Dear Ms. Laura Helmuth

Editor-in-Chief

Scientific American

Please refer to the Digital issue of Scientific American, September 2021.

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P. S. Satsange P.S. Satsangi

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Saving the **Mountain Lions** of Los Angeles

Stopping the Methane Leaks of the Permian Basin



Three new missions will reveal the mysteries of Earth's evil twin







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### SCIENTIFIC AMERICAN



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### FROM THE EDITOR

### **Progress on Autoimmunity**

One of the things we're proudest of at Scientific American is that we've helped train some of the best science writers, graphic artists and multimedia producers in the business. Our editors frequently teach classes, guest lecture, speak at scientific conferences or universities about journalism, and commission freelance articles from early-career scientists and writers. We also host fellows and interns who work with us full-time during the summer, and we've had two outstanding writers this summer. Maddie Bender has a fellowship through the American Association for the Advancement of Science's mass media program after earning a master's degree in public health focusing on microbial disease epidemiology. Tess Joosse comes to us through the University of California at Santa Cruz's graduate science writing program (which several of us on staff attended) after majoring in biology as an undergraduate. They both have pieces in this issue. We are now restarting our year-round internship program for earlycareer writers, so you'll see new names every three to four months.

A few other changes: You might have noticed that our Recommended section is now two pages, up from one, and we're running longer reviews of books you might enjoy. We added two pages to the Advances section, with a regular "Science in Images" feature for an extra burst of beauty and awe in each issue.

Our special package this month on autoimmune disorders, starting on page 26, covers some of the fastest-moving and most important research being conducted today. Autoimmune disorders such as lupus, diabetes, celiac disease, Hashimoto's thyroiditis, and many more (*page 31*) are common, and many are becom-



**Laura Helmuth** is editor in chief of *Scientific American*. Follow her on Twitter @laurahelmuth

ing more prevalent. Women are disproportionately at risk (*page 40*) and often experience frustrating and dismissive care (*page 28*). Researchers are understanding more all the time about how the disorders begin (*page 34*) and identifying promising new approaches for treatments (*page 45*).

Lots of people have strong feelings about planets. There's a long-running debate over whether Saturn or Jupiter is the most beautiful planet (team Saturn here), and of course some are still stinging that Pluto got downgraded to a dwarf planet in the Kuiper belt. The Venus people have felt neglected for decades, their favorite planet always losing attention to rover-rich Mars. But now three major missions are heading to Venus, breaking the "Venus curse," and volcanologist and writer Robin George Andrews tells us on page 52 why Venus experts are over the moon.

Venus is intriguing in part because it shows how a good planet can go so wrong. Our atmosphere isn't thick with sulfuric acid, but methane emissions are shooting up so quickly that they've become a major source of climate change. Identifying leaks of the invisible, odorless gas in time to patch them is one of the most urgent and achievable ways to slow the climate emergency. On page 62, *Scientific American* contributing editor Anna Kuchment explains where the methane is coming from and how to control and even use it.

California's mountain lion populations have been divided by habitat loss and some of the busiest freeways in the country. Where the big cats are isolated, they inbreed—or don't breed at all—and concentrate genetic mutations that further threaten their future. Now an ambitious effort to literally bridge isolated populations could help pumas find one another. As environmental writer Craig Pittman reports on page 72, crews are expected to break ground soon on the largest wildlife bridge in the world. We're all hoping the cougars make a comeback.

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May 2021

### ANCIENT HUMAN CONTACT

"Journey into the Americas," by Jennifer Raff, describes how DNA evidence has revealed a more complex picture of the peopling of the American continents. I have always wondered whether the Polynesians who got as far east as Easter Island could have reached South America. Could the anomalous archaeological sites in southern Chile that Raff describes have been the work of people who originated from the west rather than the north?

RICK NAGIN Cleveland, Ohio

RAFF REPLIES: Despite popular speculation regarding a shared ancestry among peoples of Polynesia and South America (promoted most notably by Norwegian explorer Thor Heyerdahl, who believed that Polynesia was settled by South Americans), archaeological and genetic evidence unambiguously shows separate origins for these groups.

Ancient Polynesians and ancient coastal Native Americans were superb mariners, however. And although direct archaeological evidence is scarce, there have been a number of different lines of evidence that appear to support at least some pre-Columbian interactions between them, including linguistic patterns and the presence of sweet potatoes from South America throughout Polynesia. Recently evidence of gene flow between Native American populations and Pacific Islanders has

### "Often passed over because of paternalistic bias, there are female scientists much more worthy of lending their name to 'the next Hubble.'"

been found that dates to several hundred years before European contact: as early as approximately A.D. 1150. Exactly where this gene flow took place—whether on the South American coast or in the Marquesas Islands (where it first appeared)—cannot be answered with current genetic evidence. But at present, this evidence supports more limited interactions than what would presumably be required for the founding of entire populations.

#### FEMALE SCIENCE PIONEERS

I agree with Chanda Prescod-Weinstein, Sarah Tuttle, Lucianne Walkowicz and Brian Nord that we should "Rename the James Webb Space Telescope" [Forum]. In the spirit of the great strides made by women in science, often demeaned and passed over because of paternalistic bias, there are female scientists much more worthy of lending their name to "the next Hubble": Astronomer Henrietta Swan Leavitt identified 2,400 variable stars, helping Edwin Hubble determine the expanding universe. The late researcher Katherine Johnson's mathematical genius provided unprecedented calculations for viable crewed orbital spaceflights. Physicist Chien-Shiung Wu helped to guide the Manhattan Project. X-ray crystallographer Rosalind Franklin had a central role in discovering the structure of DNA.

Any one of them better epitomizes the deeper and clearer vision the telescope will give humankind. Surely that clearer vision shouldn't just represent the vacuum of space but also the confines of our democracy.

JIM HOOVER Huntington Beach, Calif.

#### THE UNIVERSE'S EXPANSION

In "A New Map of the Universe," Kyle Dawson and Will Percival describe the early universe at a time when it "grew so fast that subatomic scales became the size of a golf ball in  $10^{-32}$  second." If we consider an ordinary golf ball with a diameter of 4.268 centimeters, the speed of expansion of this early universe would be  $4.268 \times 10^{30}$  meters per second, which is vastly faster than the speed of light. Was that possible all those billions of years ago?

DENNIS W. GORDON Waunakee, Wis.

The article notes that dark matter is driving the accelerated expansion of the universe and that galaxies that are farther away reflect earlier cosmic eras. If redshifts indicate that such galaxies are receding faster, doesn't that mean that those closer to our time frame are receding slower and thus that the rate of expansion is slowing down? JIM ROBISON Santa Rosa, Calif.

THE AUTHORS REPLY: To answer Gordon: The limit of the speed of light refers only to objects moving through space. The expansion of space itself is allowed to happen at faster rates. Our ability to consider space in this way is consistent with Einstein's theory of relativity, which itself explains the limit on how fast objects can travel through space. This difference tells us something profound about the nature of the universe and how we should consider the space in which we exist.

In response to Robison: As a simple analogy, consider a three-dimensional cake with chocolate chips, representing galaxies, expanding in an oven. The chips near to one another move apart slowly because there is little cake dough expanding between them. There is more cake expanding between those that are farther apart, so they recede from one another more rapidly. While the expansion of the universe is the same at all locations, distance matters for our observation of the recession of galaxies away from us. We see galaxies as they were in the past because their light takes time to reach us, coupling distance and age-we can see objects of a certain age only at a certain distance. Using a four-dimensional spacetime model to interpret the redshifts we observe, we find the expansion of



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the universe matches a model in which that expansion speeds up everywhereeven though the recession velocities are different at different distances and ages.

#### HANDEDNESS IN NATURE

In "The Riddle of Dolphin Handedness," Kelly Jaakkola reports on asymmetries in the directions in which dolphins spin. Earth's rotation creates the Coriolis effect, which influences the speeds of launched rockets and the spins of hurricanes. Could that effect cause dolphins' angular dives to differ in the Northern and Southern Hemispheres? It would be interesting to test whether the rotation of Earth has a role in the handedness of all biological systems.

MUSTAFA HALILSOY Famagusta, Cyprus

As a retired genetics teacher, Jaakkola's article immediately brings to mind the righthanded helix of B-DNA (the more common Watson-Crick version) and the left-handed helix of the less common Z-DNA (Z stands for "zigzag backbone"). The "right-hand rule" of electromagnetism Jaakkola mentions helps keep those straight, too.

Leslie Dendy University of New Mexico-Los Alamos

JAAKKOLA REPLIES: In response to Halilsoy: A 2004 study noted a group of dolphins in the Southern Hemisphere swam in a clockwise direction, which is opposite to the predominant counterclockwise direction often reported in the Northern Hemisphere. That is only a single report, however. And there have been a number of exceptions to the typical pattern in the Northern Hemisphere. So we need more data to explore whether a difference between the hemispheres is really there.

#### ERRATA

"A New Map of the Universe," by Kyle Dawson and Will Percival, incorrectly describes dark energy winning out over the gravitational effect of matter as decelerating the rate of the universe's expansion. The gravitational effect decelerates the rate, and dark energy accelerates it.

"What Makes a Problem 'Hard'?," by Naomi Oreskes [Observatory], should have described Garry Kasparov as the first world chess champion to lose to a computer, not the first grand master to do so.

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### Fix Disaster Response Now

2020 brought problems of capacity and inequity in the U.S. to a head

By the Editors

**Given record-breaking wildfires,** hurricanes and other weather disasters that cost lives and billions of dollars amid a pandemic that brought death to every corner of the country, the events of 2020 stretched U.S. emergency management institutions. Local governments have been unable to cope with the disasters, and the Federal Emergency Management Agency (FEMA) has been strained. This litany of destruction has brought into stark relief problems of capacity and inequity—people of color and low-income communities have been hit disproportionately hard—that have been festering for decades in the nation's approach to disaster preparedness. Now, with the climate crisis increasing the odds of calamities, we must stop kicking the can down the road and commit to the challenging work of revamping emergency management.

FEMA is supposed to be the agency that steps in when disasters overwhelm local resources, whereas cities, counties and states handle smaller events. But a FEMA National Advisory Council (NAC) report last November noted that state and local emergency management operations struggle even with routine events. Some towns and counties have only a part-time emergency manager, leaving them ill-equipped to prepare for and respond to disasters. As a result, they increasingly turn to FEMA, which ends up with fewer resources to spare when a major catastrophe does occur. When Hurricane Harvey flooded southeastern Texas in 2017 with an unprecedented 60 inches of rain, for example, almost half of the agency's emergency workforce had already been deployed to other trouble spots. To free itself up, FEMA is now proposing to raise the damage threshold that triggers federal assistance. But that proposal simply will leave local areas more vulnerable. Congress or state legislatures need to supply sustainable funds that build and maintain local emergency management departments, along with any change in the rules for FEMA involvement.

To address the problem that all emergency agencies do little in advance to prepare for disasters, some funding could be earmarked for—and require—certain crucial mitigation work sometimes resisted by local political forces, such as elevating structures in flood-prone areas or instituting zoning laws to reduce wildfire risks. These efforts should incorporate the latest climate science—sea-level-rise projections, for example—so they do not quickly become obsolete. The National Institute of Building Sciences has found that for every \$1 that FEMA and other federal agencies spend on mitigating the risks of floods, earthquakes and other hazards, society ultimately saves \$6 in costs.

Any future mitigation and recovery funding must also be dis-



tributed in an equitable way. Research, including a 2019 study published in Social Problems, has shown that FEMA programs inadvertently entrench and exacerbate inequities because they focus on restoring private property. This approach favors higher-income, typically majority white areas with more valuable homes and infrastructure over people of color and low-income communities, which are both disproportionately affected by disaster and least able to recover from it. To remedy this disparity, FEMA, as well as state and local emergency management agencies, cannot rely solely on costbenefit analyses to determine what projects to fund, because these weigh in favor of more expensive properties. They should also use other metrics, such as the Social Vulnerability Index, which identifies the populations with the least capacity to deal with disasters. Some local governments have begun to incorporate equity into their emergency planning. In Washington State's King County, for example, floodplain managers have used census data to understand exactly who lives in flood-prone areas to better target resources and mitigation projects. Others should follow their lead.

