bits in the ocean might haunt us?

Depending on its size, plastic will get consumed by marine organisms. We have found plastic in the bellies of fish, and many, many other animals. Some research focuses on shellfish, like mussels or oysters, which accumulate microplastics and microfibers as they filter seawater to feed on plankton. When we eat an oyster or a clam, we consume the entire animal and everything it has accumulated.

Aside from sounding rather unappetizing, is it a problem eating bits of plastic?

It can be for wildlife. Seabirds like albatrosses fill their bellies with plastics, which don't provide them nutrients — so they can starve to death. But it's also contaminants the plastics can carry, either when they were produced with phthalates [to make them more flexible] or BPA [used to manufacture strong epoxy resin], or what they pick up in the environment. Even though plastics are hard materials, at the microscopic level they absorb persistent organic compounds. Persistent organic pollutants like DDT, PCBs, flame retardants and fabric treatments have an affinity for plastic. Plastics act like sponges, soaking them up.

So we could be getting a side of pesticides or flame retardants with our seafood dinner?

Marine life and humans can be exposed to those chemicals in other ways, of course, but this is another potential pathway for those chemicals to reach us. Chelsea Rochman [an ecologist at the University of Toronto] has shown that fish have absorbed some persistent organic pollutants from plastics and had lesions on their livers, which are precursors to cancer. But we don't yet understand the link between plastics, toxic compounds they carry, and what this could mean for humans.

What does it take for plastic to disintegrate, to break down into component parts?

Heat and sunlight can break down plastic. But we don't think there is a lot of biodegradation for traditional polymers in the ocean. We don't have a lot of sunlight on the ocean floor, and it's much cooler in temperature. There's a lot of abrasion and mixing near the surface to grind them up. And science has isolated a couple of strains of microbes and bacteria that can metabolize carbons in plastic. But our common understanding is that the long-chain polymers don't really biodegrade.

We often hear about schemes to clean up the plastic debris in the ocean. Is this the right solution?

I like to use the analogy of the overflowing bathtub. If your bathtub is overflowing, the first you thing you do is turn off the tap. There are some worthwhile ocean cleanup efforts, such as collecting nets and fishing gear. But we need to focus on stopping the input from land.

How do we do that?

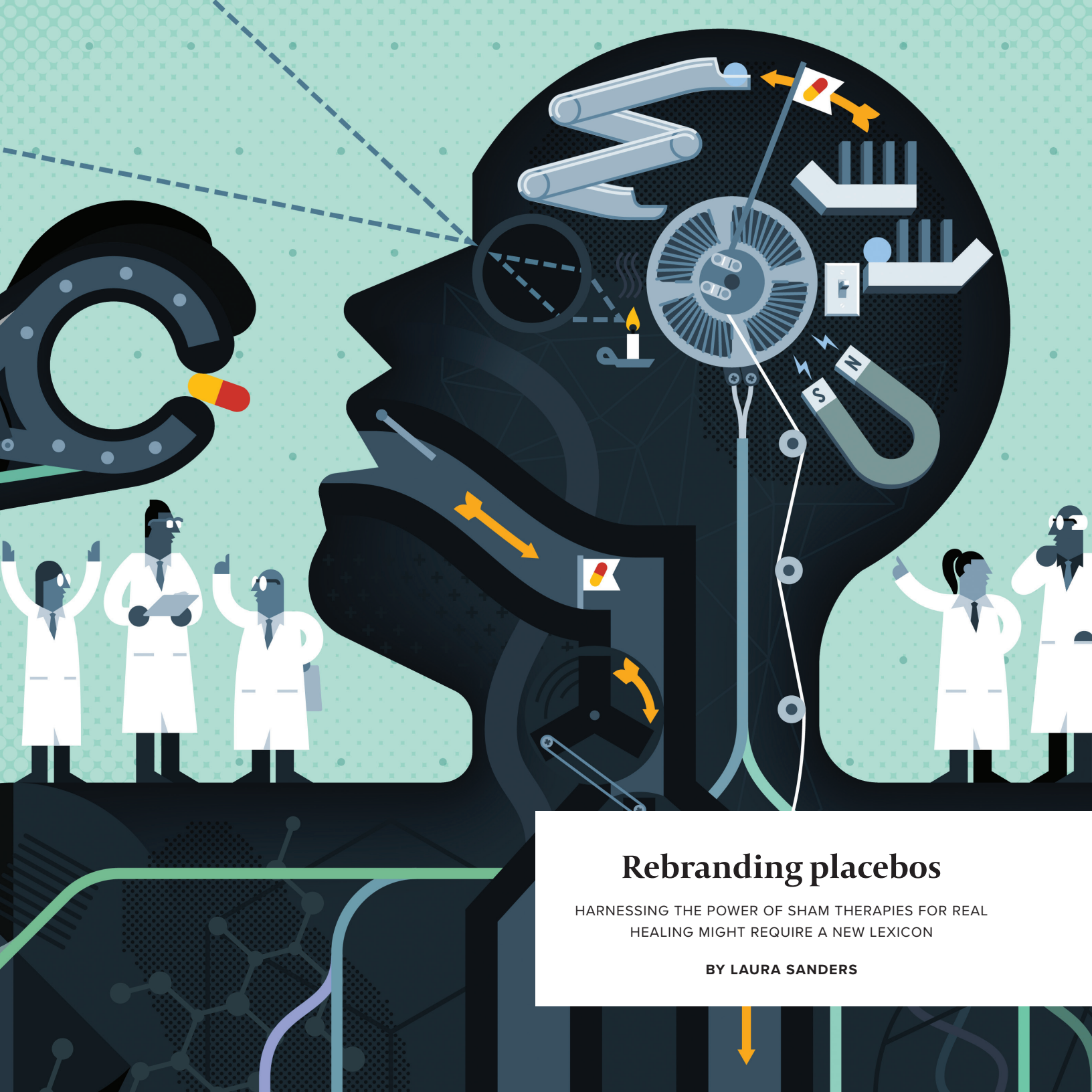
There is a whole continuum of solutions upstream that will affect downstream: reducing plastic production and devising ways to deliver products with less waste. We produce almost four times as much waste on a per capita basis as many middle-income countries. There's talk about new materials, and designing them in a way to retain their value so they can be recycled. When needed, plastics should be properly treated and contained at a disposal site, but that is the least desirable option.

When did you begin to focus on plastic debris flowing into the ocean?

I started looking at the issue in 2001 and I was laughed at. Fewer people cared about the issue back then, and the field wasn't respected as a scientific discipline. But I felt instantly passionate about it. And things have changed. It's really grown as a research field with recognition that this is a serious issue. If the goal is zero input into the oceans, one important thing you can do downstream is collect data. That's why I developed an app. It's called Marine Debris Tracker and available for iOS and Android. It's for citizen-science work. People can take a picture of, or tell us, what they find and send it to our database. We also hope they pick up whatever litter they find. We make all of the data available to the public.

Your review calls for a global convention on plastic pollution. Is this really needed?

I think it is, because it's inherently a global problem. Once plastic ends up in the ocean, it can ride the currents and end up anywhere. There are national efforts, and there are regional agreements that can help. But a global convention could bring everyone together to tackle this problem. ●



Rebranding placebos

HARNESSING THE POWER OF SHAM THERAPIES FOR REAL HEALING MIGHT REQUIRE A NEW LEXICON

BY LAURA SANDERS

IN APRIL 2017, SEVERAL hundred scientists converged in the Netherlands for the first meeting of the Society for Interdisciplinary Placebo Studies. The topic drew psychologists, psychiatrists, physiologists, ethicists and neuroscientists, all enthusiastic about focusing a wider lens on a booming area of study: how beliefs, expectations and motivations can shape health. The well-documented, if often incidental, effects of placebos — drugs with no active ingredients, or other shams concocted to better measure another therapy's effect — have triggered that boom.

But even before the conference date had been set, something was bothering some prospective attendees, an annoyance that had gnawed at them for years. It was the word *placebo* itself. And though it seems like a small issue — a word choice, a semantic nuisance — it struck scholars like clinical psychologist John Kelley of Harvard that the name was having an outsize effect on doctors' ability to harness the power of placebos for good.

For starters, the name defies logic. "The 'placebo effect' in and of itself is an oxymoron," Kelley says. "The placebo effect is the effect of something that has no effect. That can't be true."

Even if it were true, the name comes with baggage. Studies have found that placebos can dampen pain, relieve anxiety and help headaches. Yet despite its growing resumé, *placebo effect* still carries a strong whiff of woo. That name implies a fake, a sham, an intention to deceive, says neuroscientist Vitaly Napadow of Massachusetts General Hospital and Harvard Medical School. "The word *placebo* has a really bad connotation that's holding it back in a way from actually being something we use."

That bad rap came up again in Leiden during a small gathering the day before the official placebo meeting began. Napadow, Kelley and about two dozen other scholars convened to talk about how placebos might transform clinical practice. But almost immediately, the conversation turned to vocabulary as the scientists debated the advantages and practicalities of a rebranding campaign for the poor, shamefaced placebo.

Their objection goes beyond PR. The real problem, they argue, is that the term *placebo effect* is incorrect. Sugar pills, pretend surgeries and fake acupuncture needles are supposed to be inert, existing only so that something else (the "real medicine") can shine. For people studying placebos seriously, that narrow, dismissive way of thinking is limiting. *Placebos* fails to capture the deeper essence of how beliefs actually can and do transform the body.

"Language is a real problem here," Kelley says. But if the old term no longer makes sense, what then to call it? Alternatives — "meaning response," "expectancy response," "non-specific effect," and "context effect" — come with their own squishiness. Kelley, ticking through the list of proposed substitutions, admits there's still no lexical savior.

> "The clinical picture that's emerging is that in many disorders the placebo response is quite strong."
>
> —TOR WAGER

The meeting ended with no new name, only an acknowledgment that the name, and concept, of placebos remains a roadblock to incorporating them into everyday medical practice.

Today's growing evidence of placebo power is built on more sophisticated explanations of just how beliefs can change the body, as revealed in a bevy of neuroscientific studies. Scientists are figuring out when thoughts

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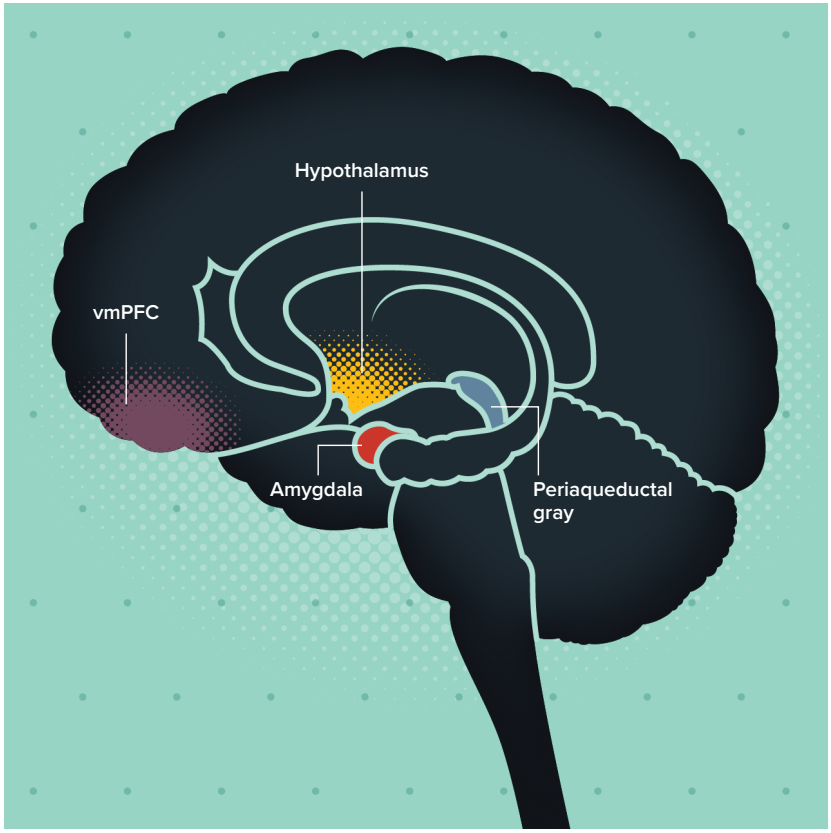
PLACEBO HOTSPOTS
Over the last decade, scientists have been tracking placebo effects to specific locales in the brain. Although many different areas appear important in mediating certain effects (including the hypothalamus, the amygdala and the periaqueductal gray), the ventromedial prefrontal cortex (vmPFC) has garnered recent scientific interest.



CREDIT: TEXTBOOK EXAMPLE

and expectations can change outcomes, and when they can't. More interestingly, these effects aren't always due to simple learned associations — take a sugar pill, feel better. Instead, the placebo effect appears to hook into a much more active and broad-based neural process, one in which the brain builds its own expectations from a wide range of clues. And that active construction of reality may simply be how our brains work in all situations, making guesses about what will happen next based on past experience and present cues.

Researchers looking at how the brain builds the expectations that fuel the placebo response have recently identified one brain region — the ventromedial prefrontal cortex — as particularly important, serving as a neural hub for transforming beliefs into body responses. This brain network helps place a person in context relative to the outer world, a situational awareness that then leads to predictions about, among other things, whether a treatment, sham or real, might work. Other neural networks are no doubt involved, too, depending on the situation. The search for a better name may signal a field coming of age, helping scientists define the mysterious process by what it is and what it isn't.

This, not that

One scenario where the term *placebo effect* fails is in talking about active drugs. Morphine behaves very differently based on whether people know they're getting it or not. A powerful opiate falters when people don't know they've taken it. That's not a placebo effect, because there is no placebo. Still, it feels like it should be, since it's based on the user's expectations, Kelley says. "It seems to me that it is exactly the same thing." Similarly, people can experience negative side effects from a placebo, if that's what they are expecting. This phenomenon is called the *nocebo effect* (more problematic vocabulary).

Another example comes from studies in psychologist Alia Crum's lab at Stanford. She and her colleagues gave two groups of people shakes to drink. One group was told the shakes were healthful; the other was told the shakes were an indulgent treat. The shakes were identical, but the people's bodies responded very differently. The hunger-stimulating hormone ghrelin, produced in the gut, was three times lower in the people who had the "indulgent" shake, as if they knew they should feel sated, Crum and colleagues reported in 2011. In that study, "there's no doctor, there's no patient, there's no placebo,"

Kelley says. “Is this the same phenomenon? Not exactly, but to me, it’s very similar.”

What these studies have in common is that they deal with psychological adjustments, tweaks to people’s perspectives, beliefs and expectations. As with some types of psychotherapy, people may reframe their beliefs to make space to believe something will help or not (or even hurt them). And these beliefs can have profound influences on the body.

Pain and disorders such as depression, anxiety and Parkinson’s disease seem especially amenable to psychological manipulations delivered as medicine, research suggests. In a study of people with Parkinson’s, brain surgery to implant a virus that enhances dopamine production produced improvements in symptoms for two years. Those gains should have been exciting, but the trial, reported in 2015 in *Annals of Neurology*, failed. That’s because the same two-year improvements were experienced by the people who underwent sham surgery — a very potent placebo, it turns out.

Medically meaningful placebo effects have turned up elsewhere. “The clinical picture that’s emerging is that in many disorders the placebo response is quite strong,” says cognitive neuroscientist Tor Wager of the University of Colorado Boulder. And that response is shaped by a variety of psychological forces.

Pavlov’s placebo

One of these psychological ingredients may be simple conditioning, a study from Napadow’s lab makes clear. After regularly coming into the lab to receive a small injection of an allergen in their skin, participants learned that the skin prick made them itch. But after a while, the researchers switched the allergen for salt water. “They were led to believe that this is the same allergen they’d been feeling all along,” Napadow says.

And lo, they believed it. Participants rated the sensation as itchy, and their brains showed itch-related activity similar to the traditionally acquired itch, Napadow and colleagues reported in *Allergy* in 2015. “You imagine the itch and you are in fact itching,” he says. “Your perception becomes your reality.”