One current FEMA program has tried to tackle inequity issues by allowing small, low-income communities to pay less in cost matching, which is a precondition of some FEMA aid. But these smaller governments may not have dedicated staff with the expertise to navigate the complex FEMA application process. In some cases, communities may not have the funds to meet even a lowered threshold for local spending. FEMA can begin to solve this by simplifying its funding requirements and instituting a single application process; both actions were recommended by the NAC report and in February by the Government Accountability Office.

Everyone, not just the well-to-do, should have the opportunity to build back their lives with the resources they need in the wake of disaster.  $\mathbf{x}$ 

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### SACRED STONE OF THE Southwest is on the **BRINK OF EXTINCTION**





enturies ago, Persians, Tibetans and Mayans considered turquoise a gemstone of the heavens, believing the striking blue stones were sacred pieces of sky. Today, the rarest and most valuable turquoise is found in the American Southwest- but the future of the blue beauty is unclear.

On a recent trip to Tucson, we spoke with fourth generation turquoise traders who explained that less than five percent of turquoise mined worldwide can be set into jewelry and only about twenty mines in the Southwest supply gem-quality turquoise. Once a thriving industry, many Southwest mines have run dry and are now closed.

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### Tragedy of the White Tiger

They are mostly the result of inbreeding, which is bad for the big cats' health

By Azzedine Downes

**The white tiger** is produced by a genetic fluke that occurs when two orange tigers with rare recessive forms of a gene, called alleles, happen to breed. White tigers are so rare in the wild that they have been seen only a few times in recorded history, with the last known wild white tiger killed in 1958. Their rarity could be because the recessive allele is the result of a one-time mutation or because white tigers lack adequate camouflage, reducing their ability to stalk prey or avoid other predators.

But they are not scarce in captivity. Because they are so rare, exploitative roadside menagerie operators, exhibitors and collectors seek to maintain white tiger populations for the sake of generating profit. To continue producing white tigers, captive tigers with this rare allele expression are intensively inbred over multiple generations. In other words, parents are bred with their offspring, siblings are bred with one another, and other closely related animals are bred with one another as well. In fact, all the white tigers in captivity in the U.S. are believed to be descen-



**Azzedine Downes** is president and CEO of the International Fund for Animal Welfare.

dants of a single male Bengal tiger named Mohan, bred to an orange tiger and then to his daughter from that breeding.

The practice of continual inbreeding continues to this daynot by zoos accredited by the American Association of Zoos and Aquariums (AZA), which halted it in its member institutions a decade ago, but primarily by largely unregulated commercial enterprises that use white tigers as a draw for paying visitors. More than 60 years since Mohan and roughly 11 tiger generations later, white tigers are suffering the consequences of extensive inbreeding, which has produced tragic results. Neonatal mortality among white tiger cubs can be high and increases with the degree of inbreeding: one study showed that more than 80 percent of intensively inbred cubs died shortly after birth. Forced inbreeding of captive white tigers can also lead to reduced litter size and shorter average life spans, as well as a host of health problems such as impaired vision, cardiac defects, serious spinal and facial deformities, and compromised immune systems. In its 2011 white paper prohibiting this kind of breeding, the AZA cites the "abnormal, debilitating, and at times lethal external and internal conditions and characteristics" that result.

Pseudo sanctuaries—exploitative, unqualified wildlife exhibits masquerading as legitimate rescue sanctuaries—continue to breed and abuse white tigers under the guise of conservation. This is a far cry from true conservation. Captive-bred white tigers serve absolutely no conservation or educational purpose. Their lack of genetic diversity, high degree of inbreeding and resultant physical afflictions remove them and their offspring from consideration for any hypothetical release programs. These animals have no place in any conservation program, which explains why no legitimate conservation organization today endorses the breeding of white tigers.

The only reason white tigers are bred today is because they are incredibly lucrative for breeders and exhibitors who charge visitors at entertainment venues to play with cubs, using them as photo props. Once cubs age out of this vicious pay-for-play system, they may be sold to the general public as "pets," warehoused, intensively bred to create the next generation of money-making white tiger cubs or otherwise subjected to abusive treatment. When the unsuspecting public buys into an exhibitor's false conservation claims and pays to see or handle a white tiger, they are unknowingly perpetuating irresponsible inbreeding, poor population management and exploitative practices.

Federal legislation has been introduced in the U.S. Senate, including the <u>Big Cat Public Safety Act (H.R. 263/S. 1210)</u>, to strike a blow at the key financial driver behind the incessant and highly unregulated breeding of big cats and the resultant proliferation and "breeding to death" of white tigers.

Pop culture has romanticized the keeping and breeding of tigers and other big cats in a terribly harmful way. Now that our collective eyes are open to what we need to do to protect these magnificent animals, we must mitigate their greatest threat: us.

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# ADVANCES



### DISPATCHES FROM THE FRONTIERS OF SCIENCE, TECHNOLOGY AND MEDICINE



### INSIDE

- Birds' eye size predicts their resilience to habitat change
- Record-breaking image reveals atoms in high resolution
- Mice are studied at the wrong time of day
- "Iconic" vocal sounds can be understood across cultures

### Kidney Stone Geology

Rather than crystallizing all at once, the jagged stones can dissolve and re-form again

Medical researchers are poised to map the entire process of kidney stone formation for the first time, thanks to insights from an unlikely source: geology. Combining this framework with a suite of cuttingedge microscopic tools and a new device that grows kidney stones in the laboratory, they are developing novel ways to stop or slow down the stones' growth.

Stone disease occurs when jagged mineral crystals form in urine within the kidney. This excruciating problem affects roughly one in 10 adults and is steadily rising, especially in women and adolescents. "It's common, debilitating and costly, both to the health-care system as well as individuals. To top it off, it's also recurrent—if you've had one, there's about a 50 percent chance of having another soon," says urologist Margaret Pearle, who treats stone disease at the University of Texas Southwestern Medical Center and did not participate in the new research.

Geobiologist Bruce Fouke turned his microscope lens from coral reefs to kidney stones about a decade ago. Working with biologists and doctors at the Mayo Clinic and the University of Illinois at Urbana-Champaign, he found that kidney stones form similarly to many other stones in nature: they partially dissolve and reform many times rather than crystallizing all at once. "That's when we realized that stones are quite dynamic and have phases where they're dissolving, so maybe there's a way to harness that dissolution phase

### ADVANCES

and treat stones," says Fouke's collaborator Amy Krambeck, a urologist at Northwestern Medicine.

There have been few good animal or lab models to study kidney stone formation, Krambeck says. So the team developed a new device called the GeoBioCell, a cartridge designed to mimic the kidney's intricate internal structures. It lets scientists measure and link how various factors-including kidney cell activity, as well as the urinary microbiome, chemistry and flow-can affect stone growth. Varying any one factor can make stones develop and dissolve differently.

In their recent research, summarized in Nature Reviews Urology, the researchers primarily used GeoBioCell to study growing calcium oxalate crystals, which account for about 70 percent of kidney stones. Until Fouke's preliminary work, these crystals were thought to be almost impossible to



dissolve—but he and his colleagues found the stones do, in fact, partially dissolve in the body before regrowing. The scientists are now using GeoBioCell to examine precisely how stones form, and they hope to identify ways of initiating or prolonging the dissolution phase with drugs. They are also using the new device to test a variety of proteins (including the bone-related osteopontin) that could potentially inhibit growth if administered as a drug. Additionally, they are investigating the impact that specific microorganisms and microbial communities might have on stone formation.

This research has tremendous potential to identify kidney processes that can be targeted with drugs or other interventions, Pearle says, and will likely improve doctors' ability to predict and treat stone recurrence. —Harini Barath



studied in Peruvian fieldwork

### ORNITHOLOGY

### **Bird's-Eye** View

Eyeball size may reveal vulnerability to habitat destruction

For most birds, eyes are essential to life on the fly. They inform split-second aerobatic maneuvers amid dense branches and pinpoint distant predators or prey. Yet when studying how birds might adapt to our quickly changing world, ornithologists have largely overlooked eye size in favor of traits such as wing length and beak shape. Now, though, a lost "treasure trove" of avian eyeball measurements offers a new view.

In 1982 University of Chicago graduate student Stanley Ritland, using pickled museum specimens, meticulously measured the eyeballs of nearly 2,800 species-a third of all terrestrial birds. He never published his data, but Ian Ausprey, a graduate student at the University of Florida and the Florida Museum of Natural History, has just given it a second look. Ausprey's analysis, published in the Proceedings of the Royal Society B, supports previous work in Peru showing that smaller-eyed birds adapt better to changing habitats.

"We're able to show strong correlations between eye size, the type of habitat the birds use, their foraging behavior, as well as where in the world they live," Ausprey says. Ritland's measurements indicated an inverse relation between

eye and range size. Birds with smaller eyes tended to be migratory, traveling across many habitats; larger-eyed species had tighter ranges, concentrated around the equator and often shrouded by dense forest canopy. The study posits that smaller-eyed birds can seamlessly handle varying light levels as they travel, whereas larger-eyed birds struggle with glare outside of their dim woodlands.

Ausprey had already seen this play out in Peru's mountainous cloud forests. In these biodiversity hotspots, he says, "eye size is strongly related to how [birds] respond to agricultural disturbance." Larger-eyed birds tend to disappear from brightly lit agricultural and deforested landscapes; smaller-eyed birds adapt. The new study expands Ausprey's Peru observations to a wider variety of birds elsewhere, including parrots, woodpeckers and finches.

Allison Shultz, an ornithologist at the Natural History Museum of Los Angeles County, who was not involved in the research, praises it for highlighting the importance of birds' light exposure. Her own work has found a link between bird coloration and environmental light, and she says she looks forward to future research exploring how light pollution and deforestation might further shape bird eyes. "I'd be very curious if we're actually seeing eves evolving to better match newer light environments," Shultz adds.

Ausprey says the study underscores the importance of conserving habitats across the light-availability spectrum, especially patches of dense rain forests, to protect birds with eyes of all sizes from habitat loss. —Jack Tamisiea

### Quick By Maddie Bender

### MEXICO

Eighteen black-footed albatrosses hatched on Guadalupe Island after their eggs were flown by commercial airliner from the North Pacific's Midway Atoll. The atoll, which houses a third of the near-threatened birds' breeding population, is vulnerable to flooding and sea-level rise.

For more details, visit

Jays and gray squirrels may have "planted" more than half of the many trees growing on two swaths of farmland abandoned in lowland England in 1961 and 1996, researchers found. The new growth consisted largely of oaks, whose seeds the animals bury in winter.

The domesticated watermelon has long been thought to have come from South Africa,

genetic sequencing, ancient Egyptian iconography and Russian cold war-era botany

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texts to identify the sweet, whitish-pulped melon as watermelon's closest relative.

but it may instead have originated with Sudan's Kordofan melon. Scientists used

### LATVIA

Scientists found evidence of the oldest-known bubonic plaque case in the skull of an infected hunter-gatherer from 5,000 years ago. Remnants of the ancient bacterial strain suggest it could not infect fleas and instead may have been transmitted through a beaver bite.

#### TURKEY

"Sea snot." a type of mucus released by phytoplankton, smothered shellfish and gummed up fishing nets in the Sea of Marmara. Turkey's president called the slime a "mucilage calamity," and workers were dispatched to vacuum it up using hoses.

#### MALAYSIA

**Divers** noticed white lesions atop the heads of up to hundreds of whitetip reef sharks near Sipadan Island. Scientists suspect the cause is a fungus that thrives in warming oceans.



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### <u>ADVANCES</u>

#### PHYSICS

### Atomic Dodgeball

New imaging technique could help develop future electronics

Behold the highest-resolution image of atoms ever taken. To create it, Cornell University researchers captured a sample from a crystal in three dimensions and magnified it 100 million times, doubling the resolution that earned the same scientists a <u>Guinness World Record</u> in 2018. Their imaging process could help develop materials for designing more powerful and efficient phones, computers and other electronics, as well as longer-lasting batteries.