That type of linking of two events may help explain much of the placebo effects observed in creatures with very little psychological baggage: animals and infants, who, it’s been shown, can learn to expect certain outcomes after taking a drug or undergoing a procedure. While this type of Pavlovian learning is certainly part of the placebo spectrum, such conditioning “doesn’t explain the whole story,” says Katja Wiech, a pain researcher at the University of Oxford.

People are very good at remembering something that hurts. After a back injury, a person knows exactly which movements to avoid. But “forgetting pain is so much harder,” Wiech says. At the placebo conference in the Netherlands, she presented data that suggest it takes about three times as much evidence for people to learn that the pain is gone.

If perception were as simple as receiving input from the senses, that difference in learning and unlearning pain might not exist. People would be keen observers of the sensory cues coming in and adjust their experiences to fit with them. But incoming sensory information — a throbbing toe, for instance — is not the only signal that matters. “Over time, we’ve learned that there’s not a direct proportional relationship between tissue damage and the pain,” Wiech says. People can learn to feel pain when they expect it, whether it’s there or not.

The pain signals that zing from the toe to the brain are but one piece of evidence the brain uses to build its narrative. Some information is more powerful than others, and we weigh it accordingly. “It’s not about the experience,” Wiech says. “It’s about the sense you make out of your experience.”

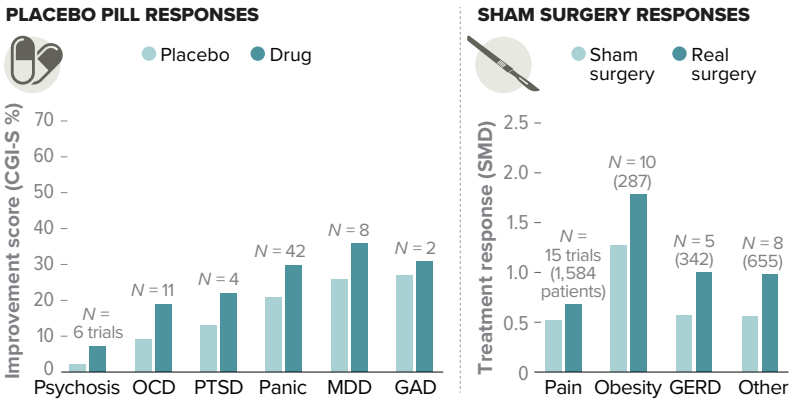
Mapping placebos in the brain

No matter what they are called, some placebo effects take hold of a compelling piece of neural real estate, Wager and colleagues argue: the ventromedial prefrontal cortex, or vmPFC. This cortical patch lies near the very front of the brain, behind the eyes. From its perch, the vmPFC forms neural connections that enable it to both help form beliefs and execute their orders. Drawing on memories, sensory cues and emotional input, the vmPFC evaluates relationships between things and creates an idea of the self, positioning a person in the context of her world.

Because of its far-flung connections to the spinal cord, skin, heart and immune system, the vmPFC and its vast neural networks may also orchestrate the body’s responses to these beliefs. Scientists are drawing increasingly detailed maps of the roads that lead from beliefs in the brain to changes in the body, progress detailed by Wager and his colleagues in 2017 in the *Annual Review of Neuroscience*.

TESTS OF PLACEBO POWER

Placebo interventions have shown effectiveness across a range of different psychiatric disorders (left) and types of surgeries (right) when compared with a real drug or surgery, although placebos' strength varies. Numbers of study participants are in parentheses.



OCD: Obsessive compulsive disorder; **PTSD:** Post-traumatic stress disorder; **MDD:** Major depressive disorder; **GAD:** Generalized anxiety disorder; **GERD:** Gastroesophageal reflux disease.

Take pain, for example. Scientists have traced a pathway that converts neural activity into perception of a throbbing toe, for instance, and the vmPFC seems to be a key node. Neurons in the vmPFC send signals to a part of the spinal cord called the periaqueductal gray, a hotbed of pain-detecting and pain-alleviating neurons. Other signals arrive here from the amygdala, involved in emotions; the nucleus accumbens, linked with motivation and addiction; and the hypothalamus, a brain structure with jobs of regulating temperature, hunger and sleep. These brain structures are all in deep communication with the vmPFC.

This mixture of signals, which can dial pain up or down, gets shuffled through several more middlemen before creating the sensation of back pain, for instance. Imaging studies suggest that placebos can tweak signals all up and down this pathway. One of the strongest responders to placebos is the vmPFC, Wager and others have found.

A similar pathway exists for a parallel but distinct part of the nervous system called the autonomic nervous system. This network can soothe the body or turn it into a sweaty, heart-thumping lump of panic. Recent work on Cebus monkeys revealed synaptic fibers that run from a part of the prefrontal cortex near the vmPFC and other cortical areas to a part of the adrenal gland, which can flood the body with adrenaline. The immune system is within the vmPFC's reach, too. Activity in the region is thought to spur the body to produce inflammatory cytokines and other immune system signals.

Placebos' influences on these pathways remain to be worked out, but Wager and others suspect that the vmPFC may turn out to be a key regulator. What's more, this brain area and its many collaborators may be involved in triggering a positive experience that lasts, Wager believes. His talk at the placebo meeting was about why some placebo effects seem to linger far beyond the time they'd be expected to fade.

Wager's idea, one that recent work from his lab backs up, is that placebo effects kick off feedback loops of goodness. "Once you have a positive expectation, you're biased toward looking for and learning from things that match those expectations," he says. "You value the good stuff and discount the bad stuff." Those rose-colored assessments mean that a person might selectively see what she already believes. A self-fulfilled prophecy is built.

Better living through placebos

But despite the positive results, placebos as treatments haven't overcome their stigma to reach doctors' offices yet. "We have some pretty good success" with disorders like depression, anxiety and migraines, Kelley says. "But I don't think anyone is prescribing them. It just feels wrong."

People could seek out a placebo prescription. It turns out that's not necessary, since commercial, over-the-counter "honest" placebos exist. You can Amazon Prime yourself 45 Zeebo brand pills for $24.90. That may seem like a lot to pay for gelatin capsules clearly labeled as containing "no active ingredient," but there's evidence that more

CREDIT: ADAPTED BY 5W INFOGRAPHICS. SOURCE: Y.K. ASHAR *ET AL / AR CLINICAL PSYCHOLOGY* 2017

expensive placebos work better than cheap ones. "Yes, kind of weird, but in a somewhat mysterious way, empowering," a top reviewer writes.

More palatable to physicians may be ideas such as, with the patient's agreement, slowly tapering a patient's dosage of an opioid painkiller or other drug. That way, a patient might get pain relief without the risk of side effects or addiction.

Still, as the more expansive concepts of mind-set and beliefs imply, patients' outlooks can be tweaked without pills, creams or sham surgery. Doctors can sit down, talk through the rationale of why a certain treatment might work, smile. Some people believe that those actions, called the "common factors," are responsible for much of psychotherapy's benefits. (The controversial "Dodo Bird Verdict," proposed in the 1930s by psychologist Saul Rosenzweig, posits that most forms of psychotherapy are equally effective, thanks to these common factors. As the dodo said to Alice and her companions in Wonderland after a circular race with no start and no stop, "*Everybody* has won, and all must have prizes.")

But even the low-tech approach of smiling and seeming to care has not yet made it into the clinic in a rigorous way. "The science of motivation, expectation and decision-making hasn't percolated into medical practice," Wager says. "And that would be such an exciting thing to see happen. The science we're doing is preparing the way for that."

Of course, placebos — or more general psychological adjustments — won't work for everything, or perhaps even most things. You can't think your way out of a brain tumor, Napadow says. "There are obviously going to be limits to how much our brains can control the diseases that are ravaging our bodies."

One telling example of placebos' shortcomings appeared in the *New England Journal of Medicine* in 2011. People with asthma were treated with an albuterol inhaler, a placebo inhaler or sham acupuncture. Afterward, the patients reported similar levels of improvement for all treatments, but their airways felt the difference: Only after getting the active drug could people blow more air out of their lungs. People taking placebos felt better, but they still couldn't breathe.