The scientists obtained the image using a technique called electron ptychography. It involves shooting a beam of electrons, about a billion per second, at a target material. The beam moves infinitesimally as the electrons are fired, so they hit the sample from slightly different angles—sometimes they pass through cleanly; other times they collide with atoms and bounce around inside the sample before exiting. Cornell physicist David Muller likens the technique to playing dodgeball against opponents who are standing in the dark. The dodgeballs are electrons, and their targets are individual atoms. Although Muller cannot see the targets, he can detect where the "dodgeballs" end up. Based on the speckle pattern generated by billions of these elec-



trons as they hit a detector, machine-learning algorithms can calculate where the atoms were in the sample and what their shapes might be, thus creating an image.

Previously, electron ptychography had only been used to image extremely flat samples just one to a few atoms thick. But Muller and his colleagues' new study in Science describes capturing multiple layers tens to hundreds of atoms thick. This makes the technique much more relevant to materials scientists, who typically study the properties of samples with a thickness of about 30 to 50 nanometers. (This is smaller than the length your fingernails grow in a minute but many times thicker than what electron ptychography could image in the past.) "They can actually look at stacks of atoms now, so it's amazing," says University of Sheffield engineer Andrew Maiden, who helped to develop ptychography but was not part of the new study. "The resolution is just staggering."

This result marks an important advancement in the world of electron microscopy. Invented in the early 1930s, standard electron microscopes made it possible to see objects such as polioviruses, which are smaller than the wavelengths of visible light. But electron microscopes had a limit: increasing their resolution required raising the electron beam's energy, and eventually the necessary energy would become so great that it would damage the sample.

Ptychography, in contrast, uses a detector that can record all the different angles the beam can scatter to at every beam position, getting much more information with the same wavelength and lens. Researchers theorized ptychography in the 1960s and conceived its use to overcome electron lenses' limits in the 1980s. But because of computing and detector limitations and the complex math required, the technique was not put into practice for decades. Early versions worked far better with visible light and x-rays than the electrons needed to image atomic-size objects. Meanwhile scientists kept improving electron microscopes. "You

University

Cornell (

### NEUROLOGY

### Listening to Dinner

How misophonia makes common sounds physically unbearable

To a chef, the sounds of lip smacking, slurping and swallowing are the highest form of flattery. But to someone with a certain type of misophonia, these same sounds can be torturous. Brain scans are now helping scientists start to understand why.

People with misophonia experience strong discomfort, annoyance or disgust when they hear particular triggers. These can include chewing, swallowing, slurping, throat clearing, coughing and even audible breathing. Researchers previously thought this reaction might be caused by the brain overactively processing certain sounds. Now, however, a new study published in the Journal of Neuroscience has linked some forms of misophonia to heightened "mirroring" behavior in the brain: those affected feel distress while their brains act as if they are minicking the triggering mouth movements.

"This is the first breakthrough in misophonia research in 25 years," says psychologist Jennifer J. Brout, who directs the International Misophonia Research Network and was not involved in the new study.

The research team, led by Newcastle University neuroscientist Sukhbinder

Kumar, analyzed brain activity in people with and without misophonia when they were at rest and while they listened to sounds. These included misophonia triggers (such as chewing), generally unpleasant sounds (like a crying baby), and neutral sounds. The brain's auditory cortex, which processes sound, reacted similarly in subjects with and without misophonia. But in both the resting state and listening trials, people with misophonia showed stronger connections between the auditory cortex and brain regions that control movements of the face, mouth and throat, Kumar found this connection became most active in participants with misophonia when they heard triggers specific to the condition.

"Just by listening to the sound, they acti-

had to be a true believer in ptychography to be paying attention to it," Muller says.

Just in the past several years Muller and his team developed a detector good enough for electron ptychography to work experimentally. By 2018 they had figured out how to reconstruct two-dimensional samples with the technique, producing what Muller calls "the highest-resolution image by any method in the world" (and winning that Guinness record). The researchers accomplished this feat using a lower-energy wavelength than other methods, letting them better preserve what they viewed.

The next challenge was thicker samples, in which an electron wave ricochets off many atoms before reaching a detector: the socalled multiple scattering problem. The team members found that with enough overlapping speckle patterns and computing power (and, according to Muller, "brute force and ignorance"), they could work backward to determine which layout of atoms produced a given pattern. To do this, they fine-tuned a model until the pattern it generated matched the experimentally produced one.

Such high-resolution imaging techniques are essential for developing the next generation of electronic devices. For example, many researchers are looking beyond siliconbased computer chips to find more efficient semiconductors. To make this happen, engineers need to know what they are working with at an atomic level—which means using technologies such as electron ptychography. "We have these tools sitting there, waiting to help us optimize what will become the next generation of devices," says J. Murray Gibson, dean of the Florida A&M University-Florida State University College of Engineering, who was not part of the new study.

Batteries are a particularly promising area for applying imaging techniques such as electron ptychography, says Roger Falcone, a physicist at the University of California, Berkeley, who was also not involved with the research. Making batteries that can store a lot of energy safely is critical for the transition from fossil fuels to renewable energies, including wind and solar. "Imaging technologies are very important to improving batteries because we can look at the chemical reactions in detail," Falcone says.

But there is still a long way to go. For electron ptychography to lead to breakthroughs for your cell phone or laptop, it must do more than reconstruct an image it must precisely locate an individual atom in a material. Although the scientists showed how their new process could do so in theory, they have not yet demonstrated it experimentally. "With any new technique, it always takes a bit of time for your fellow researchers to try this out and see if it bears out into real, practical uses," says Leslie Thompson, a materials characterization expert at IBM, who was not involved in the new study.

"To the extent that you invent a new tool like a high-resolution microscope, my sense is you tend to be surprised [by] what problem it's applied to solve," Falcone says. "People will look at things we can't even imagine now—and solve a problem that we're not even sure we have yet." —Anna Blaustein



Some cannot stand the sound of others eating.

vate the motor cortex more strongly. So in a way it was as if they were doing the action themselves," Kumar says. Some mirroring is typical in most humans when witnessing others' actions; the researchers do not yet know why an excessive mirroring response

Images

Catherine Falls Getty

might cause such a negative reaction, and hope to address that in future research. "Possibilities include a sense of loss of control, invasion of personal space, or interference with current goals and actions," the study authors write.

Fatima Husain, a University of Illinois professor of speech and hearing science, who was not involved in the study, says potential misophonia therapies could build on the new findings by counseling patients about handling unconscious

motor responses to triggering sounds—not just coping with the sounds themselves. If this works, she adds, one should expect to see reduced connected activity between the auditory and motor cortices.

-Christiane Gelitz

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### <u>ADVANCES</u>

### BIOLOGY

### Root of the Problem

Scientists halt a CO<sub>2</sub>-sniffing corn pest in its tracks

The western corn rootworm beetle grows to only the length of a grain of rice. But this unassuming yellowish-brown pest causes up to a billion dollars' worth of damage to U.S. corn crops every year. Its larvae are particularly pesky; unseen, they wriggle through the soil to burrow into corn's branching root system.

The larval worms find tasty roots by sensing underground gases and other chemicals, says Ricardo Machado, a chemical ecologist at the University of Neuchâtel in Switzerland. Researchers knew the worms were attracted to carbon dioxide, which corn roots release as a by-product of respiration. But Machado hoped to help researchers develop better pest-management strategies by delving into how, specifically, grubs use CO<sub>2</sub> and other signals to home in on roots.

He and his colleagues used a technique

called RNA inference (RNAi) to get to the root of things. They coated corn seedlings in a solution containing particular double-stranded RNA for larvae to eat, which halted expression of the gene that encodes rootworms' CO<sub>2</sub> receptors and made them unable to smell the gas.

When tested, the newly CO<sub>2</sub>-insensitive worms could no longer locate corn plants' roots from more than nine centimeters away, the team reports in *eLife*. But closer in, the worms could still sniff them out regardless of CO<sub>2</sub> perception. Machado says this capability suggests the worms must use additional scents to narrow down their search—a "spectacular" display of the humble larvae using multiple inputs to reach their target.

Elisabeth Eilers, a chemical ecologist at Bielefeld University in Germany, says that while CO<sub>2</sub> sensing was previously observed in rootworms, identifying and turning off the gene responsible is particularly revealing. "They went way deeper into this system than we had ever known before," says Eilers, who was not involved with the study.



Western corn rootworm larva

She notes that many experiments test a bug's sensing preferences and abilities by manipulating its body, such as by removing bits of antennae. The new method, she says, "is more straightforward and elegant than cutting an actual piece off of an insect."

CO<sub>2</sub> may play an important role in attracting the rootworm, "but roots are emitting a lot of different compounds," Eilers says. She wonders how the worm might use those other chemical calling cards—a question Machado plans to investigate next by silencing more genes.

From the worm's point of view, its underground sensing ability is a lifeline: it saves the tiny bug precious time looking for its next meal. "If an insect spends two days looking for its food," Machado says, "for us that is like 20 years." —Tess Joosse

### **Study Hour** Dilemma

Waking up lab mice in the daytime may skew research

Mice are at their best at night. But a new analysis suggests researchers often test the nocturnal creatures during the day which could alter results and create variability across studies—if they record timeof-day information at all.

Of the 200 papers examined in the new study, more than half either failed to report the timing of behavioral testing or did so ambiguously. Only 20 percent reported nighttime testing. The analysis was published in *Neuroscience & Biobehavioral Reviews*.

West Virginia University neuroscientist Randy Nelson, the study's lead author, says this is likely a matter of human convenience. "It is easier to get students and



techs to work during the day than [at] night," Nelson says. But that convenience comes at a cost.

"Time of day not only impacts the intensity of many variables, including locomotor activity, aggressive behavior, and plasma hormone levels," but changes in those variables can only be observed during certain parts of the diurnal cycle, says University of Wyoming behavioral neuroscientist William D. Todd. This means that "failing to report time of day of data collection and tests makes interpretation of results extremely difficult," adds Beth Israel Deaconess Medical Center staff scientist Natalia Machado. Neither Todd nor Machado was involved in the new study.

The study researchers say it is critical that scientists report the timing of their work and consider the fact that animals' behavioral and physiological responses can vary with the hour. As a first step, Nelson says, "taking care of time-of-day considerations seems like low-hanging fruit in terms of increasing behavioral neuroscience research reliability, reproducibility and rigor."

University of Calgary psychologist Michael Antle, who was also not involved in the analysis, says such differences in how studies are run contribute to a "replication crisis" in science, with other laboratories unable to re-create study results. "Running a study at the wrong time," he says, "could lead to us completely missing a finding altogether." — Jillian Kramer

### LINGUISTICS

### Sounds about Right

Newly created vocalizations are understood remarkably well across cultures

**Some gestures** can be understood almost anywhere: pointing to direct someone's attention. for instance. New research shows that certain vocalizations can also be iconic and recognizable to people around the world-even when a speaker is not simply imitating a well-known sound. These findings, published in *Scientific* Reports, may help explain the rise of modern spoken language.

In 2015 language researchers challenged some English speakers to make up sounds representing various basic concepts ("sleep," "child," "meat," "rock," and more). When other English speakers listened to these sounds and tried matching them to concepts, they were largely successful. But "we wanted to be able to show that these vocalizations are understandable across cultures," says study co-author and University of Birmingham cognitive scientist Marcus Perlman.

So Perlman and his colleagues conducted online and in-person experiments in seven countries, from Morocco to Brazil. They recruited more than 900 participants, who spoke a total of 28 languages, to listen to the best-understood vocalizations from the 2015 investigation and select matching concepts from a set of words or images. Vocalizations that evoked well-known soundsfor example, dripping water-performed best. But many others were also understood at rates significantly above chance across all languages tested, the team found. "There is a notable degree of success outside of just onomatopoeia," Perlman says.

Incorrect

This is likely because certain acoustic patterns are universal, the team suggests. For example, short and basic sounds often convey the concept of "one," and repeated sounds are typically associated with "many." Likewise, low-pitched sounds accompany something big, and highpitched sounds convey small size. These findings of "iconic" sounds could help scientists understand how human ancestors started using rich acoustic communication, says co-author Aleksandra Ćwiek, a linguist at the Leibniz-Center General Linguistics in Berlin. The human voice, she says, might "afford enough iconicity to get language off the ground."

University of Tübingen linguist Matthias Urban, who was not involved in the research, agrees. "It's unclear how words came into being in the first place," he says. Iconic vocalizations are "potentially one pathway that could have been involved." -Katherine Kornei

### **Results of the In-Person Experiments**

The in-person portion of the study involved 143 people from seven language cohorts. Participants listened to sounds and guessed the meaning of each one by selecting from a set of 12 images. Researchers used three different sounds to represent each meaning and told participants, "More than one sound can be matched to one picture." Sounds meaning "child" yielded the most correct responses, whereas those depicting inanimate entities such as "fruit" had mixed results.



### **ADVANCES**



When it comes to humans admiring plants, flowers tend to hog all the glory. But even though these ephemeral blooms may be dazzling, the things that appear after the petals fade-the fruits and seeds—are elegant in their own right.

A new book by photographer Levon Biss displays some striking and unusual examples of the functional plant elements that emerge after most people have looked away. Entitled The Hidden Beauty of Seeds & Fruits: The Botanical Photography of Levon Biss, it showcases subjects from the Royal Botanic Garden Edinburgh's carpology collection. Such repositories help scientists preserve plants to learn about how they function. Each delicate, dry and sometimes fuzzy specimen reveals a little bit more about the range of tools life uses to persist.

This is the circular fruit of Anthyllis circinnata, which ranges from the Mediterranean region to the Arabian Peninsula. Other members of the genus Anthyllis are known for absorbing heavy metals, so scientists have explored using the plants to draw contaminants out of land.

1

Castor oil plant seeds contain 2 ricin and are thus extremely poisonous. But at one end, each seed has a yellow nodule full of fats that are nutritious for ant larvae. After hauling their harvest into their nests and pulling off the delicious part, ants chuck the rest of the seed into their trash pile, where the future plants start to grow.

These dangerous-looking seed 3 **pods** come from water chestnuts, a plant that has been part of the human diet since Neolithic times. When the green, leaflike petals protecting the base of the flower harden, they turn into the sharp spines seen here.





The white fruit of the Eriosyce aurata plant keeps its internal seeds moist and shields them from extreme heat. And the fruit itself has its own protection: the prickly sheath on top foreshadows the needles to come on the fully grown cactus.

4

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4

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### MICROBIOLOGY

### Living Color

Common bacteria pump out nontoxic dyes

**Researchers have modified** a common bacterium to spit out an entire rainbow of dyes for food, clothing, cosmetics, and more. The proof-of-concept research also detailed the natural production of two colors—green and navy blue—for the first time.

Some dyes can be produced naturally from plants. Indigo, for example, is extracted from leaves of species in the genus *Indigofera*. But the task is labor-intensive, with variable results. Synthetic alternatives can involve toxic precursors and by-products, sometimes released as pollutants. And consumers are willing to pay more for natural colorants, says Sang Yup Lee, a chemical and biomolecular engineer at the Korea Advanced Institute of Science and Technology. So he and his colleagues set out to <u>engineer Escherichia coli</u> to make seven natural hues.

The researchers not only had to tweak the microbes by adding specific genes to

### SUSTAINABILITY

### Tiny Trash Microrobots target microplastics

**Microplastics**—minuscule, hard-to-degrade fragments of clothing fibers, water bottles and other synthetic items—have made their way into air, water and soil around the world.

Now new research published in ACS Applied Materials & Interfaces shows a way to promote their deterioration, at least in water, with technology on an even smaller scale: microrobots. When added to water along with a bit of hydrogen peroxide, the bacterium-sized devices glom onto microplastic particles and begin breaking them down.

The metallic microrobots are shaped like four-pointed stars and coated with magnetic particles. Exposure to visible light causes electrons in the devices to absorb energy from and react with the surrounding water and hydrogen peroxide (a process called photocatalysis), making the bots move. "They can sweep a much larger area than



produce the dyes, they also had to help the bacteria push the colors out into the world. Because the involved dyes are hydrophobic (water-repellent), they typically cannot pass through bacterial cell membranes; they would instead accumulate inside the cell and ultimately kill it. Synthetic biology researchers seeking to produce self-sustaining "cell factories" for chemicals have long been stymied by this problem.

Lee and his team genetically altered their *E. coli*, first to grow longer cells and then to convert some of the extra membrane surface area into sacs that could encircle and expel the accumulated chemicals. Rather than cutting out the relevant genes entirely, which might in some instances kill the bacteria, they introduced small RNA sequences that "silenced" such undesired but essential

you would be able to touch with stationary technology," says study co-author Martin Pumera, a researcher at the University of Chemistry and Technology, Prague. As the microrobots adhere to plastic, photocatalysis also produces charged molecules. These break chemical bonds in the plastic's molecules, like a jeweler snipping bracelet links.

The researchers tested the microrobots on four types of plastic. After a week, all four had begun degrading, losing between 0.5 and 3 percent of their weight. In another test, the microrobots propelled themselves through a small channel and were collected by a magnet, bringing up to 70 percent of microplastic particles along for the ride.

Pumera envisions releasing future iterations of the bots into the sea to latch onto microplastics, then collecting the bots for reuse. But Win Cowger, who studies plastic pollution at the University of California, Riverside, and was not involved in the study, says any microrobots' potential usefulness is



Lee says that his *E. coli* production method has no toxic properties and could be incorporated into industry today—but that "some colors will be more expensive because the [concentrations] are still quite low and difficult to produce."

The new technique could eventually help engineer microbes to produce hydrophobic antibiotics, says Duke University biochemist Meta Kuehn, who was not involved in the research. This capability "would be tremendous as far as a good source for producing some really difficultto-synthesize antibiotics," she says.

Lee has worked on metabolic engineering for 26 years and describes these rainbow food and clothing dyes as his latest forays into industrial chemical production—which have also included making compounds involved in cosmetics and pharmaceuticals. It's a running joke among his colleagues, he adds with a smile, that his goal is to produce every compound in the chemists' go-to Sigma-Aldrich catalog. —Maddie Bender

likely limited to closed systems such as those used to treat drinking water or wastewater.

Cowger notes that the current bots can also adhere to substances other than plastic and might not be safe if left in the water in large numbers. Pumera's team is now testing microrobots made from different materials that could address both concerns and

> could operate without hydrogen peroxide.

"The work is indeed highly interesting, but it needs further investigation to make this approach a really viable and potentially attractive technology to deal with the huge scale of microplastics," University of

Oxford chemists Peter Edwards and Sergio Gonzalez-Cortes wrote in an e-mail. The two researchers, who were not involved in the study, have proposed using microwave radiation to break down plastic waste.

For now, Cowger says, "the best way to remove microplastics from the environment is to stop them from getting there in the first place." —Scott Hershberger



Microrobot



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### ADVANCES



Antibiotic-producing mold P. rubens

MEDICINE

### **Bacterial Bipartisanship**

Illinois selects an official state microbe

U.S. states have long designated their own official flowers, birds and mammals, local symbols that fire up affection or pride. Now the Illinois legislature has taken things to the next (microscopic) level by adopting *Penicillium rubens*—a mold that produces penicillin—as the official state microbe.

Scottish microbiologist Alexander Fleming discovered in 1928 that a fungus called *Penicillium notatum* produced penicillin, which became the world's first widely effective antibiotic. But *P. notatum* could not generate large-scale quantities of the drug, which became especially crucial when World War II broke out. So scientists at the University of Oxford sought help from the U.S. Department of Agriculture's Northern Regional Research Laboratory (since renamed the National Center for Agricultural Utilization Research, or NCAUR), in Peoria, Ill. Andrew Moyer, a microbiologist there, took on the problem.

Moyer's fellow researcher Mary Hunt found a moldy cantaloupe at a Peoria market and brought it to the lab for analysis, says NCAUR biochemist Neil Price, who championed the state microbe designation. As was the case with many women conducting research in that era, Hunt's contribution to the discovery and study of that mold—which turned out to be *Penicillium rubens*—was diminished at the time. Moyer's 1944 publication on *P. rubens* mentions Hunt only in the paper's acknowledgments, and the press referred to her as "Moldy Mary." *P. rubens* could better tolerate a new fermentation process that let it quickly produce hundreds of times more penicillin than previously studied strains, which let the Allies massively scale up antibiotic production. The same strain is still used to manufacture penicillin today, Price says. "To think—a moldy cantaloupe from a fruit market in Peoria revolutionized the medical field for millions of people," says State Representative Stephanie Kifowit, who co-sponsored the Illinois House version of the *P. rubens* bill.

Price discussed his idea for making P. rubens the state microbe with State Senator David Koehler, who ultimately sponsored the Senate version of the bill. "I thought, 'We have a state bird," Price says. "'Why not a state microbe?" Illinois is only the third state to take this step, joining the ranks of Oregon (which similarly honors Saccharomyces cerevisiae, or brewers' yeast) and New Jersey, whose state microbe Streptomyces griseus also produces an antibiotic. Some efforts to designate official microbes have faltered: Wisconsin failed to pass legislation honoring Lactococcus lactis in 2010. and Hawaii was unable to choose between Flavobacterium akiainvivens and Aliivibrio fischeri in 2013.

But the Illinois effort attracted bipartisan support and sailed through both houses of the General Assembly, passing unanimously in May. The *P. rubens* discovery "is an important part of Illinois history," Koehler says. "I am glad to know that it will be forever tied to the state as our official microbe." —*Jim Daley* 

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**Roald Hoffmann** is Frank H. T. Rhodes Professor of Humane Letters Emeritus at Cornell University. He shared the 1981 Nobel Prize in Chemistry with Kenichi Fukui. His many published works include the play *Oxygen*, co-written with Carl Djerassi, and several poetry collections, the most recent of which is *Constants of the Motion* (Dos Madres Press, 2020).





### sap pitch and resin

First it fell just fell at my feet no wind no squirrel or bird to give it a push a green green pine cone with brown accents heavy with sealed overlapping rounded rhomboid structures in spirals I have to restrain myself from seeing here the condensed aromatic hydrocarbons I leave it on a plate and look on the web for the names of cone parts names are important even if my last name changed three times what I learn is that I have a female cone that the plates are scales and that each comes in two types bract or seed I think I am seeing seed scales in formation tightly fitting each scale at its center begins to ooze ever-so-slowly a tiny pitch droplet a spiral of spherical diamonds now I know it's pitch and not sap because it is damn sticky I can't get it off my fingers we enter the world of science dealing with the world of words and the world of things being farmed and manufactured and sold sap is not pitch which is not resin resin and rosin and turpentine and pine tar what's in it for plants is not what's in it for us see water-based sap gets molecule A from site B to C in the inner tree while pitch is an organic soup moving in its own pipelines near the bark ready to flow out if bark or wood is damaged to push out with some force an insect to seal in time forming a solid resin odoriferous to repel insects that might enter the damage or attract some others and we thought we humans made things complicated damned chemist in me can't stop wondering what smells what makes things sticky it's terpenes oligomers of isoprene with appropriate names monoterpenes like pinene and diterpenoid resin acids like abietic acid I could tell you how they're made in pine or the lab and before long we have the whole lovable interconnected and thoroughly messy world meanwhile the cone rests oozing gently maybe the small globules of pitch are a survival strategy to be pollinated by any pollen from male cones that might be left over vain hope wrong season no males and the premature cone begins to darken to brown waiting for dispersal.