That study illustrates some newfound rigor for placebo research, which has been plagued by a pro-placebo bent in some cases, Wager says. "I feel pretty good that there are some people doing placebo research who just really want to know the answers," no matter how the results turn out, he says. "And we need that. Desperately."

For now, the questions still outweigh the answers. Wager and colleagues are adressing some of those questions by combining data from about 20 brain imaging studies on pain and placebos. Overall, placebos' effect on the pain network in the brain — the one that supposedly jumps into action when something hurts — seems surprisingly small. "For me, that opens up the door to say, 'OK, it might be pretty rare for placebo manipulation or treatment to have a deep impact on the things that cause pain,'" Wager says. That said, other brain circuits, such as those that handle motivation and value, might have the power to override this pain signal in the brain to make people feel better, he says.

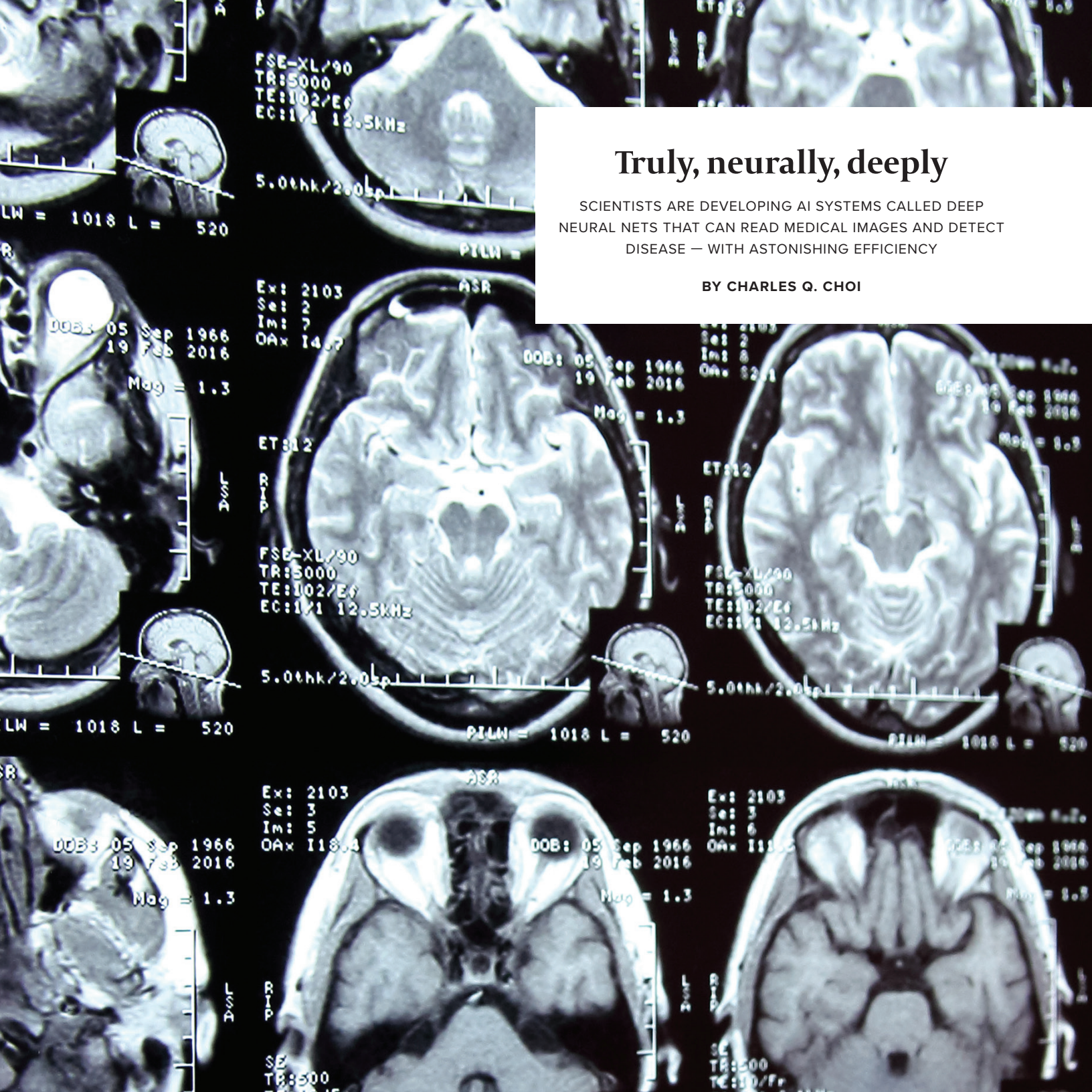
Untangling the various ingredients that shape our mind-sets may well alter clinical practice one day. "There are principles to how we come to those beliefs and how we change them," Wager says.

And now, those principles are beginning to take shape, emerging from their shady history and asking for proper names. ●

ASSOCIATED ANNUAL REVIEWS CONTENT

Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account

Y.K. Ashar *et al* / *Annual Review of Clinical Psychology*



Truly, neurally, deeply

SCIENTISTS ARE DEVELOPING AI SYSTEMS CALLED DEEP NEURAL NETS THAT CAN READ MEDICAL IMAGES AND DETECT DISEASE — WITH ASTONISHING EFFICIENCY

BY CHARLES Q. CHOI

ON A NOVEMBER EVENING IN 1895, German physicist Wilhelm Röntgen was running an electrical current through a glass tube filled with gas to learn more about how such tubes emitted light. The scientist had covered the tube with black cardboard, but to his surprise — though the lab was dark — he saw a light-reactive screen nearby fluorescing brightly.

Röntgen soon found that the mysterious invisible rays coming from the tube could penetrate his body — he could see flesh glowing around his bones on this screen. He replaced the screen with photographic film — and captured the world's first X-ray image, revealing that the inner workings of the body could be made visible without surgery.

Röntgen took an X-ray of his wife Anna's hand, complete with wedding ring. She apparently did not care for it ("I have seen my death," she said), but the revolution in medical imaging that X-rays triggered has meant life for countless others.

Now a new frontier is opening up that promises to help this field save even more lives: Artificial intelligence is helping to analyze medical images. AI systems known as deep neural networks promise to help doctors sift through the huge amounts of at-times incomprehensible data gathered from imaging technologies to make lifesaving diagnoses, such as cancerous spots in X-rays.

"Image recognition is a solved problem for computers," says biomedical informatician Andrew Beam of Harvard Medical School. "That's a task deep learning will do better than the average doctor — full stop."

Artificial brains

In an artificial neural network, software models of neurons are fed data and cooperate to solve a problem, such as recognizing abnormalities in X-rays. The neural net repeatedly adjusts the behavior of its neurons and sees if these new patterns of behavior are better at solving the problem. Over time, the network discovers which patterns are best at computing solutions. It then adopts these as defaults, mimicking the process of learning in the human brain.

A renaissance in artificial intelligence has taken place in the past decade with the advent of deep neural networks. Whereas typical neural networks arrange their neurons in a few layers, each focused on handling one aspect of a problem, a deep neural network has many layers, often more than a thousand. This, in turn, enhances its capabilities to analyze complex problems.

These systems became practical with the aid of graphical processing units (GPUs), the kind of microchips used to render images in video game consoles, because they can process visual data at high speeds. In addition, databases holding vast amounts of medical images with which to train deep neural networks are now commonplace.