### THE SCIENCE OF HEALTH



**Claudia Wallis** is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic*. She was science editor at *Time* and managing editor of *Scientific American Mind.* 



### **Poison Ivy Relief**

A vaccine is in the works, and there are new avenues for treatment

By Claudia Wallis

**Eleven summers ago** I moved into a small house surrounded by woods but with enough sunshine to indulge my gardening habit. It was my own little Eden, complete, as it turned out, with a botanical snake in the garden: poison ivy. I learned to avoid its red shoots of spring, waxy green triad of leaves in summer, crimson foliage of autumn, and hairy vines still lurking in winter. I wore gloves to weed and sow, but still I'd wind up with the devilishly itchy rash a few times a year, lasting three weeks at a stretch.

Every year 10 million to 50 million Americans share my woes. According to some older studies, poison ivy and its cousins poison oak and poison sumac cause 10 percent of lost-time injuries among U.S. Forest Service workers and lead one third of them in California, Oregon and Washington to miss work during fire seasons. To make matters worse, the climate crisis is turning poison ivy more toxic and expanding its range. A <u>six-year study</u> conducted at Duke University in the early 2000s found that elevated levels of carbon dioxide, a driver of climate change, induce the plant to produce a more allergenic form of urushiol, the oily resin responsible for the rash.

Given the toll in suffering and dollars, you would think serious attention would be paid to this worsening public health issue. You'd be wrong. "This condition is really underappreciated," observes biochemist Sven-Eric Jordt, whose lab at Duke investigates pain and itch mechanisms. Contact dermatitis from poison ivy is usually treated by local doctors, not in big research centers, he says. And pharma companies see more profit in developing drugs for chronic skin conditions such as eczema than for an ephemeral rash. Jordt is one of a handful of scientists who take this nemesis seriously, and I am happy to report that they have made progress. Among recent discoveries: surprising pathways that cause the itchy rash, new targets for treatment and be still, my heart—a vaccine in development that aims to prevent the urushiol reaction.

If you Google poison ivy, you will get a torrent of treatment advice such as to take antihistamines and apply cortisone cream. Neither does much good. (Cortisone pills do help if given early and in sufficient doses.) Why not? Animal studies indicate that the response to urushiol has nothing to do with histamines bodily chemicals involved in many allergic reactions—so antihistamines are useless. Working with urushiol-exposed mice, Jordt and his colleagues found that an immune chemical called interleukin 33 (IL-33) plays a key role in causing the infernal itch. Released by skin cells, it acts directly on sensory neurons in the skin. If either IL-33 or its receptor is blocked, the mice stop scratching—a finding that suggests a new route for treatment. Because IL-33 is involved in asthma and eczema, at least two companies already are working on drugs to block it, but its role in poison ivy was a surprise.

Dermatologist Brian Kim, co-director of the Center for the Study of Itch & Sensory Disorders at Washington University in St. Louis, has identified a second, <u>nonhistamine pathway</u> involved in poison ivy rashes. Also working with mice, Kim, along with scientists at Johns Hopkins University, has shown that <u>immune</u> system components called mast cells trigger itch neurons in the skin. The mast-cell and IL-33 pathways are both "very new mechanisms," Kim says. In the past, dermatologists believed that urushiol rashes and itch were triggered by the immune system's T cells, which rally antibodies to attack the skin irritant. Kim believes that T cells do cause the inflamed rash of poison ivy but that these other pathways provoke the itch: "In other words, what causes the itch is very different from what causes the rash."

Both recently discovered mechanisms present new targets for treatment, but first scientists need to extend the work in humans. Jordt says it's been difficult to attract study funding and to obtain tissue samples from poison ivy patients.

Human research is proceeding with a compound called PDC-APB, which would be injected as a vaccine once every year or two to prevent poison ivy misery. Developed at the University of Mississippi, it is a synthetic version of urushiol's active component. "We believe the shot will lead to desensitization and reduce or eliminate reactions to poison ivy, oak and sumac," says Ray Hage, CEO of Hapten Sciences, which has licensed the compound. It works well in guinea pigs (I've seen photos), passed initial safety testing in humans and is about to be evaluated in <u>a small randomized controlled trial</u>. People are beating down the door to try the vaccine, Hage reports: "Every March I start to get e-mails from people asking, 'Where is the drug? Can I be in a trial?" My feelings exactly.



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# THE

Millions of people are sickened by immune systems that are supposed to defend them. There are new ideas about why this happens and how to stop it

Illustrations by Hayley Wall

# AGAINST ITSELF

### Annie, my friend

John's kid sister, got sick when she was 11. I wasn't much older so I didn't know how serious it was when John said her disease was called lupus. I didn't realize her own cells were attacking her, sometimes going after her kidneys, other times her lungs. I did know, because her brother told me, that her face got really swollen because she had to take lots of pills called steroids, which had side effects that meant she could get very sick from flus or colds that he and I shrugged off. At times Annie missed long periods of school. At times she hurt badly. As she grew, she worked in children's theater, which she adored, and in local politics. Annie never got past lupus, though. She died at age 49.

Too many stories end this way. Lupus is an autoimmune disease, in which the body's guardian immune system turns traitor and tries to destroy the organs it is meant to protect. There are about 80 of these disorders—some estimates are higher and in the U.S., almost 25 million people suffer from them, according to the National Institutes of Health. The number appears to be rising. The illnesses range from the familiar, such as type 1 diabetes and lupus, to the obscure, such as Takayasu's arteritis (in which large blood vessels become dangerously inflamed).

This special report highlights new discoveries about these ailments, too often understudied given their terrible toll. Fresh ideas are emerging about the ways such disorders get started, ideas that run counter to a century of medical dogma. And researchers now have theories that could explain the awful gender imbalance in autoimmune disease nearly 80 percent of patients are women. These advances are leading to more refined treatments, based on a more nuanced understanding of our immune systems. Progress is still slow, but the changes carry with them hopes of overwriting a past filled with ineffective therapies or drugs that could be worse than the diseases themselves.

–Josh Fischman

## BETRAYAL FROM WITHIN

Disabling symptoms, inconclusive tests, ineffective treatments, doctors who don't listen: one person's journey through the autoimmune disease world

By Maria Konnikova

**I REMEMBER EVERYTHING ABOUT THAT** morning—or as I call it in my mind, in highly scientific terms, the Day That the Shit Totally Hit the Fan. I was getting ready to go to the gym. Usually this was a cause for dread, but that day it was an exciting opportunity to wear the new shorts that had just arrived in the mail. Nothing like shiny new workout gear to get you out and about. I put them on and was about to head out the door when I noticed an intense burning sensation on my thighs. They had become covered, seemingly in seconds, in large, angry hives. I pulled off the new clothes—clearly, something must have gotten on them!—and ran for the shower. Eventually the hives calmed down. Allergic reaction, I assumed, as I returned the shorts to the store in record time. And, I thought, that's that.

My body, it turns out, thought differently. The next morning there they were again. The hives, not the shorts. Only this time they didn't go away. They spread. Within a few days my body was reacting to anything that touched it with mounting anger. It was like some awful internal cascade had been set off, and now nothing could put it back to where it had been before.

This wasn't my first bout with crazed skin reactions. When I was 22, I was diagnosed with mastocytosis. I'd suddenly developed an incredibly painful, oozing J-shaped rash around my left breast. My dermatologist, oddly enough, was overjoyed. Apparently it was rare for the condition (where the body makes too many immune system components called mast cells, which create inflammation) to manifest quite like that in an adult. Fewer than one in 30,000 adults have mastocytosis to begin with, and typically the skin rashes are associated with a childhood onset.




#### Maria Konnikova

is a science journalist and professional poker player. She is author of the best-selling books *The Biggest Bluff* (Penguin Press, 2020), *The Confidence Game* (Viking Press, 2016) and *Mastermind: How to Think Like Sherlock Holmes* (Viking Press, 2013). After confirming my diagnosis with a painful biopsy, he had asked if he could take photographs for a journal article. I agreed: I was in too much pain to give it much thought, and he just seemed so ... gleeful.

The condition has never gone away for long. When I'm too stressed or tired—or sometimes just hot—a painful raised rash appears. Sometimes it erupts in lesions. It stays for weeks. And then, just like that, it's gone for a year or two or three. The ailment is not an autoimmune disease in itself, but it does mean that my body systematically churns out an abundance of mast cells. Could they be going out of control in my newly developed full-body hives?

It wasn't mastocytosis, my doctor declared at an emergency appointment. My levels of tryptase, an enzyme released by mast cells, were normal. My thyroid, though, was out of whack. Did I have Graves' disease an autoimmune condition where the immune system attacks the thyroid gland? Or perhaps Hashimoto's, where basically the same thing happens but with the opposite result, too little thyroid hormone to Graves' too much? And if so, where were the *hives* coming from? Thyroid hormone abnormalities are not connected to hives in most patients.

The world of autoimmune disease is a murky one, often filled with vague guesses. Taken together, autoimmune conditions are common, but many individual illnesses are rare and difficult to diagnose. Oftentimes the diseases strike in infuriatingly hazy ways. Lethargy in the limbs, for instance, could be multiple sclerosis or lupus, devastating but different diseases with a lifetime of debilitating, progressing pain.

A slew of tests followed after my urgent medical visit. They showed my thyroid wasn't to blame. But nothing else was, either. I was shuffled from internists to dermatologists to allergists and immunologists. My sister, a doctor, got me in to see one of the best allergy specialists in the Harvard Medical School system. The result: a host of acronyms I couldn't quite understand, all serving to rule out condition after condition. One of them, the chronic urticaria index, declared that I have "basophil reactive factors in ... serum which supports an autoimmune basis for disease." I asked what that meant. I was told it meant that ... I have hives.

In the absence of answers, the hives continued their colonization of my body. My neck. My face. My eyes, swollen shut. The oral steroid doses increased more and more, along with many antihistamines, which knocked me out to the point where I could barely keep my eyes open. The topical steroid creams got ever stronger. They had huge warnings down the side, urging you to not use them too liberally or for too long, lest your immune system fall apart entirely. I gained weight. I slept too much or not at all. I couldn't think straight for any stretch of time. My immune system was suppressed beyond recognition. And still the cause of the hives remained a mystery. (The shorts, just a coincidence, every specialist assured me, despite my fervent belief in cause and effect.) Idiopathic, read my final diagnosis: origin unknown.

Eventually the hives did recede. Not with any new prescription or diagnosis but with time. The idiopathic hives became rarer hives which became, one glorious morning, a memory. But a memory with no known cause and no real cure. A memory that, to this day, might come back at any moment, with provocation or without. For if you never know what caused it, what's to keep it from recurring?

Autoimmune: "of, relating to, or caused by autoantibodies or T cells that attack molecules, cells, or tissues of the organism producing them." So says the Merriam-Webster dictionary, referring to certain immune system elements. In layperson's terms: attacked by your own body. Instead of your cells uniting against a foreign invader, they turn against one another. Most of the time we don't know what causes it. We don't know how to cure it. When it comes to the autoimmune, the unknowns far outweigh the knowns.

Here's what we know. There are about 80 kinds of autoimmune diseases. Nearly four of every five affected people are women. Why? We're not quite sure. Because here's the other thing we know: autoimmune research is perennially underfunded. Maybe it's because women suffer the most—and women have, historically, been often ignored in medical research. Maybe it's because many conditions are rare. Maybe it's because when a cause is unknown, it is often assumed to be psychosomatic. You make yourself sick. You stress yourself out too much. Are you sure you aren't just making it up?

My sister was thus accused. In her senior year of medical residency, she developed a strange tingling and numbness in her fingertips. For months she ignored it. But the tingling got worse, and the numbness intensified. She went to a neurologist because these could be symptoms of multiple sclerosis. Yet when an MRI test failed to show nerve abnormalities, a doctor said her numbness and pain weren't real. It was all in her head. When she asked for pain medication for what by that point was neuromuscular agony, she was dismissed.

Remember my sister is a physician, with the professional vocabulary to precisely describe what to others would have been hard to capture. And this is what she was met with: disbelief, a medical response familiar to many patients with autoimmune conditions. She pushed back and eventually got a nerve-conduction test. The results were grossly abnormal. She hadn't been lying or pretending. She had CIDP, chronic inflammatory demyelinating polyneuropathy, a rare neurological ailment with autoimmunity features. It causes pain, fatigue, and, in patients like my sister, permanent nerve damage. I can only imagine what would have happened to someone without her medical knowledge and wherewithal. The world of autoimmune disease is a tough one. It's not just the disbelief. Even with a diagnosis, relief can be elusive. A label is no guarantee of a cure. For CIDP, there is no disease-specific treatment. More than 10 years later my sister is still being treated with a medication developed for MS. Her condition remains understudied and underfunded.

She does have a label, though. I never got one. But here's what I do know. No matter how visible or invisible any given condition, autoimmune disease is incredibly real, incredibly painful—and incredibly underappreciated by those who don't suffer from it. Millions of people are casualties of that lack of awareness.

Here's my wish: that one day I will no longer have to worry whether the next item of clothing I put on will knock me out for another year because someone, somewhere, will have studied what it is that makes me so sick. That one day my sister will be cured. That one day all the countless sufferers who have been told they're imagining their symptoms are actually listened to—and that when they are, there are tools to help them. Our bodies attack themselves. Let's finally listen. Let's support the research needed to fight back.



# AUTOIMMUNE DISEASE, BY THE NUMBERS

About 80 conditions can be described as autoimmune disorders, although definitions are still changing

Text by Maddie Bender Graphics by Jen Christiansen Research by Miriam Quick



Maddie Bender is a science writer and podcaster based in New York City.

THE IDEA THAT ORGANISMS MIGHT ATTACK THEMSELVES

with immune systems that evolved to defend them from diseases in the outside world made little sense to immunologist Paul Ehrlich. In 1901 the future Nobel laureate dismissed such a theory—he called it "*horror autotoxicus*" as farfetched. Today patients and physicians know that autoimmune diseases are all too real. There are roughly 80 autoimmune conditions that affect millions of people worldwide. The variety and numbers shown in the chart on the next two pages are daunting.

Autoimmunity involves autoantibodies—immune system proteins that mark an organism's own tissues for destruction—along with the T and B cells that serve as agents of that assault. Modern techniques of molecular biology, which have allowed scientists to trace these populations of cells and proteins, have helped refine this definition.

But while the broad outlines are clearer than they were in Ehrlich's day, the details of different illnesses can still be a matter of some dispute. Matthew C. Cook, director of the Center for Personalized Immunology at the John Curtin School of Medical Research in Australia, notes that even in diseases in which scientists do not consistently detect autoantibodies related to pathology, drugs that modulate T cells can be used successfully. The skin illness psoriasis is one such example and is often described as an autoimmune disorder.

Our list includes most of the known diseases in an area where scientific understanding is still evolving. It describes the prevelance of these illnesses, the age at which they typically appear, and whether they are more likely to afflict women or men (almost always women).



in 100,000	in a million	ess than in a million	THE BODY AGAINST ITSELF
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# HOW AUTO-IMMUNITY STARTS

New research indicates body organs under stress may attract attackers from the immune system

By Stephani Sutherland



**Stephani Sutherland** is a neuroscientist and science journalist based in Southern California. **WHEN DECIO EIZIRIK BEGAN TREATING PATIENTS WITH TYPE 1** diabetes in the 1980s, he was pretty sure about what was behind the disease: an immune system gone haywire. People with the illness lacked insulin, a crucial hormone, because beta cells in the pancreas—the body's insulin factories—were being attacked and destroyed by immune system cells. "At that time, the idea was that if you could control the immune system, perhaps you could prevent diabetes," says the endocrinologist, who now has research appointments at the Indiana Biosciences Research Institute and at the Free University of Brussels in Belgium. (He no longer sees patients.)

This was the classic model of an autoimmune disorder: protector cells that turn on their bodily kin. Although treatments with extra insulin could keep people with diabetes alive, the immune assault on innocent beta cells was the root of the problem. "People saw beta cells as being like the corpse at a funeral: it's the focus of a lot of attention, but it's doing nothing," Eizirik recalls.

Now, however, those beta cells are not looking quite as innocent, and the immune



# The Target of Diabetes

When the body cannot produce enough of the vital hormone insulin, the result is debilitating type 1 diabetes. The reason for that hormone deficiency is the death of its producers, beta cells in the pancreas. They die off after attack by killer T cells from the body's own immune system. For years scientists thought T cells in people with diabetes had a flaw that made them go after beta cells. But nondiabetic people have the same kind and amount of T cells in their blood (*shown in pink*), yet such cells leave the beta cells alone. That has led researchers to suspect beta cells themselves may draw T cells to them by producing molecular lures.



system is looking like it has gotten an unfair share of blame. Over the course of several decades Eizirik and a number of other researchers—has become convinced that beta cells can actually trigger the disease. The way beta cells do this began to emerge in the late 1990s, when Eizirik measured levels of chemical signals from the cells in the pancreas. Those experiments showed that in certain circumstances the cells produce their own inflammatory chemicals, which act as flares that draw the attention, and ire, of immune system cells.

Exactly what sets off these flares is still not clear it could be a viral infection or some kind of damaging stress—but this work and more recent experiments by several other scientists strongly suggest that beta cells play an active role. "It all starts at the target tissue," says Sonia Sharma, an immunologist at the La Jolla Institute for Immunology in California. "What we know now is that the target tissue is not merely a bystander; it's an active participant in the damaging inflammation."

Type I diabetes is just one autoimmune disease, but now evidence is starting to suggest that other cellular targets in other ailments also can bring about their own demise. Recent genetic studies indicate that cells afflicted in rheumatoid arthritis and multiple sclerosis have overactive genes that code for disease-related proteins, and immune cells home in on such targets. Sharma says there could be 10 steps between an initiating event and the ultimate attack on a target tissue by immune system cells. "We've been looking at

step 10, whereas we should be looking at steps one, two and three," she says. "It's almost like we've been working backwards." If researchers could understand those early steps, she says, that could lead to better treatments, cures or even measures to prevent disease.

It is hard to fault researchers for concentrating initially on the immune system end. Autoimmune diseases seem like betrayals by an exquisitely sophisticated defense system that evolved not only to protect us from invading pathogens but also to monitor cells that threaten to turn cancerous and to clean up the cellular aftermath of an injury. It is the sentinel in our bodies that stands between us and chaos. And clearly, key parts of the immune system, particularly B cells and T cells, are critical players in autoimmune diseases. Treatments, Eizirik says, will require "a two-hit approach" aimed at these cells and at their targets. "The immune system is persistent, and it has an elephant's memory," he says. Once T cells have learned to recognize molecules on these target cells, he says, "they will keep coming."

#### AGENTS OF SELF-DESTRUCTION

MUCH RESEARCH of the past 50 years has focused on a classic hallmark of autoimmune disease: autoanti-

bodies. Antibodies are tiny proteins produced by B cells in the immune system, and they bind to proteins called antigens on foreign invaders such as bacteria and viruses; when attached in this way, the antibodies mark such invaders for destruction. Autoantibodies, however, bind to so-called self-antigens on the surface of our own cells. There they act as homing beacons for specialized assassins called cytotoxic, or killer, T cells. These cells are the actual agents of destruction, so scientists investigating autoimmunity look for these T cell-autoantibody pairs.

What scientists have recently learned is that although the killer T cells and autoantibodies are signs of an autoimmune problem, their location seems more important than the mere fact of their existence. Healthy people can have these T cells in their blood, for example, without becoming ill. In 2018 immunologist Roberto Mallone of INSERM in France and his colleagues published a study that

### "What we know now is the target tissue is not merely a bystander; it's an active participant." —Sonia Sharma, La Jolla Institute for Immunology

compared people with type 1 diabetes, others with the type 2 version of the disease (a nonautoimmune disorder in which insulin is produced but works badly), and people without either disease. The levels of killer T cells in the bloodstream were remarkably similar across all three groups, including the nondiabetic people. Everyone had them. By this measure, Mallone says, "we are all autoimmune."

But it was a different story in the pancreas. There, Mallone and his colleagues found, autoreactive T cells were present at much higher levels in people with the type 1 version of the disease. Mallone, like Eizirik before him, suspects that they are there not coincidentally but because of a problem with the target tissue, the beta cells.

Another reason researchers are considering target cells as major players in autoimmune diseases comes from genetic studies, which have shown that genes influencing these diseases are expressed not just by immune cells but also by target cells. Starting in the early 2000s, the complete sequencing of the human genome made it possible to do genome-wide association studies (GWAS), which revealed many genes that, when mutated, were linked to higher risk of autoimmune disorders. And those genes turned up not just



in B cells or T cells but also in cells that were not part of the immune system, Sharma says. For example, nonimmune cells have genes that allow them to release cytokines and chemokines, chemical messengers that summon an immune response. This activity is quite important for cellular health. All cells are susceptible to transformation into cancers, for instance, or to infection. When such harmful changes happen to cells, Sharma explains, they need to be able to tell the immune system that they are in trouble. But mutations in those genes may create apparent distress signals when the cells are not really damaged. The immune system will react as if they are and swoop in.

#### SIGNS OF VULNERABILITY

A STUDY BY EIZIRIK and his colleagues published this past January in *Science Advances* provides examples of misleading target cells in multiple autoimmune diseases. The scientists examined published

Many target cells in autoimmunity share features that make them exceptionally vulnerable to assault. They have at least three weaknesses.

> genome association research and found that more than 80 percent of identified genetic variants were expressed by target cells in type I diabetes and three other autoimmune diseases: multiple sclerosis, lupus and rheumatoid arthritis. The study showed not only that target cells contain disease-related genes but also that in people with disease, they make more of those proteins than in healthy people. Eizirik and his colleagues mined genetic databases created from biopsies of affected tissues from people with autoimmune disease: pancreas cells of people with diabetes, joint tissue from people with rheumatoid arthritis, kidney cells from those with lupus and even autopsy samples from the brains of people with multiple sclerosis.

> Their analysis showed that many candidate genes were exceptionally active in the targeted tissues, and many of these active bits of DNA appeared in multiple diseases, pointing to common threads. Among the top genes showing extra activity were those related to interferons, a class of proinflammatory cytokines that cells release to flag down immune cells when there is a problem such as a viral infection.

> Many of the target cells in autoimmune disease also share nongenetic features that make them excep-

tionally vulnerable to assault. "These cells have at least three intrinsic weaknesses," Mallone says. First, many of them reside in glands such as the thyroid and pancreas, where "they are hormone factories, pumping out hormones at high rates, which creates a lot of stress." Because they are already under a lot of strain, a little additional cellular stress could flip the balance toward malfunction and pathology, alerting an immune system cleanup crew. Second, the cells secrete hormones and other peptides directly into the bloodstream. Such molecules travel throughout the body, which means that, as signatures of these cells, they "can sensitize the immune system from a distance," Mallone says. A third weakness for target cells is that they are penetrated by lots of blood vessels, making them easily accessible. "This means that once the immune cells are sensitized, they have an easy job to get to [the targets]," he concludes.

On top of those vulnerabilities, target cells may

react to an outside threat—damage from a virus, for example—in ways that bring on a strong immune response. Some cells self-destruct when infected by a virus, taking themselves out before the harm can spread and before immune system intervention is needed. But certain cells afflicted in autoimmune diseases, such as neurons and beta cells, are in limited supply. Simply dying off after a viral infection is not an option for them, Eizirik says. "If too many cells die, we're cooked," he says. Instead they stick around, and the immune system starts interpreting the molecules they release as

signs that all cells of that class are in trouble. Then an autoimmune attack ensues.

One striking example of a weakness in target cells that leads to an immune response comes from the blood vessel disease vasculitis. The disorder is not a classic autoimmune disease, because it does not rely on autoantibodies. Rather it is an example of an autoinflammatory disease in which a cell class known as myeloid immune cells goes after other cells that form arteries, veins and capillaries. A rare, aggressive form in children results from a mutation in a gene for a metabolic enzyme called adenosine deaminase 2. The enzyme regulates activity in both the attacking cells and the attacked ones, according to a 2020 study led by Sharma and published in Science Advances. "When they lose this enzyme, the whole system becomes deregulated," Sharma says. "The end result is that the target cells start producing cytokines, and this has a bystander effect to activate the myeloid cells. What we're talking about is the target cell causing its own problem."