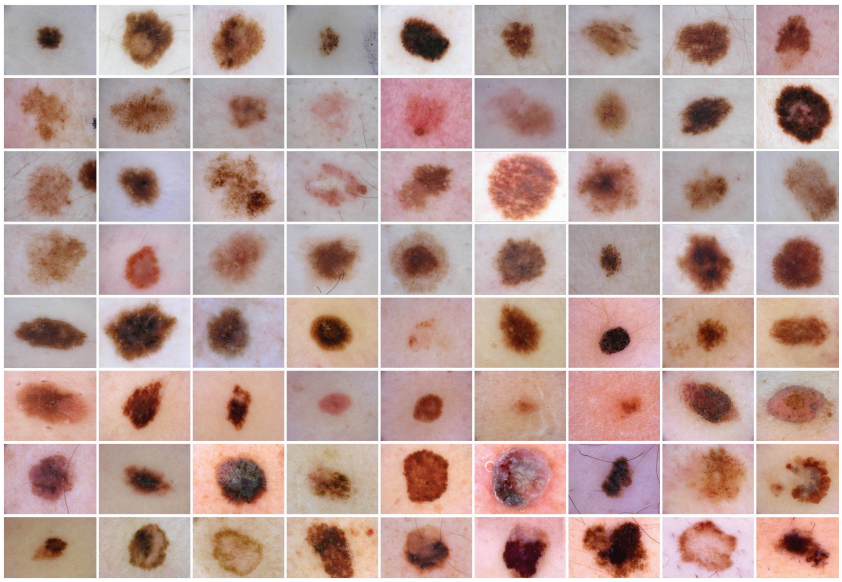
Deep neural networks made their splash in 2012 when one known as AlexNet won the best-known worldwide computer vision competition, ImageNet Classification. This work accelerated research in "deep learning," a subject that now dominates major conferences, including ones on medical imaging. The hope is that deep neural nets can help physicians deal with the flood of information they now must contend with.

> "The machine was superior to the physicians, even the most experienced ones."
>
> —HOLGER HAENSSLE

A deluge of data

Nearly 400 million medical imaging procedures are now performed annually in the United States. X-rays, ultrasounds,

OPPOSITE PAGE CREDIT: ALEXIALEX / SHUTTERSTOCK



This grid shows an array of skin lesions, some benign and some malignant. A deep neural net for skin cancer detection would be trained on thousands of images so that the algorithm could "learn" to recognize the features of probable cancers. Some of the patterns it homes in on may be undetectable by human beings.

CREDIT: INTERNATIONAL SKIN IMAGING COLLABORATION

MRI scans and other medical imaging techniques are by far the largest source of data in health care. Researchers at IBM, which developed Watson and other deep-learning AIs used in commercial applications such as weather forecasting and tax preparation, estimate that they represent at least 90 percent of all current medical data.

But analyzing medical images still requires human interpretation, leaving them vulnerable to human error. Properly identifying diseases such as cancer from medical images can be challenging even for specialists, as the abnormalities in an image that hint at such diseases can prove difficult to diagnose. A 2015 study in the *Journal of the American Medical Association*, for example, found the chance of two pathologists analyzing tissue from breasts and agreeing on whether or not they had signs of atypia — a benign lesion of the breast that indicates an increased risk of breast cancer — was only 48 percent.

Errors in medical imaging analysis can take their toll on human lives. An example is breast cancer, which kills about 40,000 women each year in the United States. Breast cancer screening involves analyzing mammograms, or low-energy X-rays of breasts, to identify suspicious abnormalities. If breast cancer is found early enough, it can often be cured.

However, doctors can miss about 15 to 35 percent of breast cancers in screened women, because they either cannot see the cancers or misinterpret what they do see. In addition to these false negatives, mammography can yield false positives in 3 to 12 percent of cases — often because lesions appear suspicious on mammograms and look abnormal in needle biopsies. Patients undergo painful and expensive surgeries to remove them, but 90 percent turn out to be benign.

One can hear similar stories with other diseases. "You see someone come into your office from a rural area where they don't have an expert physician around, and they have very late melanomas, and you think, 'If they had come to my office earlier, I could have saved a life,' " says dermatologist Holger Haenssle at Heidelberg University in Germany. "Every skin cancer may be a person's fate. If you detect a melanoma very early, you get complete healing with no side effects. So we're struggling to become better."

Strategies to improve breast-cancer screening have included more frequent screening, getting second opinions on mammograms, and new imaging technologies to make potential cancers more visible. Artificial neural networks promise to make medical imaging for breast cancer, and in general, smarter and more efficient.

The power of deep neural nets

Last May, Haenssle and colleagues found their deep neural network performed better than experienced dermatologists at detecting skin cancer. His team first trained the neural net by showing it more than 100,000 images, including ones of malignant melanomas, the most lethal form of skin cancer, and benign moles. Researchers told the net the diagnosis for each image.

The scientists then tested their neural net and 58 dermatologists against detailed skin images. Whereas the dermatologists accurately diagnosed 88.9 percent of malignant melanomas and 75.7 percent of lesions that were not cancer, the neural net accurately diagnosed 95 percent of malignant melanomas and 82.5 percent of benign moles.

"We had 30 global experts who thought, 'Nothing can beat me,' but the computer was better," Haenssle says. "The machine was superior to the physicians, even the most experienced ones."

These findings suggest that neural nets could be lifesaving. Skin cancer is the most common cancer in the United States, and early detection via neural nets could have a major impact on survival. While the five-year survival rate for melanoma is about 15 to 20 percent if detected in its latest stages, it rises to about 97 percent if discovered early, according to the American Cancer Society.

Similar promising findings have occurred with breast cancer, cervical cancer, lung cancer, heart failure, diabetic retinopathy, potentially dangerous lung nodules and prostate cancer, among other diseases.

Adding the human touch

Although deep neural nets are currently not in clinical use for medical imaging, a few are in clinical trials. For example, biomedical engineer Anant Madabhushi at Case Western Reserve University in Cleveland and his colleagues are applying a deep neural net to analyze digitized biopsy samples at Tata Memorial Hospital in Mumbai, India. The aim is to predict the outcomes of early-stage breast cancer to see which women require chemotherapy and which don't, providing low-cost diagnoses in parts of the world that cannot afford more expensive conventional approaches, Madabhushi says.

But even though neural nets can outperform humans on image recognition, that doesn't mean doctors are out of a job. For one thing, Beam notes, while machines are currently good at perceptual tasks such as seeing and hearing, they are nowhere near as good at long chains of reasoning — skills needed for deciding which treatment is best for a given patient, or for a specific population of patients. "We shouldn't overinterpret the successes we've had so far," he says. "A general-purpose medical AI is still a long way off."

And while scientists may train a neural net to spot a specific anomaly better than a person could, this net might not do as well if trained to recognize many different kinds of anomalies. "You can play chess against a computer, and it will win, but if you try to get a computer to play all the board games in the world, it will not be as good with its results," Haenssle says.

The future of deep neural nets will likely have them working in conjunction with physicians instead of replacing them. For example, in 2016 scientists at Harvard developed a deep neural net that could distinguish cancer cells from normal breast-tissue cells with 92.5 percent accuracy. In this case, pathologists beat the computers with a 96.6 percent accuracy, but when the deep neural net's predictions were combined with a pathologist's diagnoses, the resulting accuracy was 99.5 percent.

The many advances made with X-rays stem in part from Röntgen's decision not to patent his discovery so that the world could benefit from his work. More than a century after Röntgen won the first Nobel Prize in physics in 1901, artificial brains promise to advance medical imaging to breakthroughs he never imagined. ●

ASSOCIATED ANNUAL REVIEWS CONTENT

Deep Learning in Biomedical Data Science

P. Baldi / *Annual Review of Biomedical Data Science*

Nudging grows up (and now has a government job)

TEN YEARS AFTER AN INFLUENTIAL BOOK PROPOSED WAYS TO WORK WITH — NOT AGAINST — THE IRRATIONALITIES OF HUMAN DECISION-MAKING, PRACTITIONERS HAVE REFINED AND BROADENED THIS GENTLE TOOL OF PERSUASION

BY BOB HOLMES

CREDIT: TEXTBOOK EXAMPLE

EVERY DAY, 20 AMERICANS DIE BECAUSE they need an organ transplant and no donor organ is available. More than 100,000 people are now on transplant waiting lists in the United States alone. The public overwhelmingly supports organ donation — yet barely half the population has registered as donors. We just never get around to it, somehow.

That's not the only place where our actions don't match up to our good intentions. We promise ourselves that we'll eat a healthier diet and exercise more, yet more than a third of American adults are obese, with a medical price tag approaching $150 billion annually. We know we should be putting money aside for a more comfortable retirement, yet the median American family has saved just $5,000. So often, it seems, we need a bit of help to do what we know we should.