#### **OUTSIDE TRIGGERS**

BUT EVEN CELLS with inherent weaknesses do not get into autoimmune trouble all by themselves. Remember that in nondiabetic people, Mallone found T cells that could have assaulted beta cells, but they held their fire. Something tips the balance, initiating events in target tissues that seem to start immune system interference. Many scientists think that thing is often a passing viral infection or perhaps exposure to toxic chemicals, and it may occur years before an autoimmune disorder becomes obvious enough to be detected.

One long-suspected culprit in type 1 diabetes is the Coxsackie virus, a common pathogen. It usually causes a mild illness that shows up as passing skin rashes and mouth sores. But Coxsackie can attack the pancreas under the right circumstances, Mallone says: "These viruses can infect beta cells, so they can kill some if there's enough of a viral load." That could lead to inflammation that draws more immune cells to the place where beta cells are dying. In their death throes, the betas could release signature self-antigens that sensitize nearby immune cells, causing them to go after other beta cells, because such cells have similar antigen signatures.

That multipart mix is crucial, Mallone says. "Basically, you need three ingredients: self-antigen, an inflammatory environment and autoimmune predisposition," he says. "And these ingredients have to meet at the same place and the same time. This is probably one reason it's so difficult to identify environmental triggers: because we're all exposed, but it depends on specific conditions."

This view is replacing an older idea: that viruses trigger autoimmune reactions when the viral proteins look, molecularly, a lot like self-antigens, leading immune cells to get confused by the similarity and attack the self. Support for this idea, called viral mimicry, began to crumble as researchers amassed evidence that such molecular doppelgängers are fairly common but very rarely cause disease. There are a number of molecules in human bodies and infectious agents that look like one another, and they are called cross-reactive. "Cross-reactivity is extremely abundant; you can find it everywhere," says DeLisa Fairweather, an immunologist at the Mayo Clinic in Jacksonville, Fla. If cross-reactivity led to illness, she says, "we should see diseases at higher levels. It's not the answer." Thus, the idea has gained currency that a virus kills some target cells and creates some inflammation, and in the middle of all this, some immune cells become sensitized to the dying cells' proteins.

#### A RISING COUNT

OTHER IRRITANTS FROM OUTSIDE the body, such as drugs and other chemicals, can create these inflammatory conditions, providing more occasions for encounters with immune system sentinels to go wrong. Some scientists think encounters with such substances can explain a spike in autoimmune disease frequency over the past few decades. In 2020 rheumatologist Frederick Miller of the National Institute of Environmental Health Sciences and his colleagues published an analysis that tracked the prevalence of antinuclear antibodies, a subset of autoantibodies that go after proteins in a cell's nucleus. The study followed more than 14,000 participants in the U.S. over a 25-year period. Between 1988 and 1991, 11 percent of those tested carried the antibodies. That number stayed roughly stable through 2004, with a small rise toward the end of that period. But by 2012 the data showed a big jump in the number of people carrying the antibodies, to nearly 16 percent of participants. The rise was particularly striking in adolescents, Miller says, "which to me was the scariest thing." That could indicate a coming wave of autoimmune diseases.

THE BODY

AGAINST

TSELF

What has changed to cause the increase? "We don't know yet," Miller says. He can, however, rattle off a number of possible environmental and behavioral factors: during the time span of his study, approximately 80,000 to 90,000 new chemicals have been approved for use, he says. "We have a completely different diet," he continues. "Our use of electronics, while handy and useful, has also meant we're not getting enough sleep." People have also encountered increases in air, water and food pollution. "There are hundreds of differences in our lifestyle and exposure in the past 30 years," Miller says.

Another, somewhat paradoxical idea is that our immune systems now get too little exposure to the outside world and consequently overreact when they encounter relatively benign molecular representatives from it. The theory is related to a notion called the hygiene hypothesis, put forth in the early 2000s, which was based on changes to sanitary conditions. This iteration is more closely tied to changes in our intestinal bacteria, our gut microbiome, that come with the habits of modern society. A quirk of geopolitics has presented a unique opportunity to study this effect. After World War II, a region in northeastern Europe called Karelia was split into Finnish and Russian territories. The populations are genetically similar, but Finnish Karelia rapidly modernized after the war, whereas living conditions in rural Russian Karelia remained similar to those of 60 years ago. You might think an improvement in living conditions would reduce the burden of disease, but that has not happened with autoimmune illnesses. In fact, the reverse effect has been observed. The incidence of type 1 diabetes in Finland is the highest in the world and about six times that in Russian Karelia. Rates of other autoimmune diseases such as celiac disease are also six to 10 times higher in Finland compared with Russia.

Mikael Knip of the University of Helsinki and his colleagues think these changes in disease prevalence can be tied to changes in the microbiome in the Karelian populations. Our internal ecosystem of gut bacteria becomes established during infancy



and is heavily influenced by our surroundings. For a 2016 study published in *Cell*, Knip's team collected stool samples from infants on both sides of the Finnish-Russian border for the first three years of their lives. "When we analyzed the data, we did see a clear difference between the infants in Finnish and Russian Karelia," he says.

The microbes in Russian children were dominated by a nonpathogenic form of Escherichia coli. Finnish children, in contrast, were home to high levels of a bacterial genus called Bacteroides, which typically does not prompt a strong immune reaction. "Exposure to various microbes in the environment has an effect on training the immune system, particularly in the first year of life," Knip says, and it looks as if the Finnish systems did not get very rigorous training. The Finnish microbiomes also lacked the variety seen among the Russians. Although Knip emphasizes that it is too soon to cement a causeeffect relation between any drop in microbiome diversity on the Finnish side and the rise in autoimmune problems, he does think there is a connection. "I'd say we need to rename the hygiene hypothesis to the biodiversity hypothesis," Knip says.

and exposure to variety—for example, by eating nonprocessed foods or at least much less heavily processed versions—is key for training the immune system. "That makes our gut flora more abundant and more diverse," she says. And it gives our immune system a chance to get used to molecules that are not inherently dangerous so that it does not overreact when it encounters them.

Ultimately a better understanding of the causes of autoimmune diseases-and improved treatments for them-will come from an approach that is quite different from narrow studies of immune cells or target tissues or the microbiome, Miller says. It will come from a more holistic view. Much like in the old Indian parable, he says, "everyone's looking [at autoimmunity] like the blind men feeling around the elephant, where every person is seeing different things, and they're not able to connect these to the whole." Seeing the entire immunological picture will require more studies on different types of biomolecular dynamics, and that research will have to be done in large populations of people. Such an approach could amount to "millions of data points," Miller says. "We need to embrace the complexity."

Sharma agrees that gut biodiversity is important,

# WOMEN AT RISK

Nearly four of every five people with autoimmune disorders are female. Sex hormones, genes and even gut bacteria may be reasons why

By Melinda Wenner Moyer

**MELANIE SEE'S FIRST BOUT OF ODD SYMPTOMS** began in 2005. Suddenly she started sweating a lot. She rapidly lost 10 pounds. She got dizzy walking from the bedroom to the couch. She started lactating even though she was not nursing a baby. After a slew of laboratory tests, See, then 45, was diagnosed with Graves' disease, an autoimmune disorder that makes thyroid hormones surge.

Three years later, when See's symptoms from Graves' were under control with medication, her health took another rapid downturn. She lost more weight. She felt extremely tired. Her doctors diagnosed her with celiac disease, another autoimmune disease, which in affected people is set off by eating foods with gluten. Then, in 2015, See, who lives in Chapel Hill, N.C., began experiencing terrible digestive symptoms and muscle pain. This time her doctors were stumped. "Initial diagnoses were all over the place—vasculitis, lupus, I can't remember what all," See says. "My bloodwork showed something was going on, as did the muscle biopsy I had in June 2016, but I didn't fit into any particular box."

After many tests, See was diagnosed with yet a third autoimmune illness: mixed connective tissue disease, a rare ailment that shares some features of lupus.

Women account for an estimated—and astonishing—78 percent of people who have these disorders, which include See's afflictions, as well as lupus, multiple sclerosis, rheumatoid arthritis, and other illnesses in which the body's immune system mistakenly attacks its own cells and tissues. Autoimmune diseases are now the fifth-





Melinda Wenner Moyer, a contributing editor at Scientific American, is author of How to Raise Kids Who Aren't Assholes: Science-Based Strategies for Better Parenting from Tots to Teens (G. P. Putnam & Sons, 2021). leading cause of death in women younger than 65.

Why women are so much more likely than men to be plagued by autoimmunity has long been a mystery, but researchers are beginning to narrow down the causes: the different effects of sex hormones, of women's X chromosomes, and even of the community of microbes inside us, which develops differently depending on sex. Evolution may also play a role in the staggering differences observed in autoimmunity, some scientists think. Because autoimmunity is much more common in women, researchers have suggested it might be an evolutionary relic—immune hypervigilance could have given women a reproductive advantage by improving the chances of a successful pregnancy, even if it came at the cost of increased disease risk.

"It is important to understand the underlying biology of these sex differences," says Shannon Dunn, an immunologist at the University of Toronto. "If we can unravel this, we will not only better comprehend how autoimmune diseases get started and find new ways for intervention, but we will also shed light on the sex differences in how humans respond to infection, vaccination, injury and cancer."

#### HORMONAL PATTERNS

THE WILDLY UNEVEN BURDEN of autoimmune diseases is not a new observation. Well over a century ago, when doctors first began diagnosing these conditions, they noticed that women were much more likely to develop such illnesses than men. But back then doctors tended to think of individual autoimmune diseases as distinct entities with their own unique causes. There was little awareness that they might all be connected in fundamental ways and that they might affect women more often for these shared biological reasons.

Everything changed in the early 1990s, when scientists found that some autoimmune diseases have biological mechanisms in common. Among other things, researchers discovered that immune cells known as CD4<sup>+</sup> T helper cells were involved in rheumatoid arthritis, multiple sclerosis and type 1 diabetes. And in 1991 a woman with lupus named Virginia Ladd founded the American Autoimmune Related Diseases Association after discovering that a number of autoimmune diseases plagued various members of her family, suggesting a shared genetic inheritance.

Once researchers began to think of autoimmune diseases as a collection, they started to notice interesting patterns. One was that some of these conditions arise in women after key life transitions. (Almost all of this research has involved cisgender women.) Lupus and multiple sclerosis, for instance, tend to first appear during the childbearing years. Other diseases, such as rheumatoid arthritis, most commonly arise after menopause. Big autoimmune changes can also take place during pregnancy: symptoms in women with rheumatoid arthritis, multiple sclerosis and Graves' disease often wane during pregnancy, whereas in women with lupus symptoms often get worse. What do all these transitions—puberty, pregnancy and menopause—have in common? They all involve major changes in the hormones estrogen, progesterone and testosterone. Estrogen levels go up, for instance, during puberty and pregnancy. It is now clear that, although there are exceptions, many autoimmune diseases "are driven by estrogen," says DeLisa Fairweather, a microbiologist and immunologist at the Mayo Clinic in Jacksonville, Fla. Indeed, the use of oral contraceptives and hormone-replacement therapy, both of which add estrogen to the body, has been linked to an increased risk for lupus.

Estrogen, like the other sex hormones, directly influences the expression of a number of genes involved in immunity. For instance, it attaches to and turns on the gene that codes for interferon gamma, a chemical that orchestrates immune responses against pathogens but that can also escalate autoimmune responses. Estrogen also activates B cells, which produce antibodies, proteins that mark and attack foreign substances. But some, known as autoantibodies, can also attack cells made by the body.

Hormones that play key roles in pregnancy, such as progesterone, have dramatic immune effects, too. Many critical immune cells, including T cells and macrophages, feature receptors for progesterone on their surface. When progesterone binds to these receptors, it shifts the body toward a kind of immune response that favors the production of antibodies and autoantibodies. This reaction is known as a Th2 immune response, for type 2 T helper cells. It contrasts with Th1 immune responses, which move the body away from antibody manufacturing and instead activate cells that attack other cells directly.