That's where nudging comes in. Nudges — tiny changes that have surprisingly large effects on how we act — offer policymakers a way to gently push us toward doing the right thing: Automatically sign up drivers as organ donors, or enroll employees in the company retirement plan, unless they opt out. Put the fruit at eye level and hide the cake and candy somewhere inconspicuous. These nudges work because real-world humans don't make decisions like coldly rational Mr. Spocks, but like flawed, idiosyncratic Captain Kirks. Nudges are essentially ways to harness our less-than-rational behaviors to help ourselves, or those around us.

The idea first came to public view a decade ago through the best-selling book *Nudge*, by economist Richard Thaler and legal scholar Cass Sunstein. Nudging's profile rose even higher in 2017, when Thaler, of the University of Chicago, was awarded the Nobel Prize in economics for introducing irrationality — and hence, nudging — into that overwhelmingly rational field. Nudges offer gentle, non-coercive — and, best of all, cost-effective — ways to guide people toward better choices.

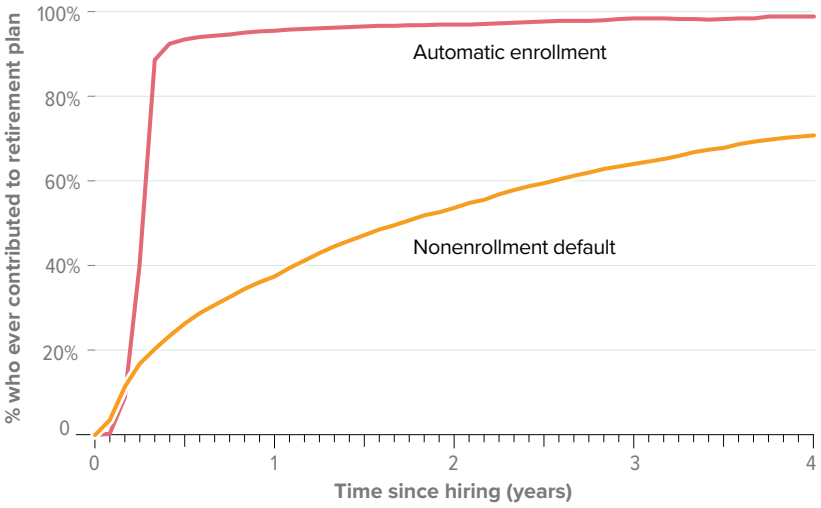
And governments and other nudge specialists have jumped on the nudging bandwagon. "The biggest change is the sheer explosion of initiatives, from private and public sectors alike," says Sunstein, of Harvard University.

At last count, more than 60 government departments and international agencies have established "nudge units" tasked with finding and pulling the right behavioral levers to accomplish everything from increasing retirement savings to boosting diversity in military recruits to encouraging people to get vaccinated against flu. The United Kingdom's Behavioural Insights Team, one of the first and largest such units, has expanded from a handful of people in 2010 to about 100 today, with global reach. Clearly, nudging has moved into the mainstream.

But that growth is not the only thing that has changed. As nudgers gain experience, they are getting better at analyzing behavioral obstacles and designing nudges to overcome them. At the same time, they have begun to expand the domain of nudging beyond mere procedural tweaks, toward redesigning entire government programs to take into account behavioral insights. This broader philosophical shift in governance may be nudging's most significant contribution.

NUDGING PAST PROCRASTINATION

If people have to act to enroll in retirement savings plans, many never get around to it. Changing the default so that they are automatically enrolled (unless they opt out) dramatically increases the number of people who save.



CREDIT: 5W INFOGRAPHIC; SOURCE: J.J. CHOI / *AR FINANCIAL ECONOMICS* 2015

Context and details matter

One of the biggest lessons from a decade of practical experience is that nudging is harder than it looks, says economist Pete Lunn of the Economic and Social Research Institute in Dublin, a nudging think tank. Tiny differences in context can mean that a nudge that works well in one circumstance can fail miserably in another. For example, appealing to social norms, through a letter noting that most people pay their taxes on time, cut the number of tax delinquents in the UK nearly in half. Similar reductions have been seen in several other countries. But not all. "We've done experiments like that in Ireland, and guess what? Social norm manipulations don't work here," says Lunn. "I genuinely do not know why, but I've seen it in multiple studies, to the point where it cannot be a coincidence."

Often, seemingly insignificant changes in a nudge can send vastly different messages to nudgees. One reason people often fail to save for retirement, for example, is that they are reluctant to give up spending power today for future rewards. To bypass that obstacle, Thaler and colleagues proposed offering people the chance to earmark part of their next raise for retirement savings — a "save without cutting back" nudge that, over time, boosted savings from 3.5 percent to 13.6 percent of earnings. That's impressive, but it only works if done right. If companies offer both options at once — now or later? — savings actually go down, one study found. The dual-option scenario "sends a signal that maybe my employer doesn't think that saving for retirement is very urgent," says Craig Fox, a behavioral decision theorist at the University of California, Los Angeles.

Even the most trivial details of a nudge can matter. Telling householders how their consumption of electricity compared with their neighbors' was enough to nudge heavy users to cut their power use by about 5 percent. But the information actually increased power consumption by those who used *less* power than average — unless researchers included a smiley face on the electricity notice to praise and encourage continued thriftiness.

Surprises like these — and every behavioral scientist has their own stories — have led to a key step in the evolution of nudging: the realization that testing is crucial to the process. "We're doing more large-scale experiments, which is what we have to do to figure out what works in the wild," says Katherine Milkman, a behavioral economist at the University of Pennsylvania's Wharton School. Governments still sometimes balk at the time and money such experiments demand, but many agencies increasingly accept that testing for effectiveness before rolling out a nationwide program can save embarrassment later.

> "There are legitimate questions about the ethics of nudging that we're only starting to look at now."
>
> —CRAIG FOX

Targeting behaviors

Because what works is so context-dependent, experienced practitioners say there can never be a standard recipe for choosing the right nudge for any particular situation. Instead, nudgers need to dig into the details of each case. Nonetheless, researchers are zeroing in on a general approach for building good nudges.

The key first step in the process sounds obvious, but isn't: Identify exactly what behavior you're trying to change. "There's been a recognition that whether a nudge succeeds really depends on whether you have developed a good understanding of the problem," says Pelle Guldborg Hansen, a behavioral scientist at Roskilde University in Denmark, who heads the Danish nudge unit.

Consider the problem of encouraging people to donate their organs after death. Typically, people need to give explicit consent on a donor form, but relatively few do so. A classic nudge addresses this by changing the default so that everyone is presumed to have given consent unless they explicitly opt out. That nudge dramatically increases the proportion of people listed as organ donors. But the Canadian province of Ontario found that this didn't translate into more organs actually being used for transplants, because it solved the wrong problem. Doctors in Ontario still sought consent from next of kin before harvesting organs — and getting that consent was the real bottleneck in the process, says Dilip Soman, a behavioral scientist at the University of Toronto. So now Soman's team is working on a different nudges, such as mailing "conversation cards" to newly registered donors to help them discuss their wishes with family members.

Once nudge designers have targeted the behavior they really want to change, the next step is to identify the barriers that keep that behavior from changing, says Brigitte Madrian, a behavioral economist at Harvard. If people fail to act on their own wishes (such as to eat healthier meals), is that because they forget to

CREDIT: TEXTBOOK EXAMPLE

A CATALOG OF NUDGES

Behavioral scientists have developed an extensive toolbox of nudges — that is, ways to influence people's behavior so they're more likely to act in their own best interest, while still offering them the freedom to choose. Here, according to nudge pioneer Cass Sunstein, are some of the most effective:

• Set defaults, such as automatic enrollment in pension plans or organ-donor programs, but allow people to opt out if they wish.

• Simplify or clarify forms and procedures so that people face less hassle and are less likely to give up.

• Provide reminders that an action is due, so that people do not overlook it.

• Put optimal choices first in a list of options. All else being equal, people are more likely to choose the first item on the list.

• Put optimal choices where they are most visible, such as displaying healthy foods at eye level in a cafeteria.

• Add relevant information, such as calorie counts in fast food restaurants.

• Appeal to people's aversion to losing something they already have (such as, "You will lose $50 if you don't conserve energy").

• Ask people to commit to specifics of a plan of action, such as when and where they plan to vote.

• Prime people to have a desired mindset, such as by reminding them of the need for honesty before they fill out a form, or prompting them to think about their retirement before committing to a savings plan.

• Suggest an amount for a payment or contribution ("Do you want to give $100 to this charity?"). Such "anchoring" tends to focus people's choices somewhere near the suggested value.

• Tell people what others do (for example, "Most people pay their taxes on time"). This puts social pressure on them to do likewise.

act at the appropriate time, don't know what steps to take, or lack the willpower to follow through? Each will require a different nudging technique — in these examples, they could be reminders, information, and committing to a plan of action. If, on the other hand, changing behavior requires overriding an in-the-moment preference (such as saving for retirement or getting a flu shot, neither desirable in the short term), the likeliest nudges might involve providing more information about the benefits, or adding social pressure to conform.

Based on their analysis of the particular case, practitioners should ideally choose several potential nudges, then test them to identify which works best. The nudge finally chosen may look simple, even obvious. But, notes Hansen, that superficial simplicity hides an enormous amount of work behind the scenes.

Ethical issues

Even when done well, nudging carries a strong whiff of paternalism, especially when governments use it to override people's usual behavior and guide them toward what the government thinks they should be doing instead. The implications of that have not been fully examined. "There are legitimate questions about the ethics of nudging that we're only starting to look at now," says UCLA's Fox.

Consider, for example, nudging to encourage higher contributions to retirement savings. Most people benefit from higher savings, but a few — such as those who don't expect to survive for a lengthy retirement — might be better off with lower contributions. Is it acceptable to nudge in this case?

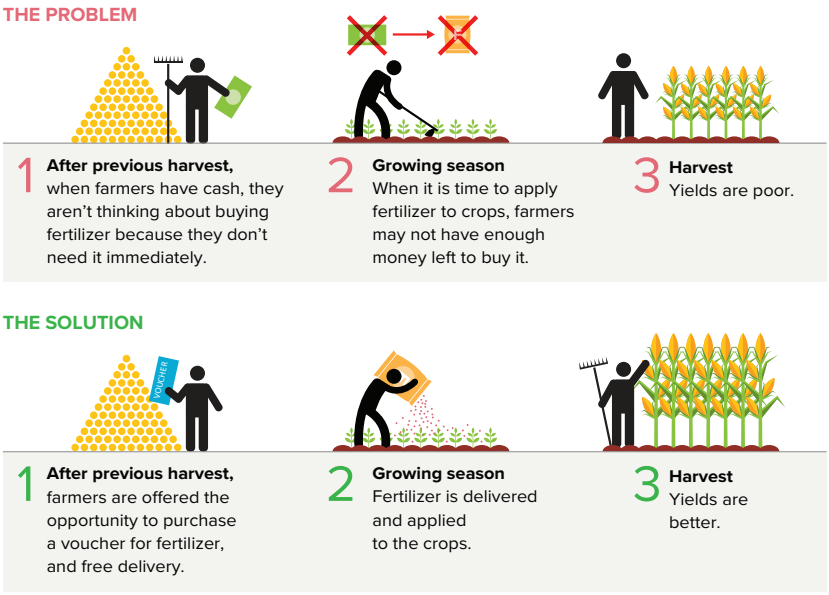
To address this problem, a few behavioral scientists are developing ways to personalize

nudges for individuals. Workers in the United States, for example, receive a maximum government pension at age 70 but instead can elect to take smaller monthly payments as early as 62. Most are better off in the long run if they wait, but almost half choose the earlier, smaller payouts, says Eric Johnson, a psychologist at Columbia University. The situation seems ripe for a nudge — for example by pointing out how much money a retiree stands to lose through early claiming. But encouraging everyone to wait will hurt those who won't live long enough to recoup the benefits. "There really is potential harm if you just do a one-size-fits-all nudge," Johnson says.

So Johnson and colleagues are developing a system of tailored nudges to guide each individual to a better decision. By answering a few simple questions about their gender, health and parents' longevity, visitors to Johnson's experimental website provide enough information about life expectancy to yield informed advice (and appropriate nudges), he finds. In other experiments by Johnson's team, questionnaires can help nudge people toward appropriate choices of health insurance plans and other financial decisions.

ALL IN THE TIMING

Poor Kenyan farmers often would like to use fertilizer but lack the cash to buy it when they need it. Prepaying for next year's fertilizer at harvest, when they have money, can make a big difference in yield, and hence income.



The need for tailored nudges may be widespread. Older people, who are seasoned but less mentally nimble than they once were, may make better choices if not overwhelmed by too many options, Johnson says. Younger people, who have less life experience to draw on, may do better with — and can handle — more detailed explanations and choices.

Behavioral scientists are also learning to find better lever points for their nudges. To get more people to use generic drugs, rather than more expensive branded versions, nudgers are finding that rather than trying to influence patients (through informational advertisements, say) it is easier to focus on the prescribing habits of doctors. "The doctors are making a single decision about treatment in a controlled clinical environment, mediated by electronic record-keeping systems, which is a perfect environment for nudging," says Fox. Sure enough, a study that had doctors' prescriptions default to generic drugs unless specified otherwise boosted the use of generics to 96 percent from 40 percent.

Nudging the nudgers

In recent years, this search for better lever points has led many nudge practitioners to take a broader view of the policy landscape. Nudges, as first conceived, used behavioral insights to improve existing policies by helping people make better choices. But as nudging matures, researchers are beginning to use the same principles to guide the development of the policies themselves. "We haven't seen a lot of that yet, but I think that's where the potential for greatest impact is," Madrian says.

Behavioral economists know, for example, that people given too many options are more likely to make poor choices through sheer information overload. Disclosures for

CREDIT: 5W INFOGRAPHIC; SOURCE: ABDUL LATIF JAMEEL POVERTY ACTION LAB

mortgages, investments, telecommunications plans and other complex offerings could be standardized into formats proven to be easy for customers to understand and compare, improving their ability to make sound decisions. The country of Colombia, for example, has revamped regulations for communications providers so that mobile phone contracts now take an average of 12 minutes to read instead of 6 hours and 15 minutes. The new contracts also give clearer notice of costs and services.

Behavioral insights can even modify the political process itself. Residents of the island of Jersey in the English Channel can now give the government their views on important local issues such as taxation and environment through an automated chatbot on Facebook, designed with behavioral principles in mind. "You can do this on your terms — on the bus, at home, on Saturday," says Simon Day, cofounder of Apptivism, the company that designed the chatbot. Each chat session is short and focused, provides personalized feedback to the user, and can easily be shared online — all features shown to nudge users toward greater engagement. The approach yields three to four times more participation than conventional ways of gathering public opinion, Day says. The company has similar pilots underway with a Scottish regulatory agency, a UK political party and several nonprofit organizations.

Apart from ethical concerns about manipulating people's decisions, nudging has few detractors. After all, nudges generally have to prove themselves in tests before they are rolled out into the wider society, so any failures — which turn up in 10 to 30 percent of attempts — are weeded out. The greatest risk is that nudging's booming popularity is attracting people who lack the training to do the job properly. The Internet is full of nudge consultants with no behavioral science background, notes Lunn. "I think that presents a challenge," he says.

The other criticism often leveled at nudging — that some practitioners share — is that its gentle tinkering may not be powerful enough for society's big issues, such as poverty, obesity and political polarization. But even gentle tinkering, if persistent enough, can make a big difference, say others. "We have this intuition that a big problem needs a big solution," says Piyush Tantia, co-executive director of Ideas42, a nonprofit behavioral design lab based in New York. "But the mistake we make is to take a big problem like poverty or racism and think there's one big solution. That's not the case. Poverty breaks down into hundreds of little problems that you have to solve to crack it. Once you break it down like that, many of the problems can be solved with a nudge."

Researchers at the Abdul Latif Jameel Poverty Action Lab, at the Massachusetts Institute of Technology, have conducted nearly 1,000 controlled trials of strategies — many of them nudges — that can help lift people from poverty. Poor farmers in Kenya, they find, often lack cash to buy fertilizer at planting time, so barely a quarter of them use it. But if offered a chance to pre-purchase fertilizer at harvest time, when they have the cash, farmers' fertilizer use rose to 38 percent. An earlier study showed that fertilizer can boost incomes by more than 10 percent. A separate study found that putting water chlorination dispensers at village wells increased social pressure to chlorinate compared with giving people chlorine at home. The result was more chlorination and, hence, less waterborne disease.

In the end, though, nudging's biggest contribution to the world of governance may come not from the nudges themselves, but from catalyzing a change in the whole mindset of government. Where once governments and their economists designed policies based on political ideology — just listen to almost any policy debate in the US Congress — the popularity of nudging is pushing some toward a more empirical approach. "It has helped to embed a culture of experimentation inside policymaking. And that is something that is definitely new," says Faisal Naru, a public policy adviser for the Organization for Economic Cooperation and Development in Paris, and one of the leaders in the nudging world.

Colombia, for example, went on to completely redesign its regulations for the telecommunications industry to be more consumer-friendly. In South Africa, the Western Cape government has embedded its nudge unit at the heart of the government, in the Department of the Premier. And in Finland, Prime Minister Juha Sipilä is leading an effort to promote experimentation in everything from recycling initiatives to guaranteed basic incomes. Citizen suggestions and crowdfunded tests are welcome. The result, both in Finland and eventually elsewhere, may be more effective and less ideologically bound policies.

Nudging, in other words, is nudging governments toward a more evidence-based, scientific style of governing. In these contentious times, that can only be a good thing. ●

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Q&A

with health and media researcher Chris Palmedo

The anti-ads

Countermarketing succeeds by exposing the motives behind the advertising of unhealthy products. It worked for teen smoking — could it do the same for junk food?

By Chris Woolston

THE ADS THAT INTERRUPT OUR daily lives usually serve as a minor distraction at best, an annoyance at worst. But when those ads encourage people to consume unhealthy food or beverages, the impact can be dire.

Fast food companies have deep pockets and evidence-based methods tailored to woo us. They aren't going to stop making the case that cheeseburgers and fries make for a cheap and delicious lunch, just as beer companies will stay committed to the subliminal message that beer is the key to fun and happiness. But researchers and public health advocates are working on a response. A 2017 paper in the *Annual Review of Public Health* suggests science-driven marketing campaigns could protect consumers by undermining the messages promoting unhealthy products.

Inspired by a successful campaign to reduce smoking among teenagers, researchers are looking to apply similar tactics to other potentially harmful products, including sugary drinks, alcohol and fast foods. The approach — called countermarketing — draws on psychology and advertising science to blunt the effectiveness of ads and the appeal of the products. Chris Palmedo, a health and media researcher at the City University of New York and lead author of paper, talked about countermarketing from his office in Manhattan.

The following has been edited for length and clarity.

What is countermarketing?

Countermarketing is an advertising strategy that breaks down the hidden motives of corporations and undercuts their messages. Inoculation is a good analogy. A countermarketing campaign helps consumers see the reality behind the ads, and that inoculates them against the message.

The best example is the Truth campaign, an antismoking initiative aimed at teens that went nationwide in 2000. The campaign recognized that kids smoked because they wanted to rebel, and they knew that tobacco companies encouraged the image of a rebellious smoker. They turned that image on its head by asking a question: Are you really rebelling by giving all of your money to these big corporations run by old white guys?

It was a game changer in public health education, and it definitely helped drive down teen smoking. In 2001, nearly 30 percent of all high school students reported smoking cigarettes. By 2016, only about 20 percent were using tobacco of any kind.

Food and alcohol ads emphasize fun, friends and good things in life. What's the hidden message that needs to be exposed?

Companies have an obvious profit motive, but there's a lot that goes unsaid. Food companies, for example, spend billions trying to turn young people into lifelong consumers. If the kids aren't buying the products themselves, they're nagging their parents.

Many companies aren't selling their products for what they really are. They're selling emotions. When it comes to marketing, emotions can be much more effective than facts. Countermarketing appeals to other emotions.

What are the emotions conjured by countermarketing?

Countermarketing harnesses the power of negative emotions such as anger, outrage and disgust. But it also taps into more positive values like the desire for social justice. People need to realize that a few large companies are investing billions of dollars to make us less healthy. Are we OK with that? If we recognize that corporations sometimes work against our best interests, a sense of justice might lead us to avoid their products.

Why was the Truth campaign so successful?

The campaign — which included a series of slick TV ads, radio spots and magazine inserts — showed

CREDIT: ISAAC HERNÁNDEZ / MERCURYPRESS.COM; F.Y. EYE / NYC DEPT OF HEALTH AND MENTAL HYGIENE; JAMES PROVOST

that young people could rebel by rejecting marketing. In one of their best and most famous ads, teenagers stacked up "body bags" in front of the headquarters of a tobacco company. The kids were using bullhorns to shout at befuddled men in suits staring down from their office windows. The symbolism was perfect.

The Truth people realized that previous antismoking efforts were actually encouraging kids to smoke. For decades, public health advocates were counting on the surgeon general and other authority figures to deliver a message about the dangers of tobacco to young people. But kids smoke because they want to rebel, so those efforts backfired. The message had to come from their peers.

How would a campaign against alcohol or unhealthy foods be different from an antitobacco campaign?

Everybody knows tobacco is unhealthy, so the Truth campaign didn't spend a lot of time talking about the health effects of tobacco. Based on the research I've done, education would have to be a much more central part of countermarketing campaigns around things like soda and unhealthy foods. Especially soda. I did focus groups with patients at a health center, and they had a lot of questions about soda. Is clear soda healthier than brown soda? Is Gatorade healthy? That sort of thing. We'd have to provide information about the dangers of too much soda, fast food or alcohol if we want a countermarketing campaign to really break through.

Besides tobacco, what have countermarketing campaigns targeted?

There's a well-known campaign in New York City called Pouring on the Pounds. It explains how many calories are in soda and how it can be converted to fat. If you're drinking liquid sugar, for all intents and purposes, you're consuming fat. Among other things, they created a disgusting video of a guy pouring fat into his gullet.

The Bigger Picture Campaign at the University of California, San Francisco created a giant inflatable soda can that looks exactly like a Coke can except it says "Diabetes" instead of Coke. They'd put it up in front of schools and other strategic locations. Defacing popular brands — a practice called culture jamming — can be an effective way to send a message. Sometimes the practice is a little more direct, as when activist groups spray graffiti on billboards selling alcohol in their neighborhoods.

Is there much evidence that countermarketing campaigns against unhealthy food or soda actually change behaviors?

So far, it's mostly hypothetical. I'm trying to do more research in that field. There was a 2016 study of eighth graders who were selecting snacks for a reward. One group had received health messages about the foods that were bad for them. Another was shown a countermarketing campaign that tapped into their feelings of social justice, autonomy and rebellion. Among other things, the kids were shown news reports describing how companies engineer foods to make them more addictive. The kids who just got the health information ended up eating a lot of unhealthy foods, but the kids exposed to countermarketing made better choices. It's just one study, but it's promising.

Who would pay for a nationwide campaign against soda, fast food or alcohol?

The money behind the Truth campaign came from the Master Settlement Agreement, a multibillion-dollar settlement that the tobacco companies signed in 1998. But unless a court finds that fast food companies have been defrauding customers, that won't work for hamburgers. The National Institutes of Health could fund a campaign, but that doesn't seem very likely in the current political climate. For now, we need to count on the patronage of public health advocates like Michael Bloomberg.

What does the rise of social media mean for countermarketing?

Social media gives us new opportunities, especially for younger people. In order for a countermarketing campaign to be successful, the message has to come from your peers, not an authority figure. Social media gives young people a forum to discuss these issues.

Then again, companies have learned how to use Twitter, too. A study in Australia compared the Twitter accounts of groups advocating safe drinking and accounts from alcohol companies. The tweets from the alcohol companies were more likely to have hashtags and to be forwarded to others. They had greater interactivity and effectiveness. But that didn't happen by accident. It took a lot of trial and error — and a lot of money — for all of these companies to figure out how to get the most out of social media. Countermarketing has some work to do to catch up. ●

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