The rise in progesterone during pregnancy could explain why symptoms of rheumatoid arthritis and multiple sclerosis often wane when women are expecting—these diseases are driven by Th1, not Th2, immune responses, so the progesterone-induced shift eases their immune burden. But "women with multiple sclerosis are at a much higher risk of having a relapse shortly after delivery. And that has to do with the dramatic change and reduction in sex hormones," says Tanuja Chitnis, a neurologist at Brigham and Women's Hospital in Boston.

Testosterone, which women produce but to a lesser degree than men, is another important hormone when it comes to autoimmunity. Receptors for testosterone are found on the surface of B and T cells, and the hormone is largely immunosuppressive. It decreases the responses of immune cells, including neutrophils, natural killer cells and macrophages—which could be one reason that men tend to have lower rates of autoimmune disease. Research has found that men with multiple sclerosis often have lower than normal levels of testosterone and that men with low testosterone because of a condition known as hypogonadism are at increased risk for lupus and rheumatoid arthritis.

All these sex hormones can also affect the expres-

sion of key immune genes. In 1997 a consortium of Finnish and German scientists discovered a gene that plays a crucial part in autoimmunity. This gene, which they named *AIRE*, for "autoimmune regulator," is expressed by cells in the thymus, an organ that makes T cells. *AIRE* ensures that key body proteins are shown to developing T cells, and these encounters teach T cells that the proteins are friends, not foes. Also thanks in part to *AIRE*, T cells that start attacking these friendly proteins are destroyed in the thymus before they can be released into the rest of the body, where they could do damage.

Not surprisingly, people in whom *AIRE* is missing or mutated are more likely to develop certain autoimmune diseases. That is because T cells that should be eliminated are not, and "they end up going out into your body and causing autoimmune disease," Dunn says.

As it turns out, *AIRE*'s activity—and that of other, similar genes—is partially controlled by sex hormones. In a 2016 study, researchers at the Sorbonne in Paris showed that in mice, estrogen and progesterone turn down *AIRE* expression, meaning they cause less of the protein it encodes to be made, whereas testosterone ensures that more AIRE protein is made. The researchers also found that after puberty, women tend to make less AIRE than men do,

perhaps because of the influence of sex hormones. Less AIRE means that more self-reactive T cells can escape from the thymus and cause autoimmune disease.

Yet despite their influential roles, sex hormones cannot be the whole story. Autoimmune diseases, including lupus and multiple sclerosis, sometimes develop in childhood, before hormones such as estrogen and progesterone ramp up during puberty. This means that other processes must be involved. To find them, some researchers are studying a primary difference between men and women that arises well before birth: the presence or absence of a second X chromosome.

#### **X FACTORS**

BIOLOGICAL DOGMA holds that women have two X chromosomes, but one copy is turned off in every cell very early in embryonic development in a process known as X inactivation. The extra X chromosome becomes a dark, misshapen mass that persists silently in each cell lineage. This shutdown ensures that the body does not express more X-linked genes than it should. But in recent years scientists have discovered that X inactivation does not happen the way they thought it did. Studies show that at least 15 percent of the genes on the supposedly inactivated X chromosome are still turned on, which means, essentially, that those genes tell women's bodies to make twice the amount of certain proteins compared with levels in men. In women with lupus, for instance, some genes are active on both X copies, and this higher activity correlates with disease severity: sicker lupus patients have more active

X-linked genes than women with milder disease.

In fact, many X-linked genes have been directly tied to autoimmune disease. One of them is a gene for tolllike receptor 7, or TLR-7, a protein that has been implicated in autoimmune disorders such as lupus, polymyositis, scleroderma and Sjogren's syndrome. TLR-7's job is to recognize pathogens and alert other immune cells to their presence; it also increases the production of inflammatory immune chemicals known as interferons, which can ramp up the autoimmune response. Another gene that is often activated on supposedly inactivated X chromosomes in women is TASL, and it, too, increases interferon production, to the point where women have at least twice as much of the protein, says Hal Scofield, a physician scientist at the University of Oklahoma Health Sciences Center who studies the role of X inactivation in autoimmune disease.

## Autoimmunity may be an unfortunate by-product of the complex immune response women need to bear children.

Recently scientists uncovered something bizarre about X inactivation that also supports its role in autoimmunity. Women's inactive X chromosome is maintained in an especially strange way in T and B cells, which are actively involved in immune responses. In 2019 Montserrat Anguera, a biomedical scientist at the University of Pennsylvania, and her colleagues observed that when young immune cells in female mice mature, the cellular mechanisms in place to cover and inactivate their second X chromosome undergo significant, dynamic changes that could make it easier for X-linked genes in these cells to get turned on when they should be off. It was a "crazy discovery," Anguera says.

No one thought that females' immune cells did anything different with regard to X inactivation than other cells did, but it turns out they do—in ways that could directly shape the risk for autoimmunity. In June 2021 Anguera and her team found that B cells in girls and women with lupus evade the normal cellular mechanisms for X inactivation, which likely allows the cells to make more X-linked proteins than they should.

What happens to people with unusual numbers of X chromosomes also points to their important role in autoimmunity. Men with Klinefelter's syndrome, for instance, have two X chromosomes along with a Y chromosome, and they are 14 times more likely than other men to develop lupus. Similarly, women with trisomy X, who have three X chromosomes, are 2.5 and 2.9 times more likely than other women to develop lupus and Sjogren's syndrome, respectively.

Why do women's bodies have these strange mecha-

#### THE BODY AGAINST ITSELF

nisms that increase the risk of disease? Typically over time evolution eliminates processes that make it harder for species to reproduce and thrive, and X-linked autoimmunity definitely hinders thriving. This paradox suggests to evolutionary biologists that the phenomenon might also provide some significant benefit.

In a 2019 paper in Trends in Genetics, Melissa Wilson, a computational and evolutionary biologist at Arizona State University, and her colleagues outlined their pregnancy compensation hypothesis, which is based in part on evolutionary observations. The evolution of the placenta—an organ that provides oxygen and nutrients to fetuses during pregnancy occurred at the same time mammals evolved sex chromosomes, and it also coincided with the sudden addition of many more genes to the X chromosome. These three developments could all be related.

During pregnancy, women have to tolerate the growth of the fetus, in which half the DNA is foreign because it comes from the father. This outside origin creates cells that the immune system would normally attack. Women also must tolerate the placenta, which is made by the fetus. Perhaps, Wilson says, X-linked genes and incomplete X inactivation evolved as a way for a woman's body to flexibly respond to the strange new immune requirements of pregnancy. During pregnancy, immunity shifts in dynamic ways: Early in pregnancy, certain healthy immune responses increase, which helps the placenta grow new blood vessels; in the middle of pregnancy, immunity decreases. Then immune responses and inflammation increase again in anticipation of labor.

Other observations align with the predictions of the pregnancy compensation hypothesis. For instance, women today spend a much smaller proportion of their lives pregnant than they did hundreds of years ago, which means that women's immune systems are not suppressed as often as they used to be. This could help explain why autoimmune diseases are increasing among women today, as well as why they were less of a burden in the past. Although validating this hypothesis requires much more research, Wilson says it is possible that "placentation and pregnancy are critical in shaping maternal immune systems, which in turn could suggest why we have these sex differences in disease." Put another way, autoimmunity may be an unfortunate by-product of the complex immune response women need to bear children.

#### **GUTTING IT OUT**

NOT EVERYTHING IN THE BODY is determined by genetics far from it. One identical twin may develop an autoimmune disease while the other twin, who shares the same genome, does not. The environment is a big piece of the puzzle. It is still unclear which outside exposures might be most important, but research is starting to implicate microbial infections, chemicals such as endocrine disruptors, smoking, diet, stress and the "good" commensal bacteria that live in the intestines. Some fascinating work in animals points to gut bacteria—collectively referred to as the intestinal microbiome—as a driver of excessive autoimmune disease risk. Jayne Danska, an immunologist and biophysicist at the University of Toronto, has spent much of her career trying to understand the relation between sex and the genetics of autoimmune disease—essentially, whether genes that increase the risk for autoimmunity have varying effects on men versus women. But in 2012 she made a serendipitous discovery that launched her work in a surprising new direction. "It's one of the adages of science that you find the best things that you weren't looking for," she says.

Danska and her team were trying to find risk genes for type I diabetes, an autoimmune disease in which the body attacks the insulin-producing beta cells in the pancreas. They were using a lab-bred type of rodent known as nonobese diabetic (NOD) mice. The mice are good models for the human disease, with one striking exception: men and women are equally likely to develop type I diabetes—it is one of the few autoimmune diseases that does not predominantly affect women—but in NOD mice, the disease is twice as likely to arise in females.

Danska knew that environmental factors sometimes interact with genes, and she had been looking at gut bacteria as a risk factor. She started to wonder whether, in her mice, gut bacteria differences might be related to the skewed diabetes ratio. To find out, she and her colleagues grew a subset of NOD mice in a germ-free environment, devoid of bacteria and viruses, including the commensal bacteria that normally populate the intestines.

That is when Danska made her first surprising discovery. When she looked at how many of the germfree animals developed diabetes as adults, "the sex difference went away completely," she recalls. The males were suddenly just as likely to develop diabetes as the females were. "This was a huge finding that we hadn't expected. I just couldn't believe it was true."

But repeating the experiment showed the same effect. Then more work led to more surprises. The researchers took the bacteria from adult male NOD mice and put them into young female NOD mice that had not yet developed diabetes. The female mice then grew into healthy adults without the disease.

Danska's findings, which were published in 2013 in *Science*, provided the first evidence that "the microbes in the gut can influence female-biased autoimmunity," says Martin Kriegel, a rheumatologist and clinical immunologist at the University of Münster in Germany. It is an important finding, he says, that scientists are still working to understand.

No one knows yet why males' gut microbes seem protective. One thing Danska and her team have determined, though, is that testosterone is crucial: When they drew blood from germ-free NOD mice, they found that the diabetes-prone males had lower levels of circulating testosterone than microbe-laden males usually do. And when female mice were colonized with microbes from males and were apparently protected from disease, they had higher circulating levels of testosterone than females with microbes usually do.

All of this suggests that there is something about the microbes in males that increases testosterone and is protective. When Danska and her colleagues took gut microbes out of male mice and put them into the guts of female mice, then blocked testosterone signaling in their bodies, they were again at an increased risk for type 1 diabetes. The findings align with lupus research in men showing that suppressed testosterone appears to raise their risk of that disorder. (The research also lines up with work in a strain of mice in which females are especially prone to lupus. Removing gut bacteria from these female rodents lowers their risk, scientists at the Medical University of South Carolina reported in 2020 in the *Journal of Immunology*.)

It is unclear how microbes might regulate testosterone, or vice versa. Danska's research suggests that the composition of commensal microbes diverges in male and female mice around puberty, so something seems to happen to the bacteria around that time. This may even explain why there is not much of a sex difference in the prevalence of type 1 diabetes in people; the disease typically develops before puberty, before microbes would have a chance to shape risk based on sex. It could be that the microbes are affected by puberty's sudden influx of sex hormones, but it is almost certainly "a twoway road," Kriegel says—the microbes respond to sex hormones, and the sex hormones respond to microbes.

#### TOWARD A BETTER BALANCE

OF COURSE, MICE ARE NOT PEOPLE. But Danska believes that her findings have significant implications for autoimmune diseases that do skew toward women. Perhaps some gut bacteria in women are critical in the development of autoimmunity. If so, tinkering with gut microbes might enable us to thwart disease.

Danska and Kriegel hope it may be possible to develop targeted microbe-based therapies for women at high risk for autoimmune diseases—therapies that can shape the microbiome in protective ways. Other researchers are looking at ways to tweak sex hormone signaling to temper risk. The more scientists learn about why women are vulnerable, the more chances there may be to intervene before diseases develop.

Given that X chromosomes, female sex hormones and female gut bacteria all appear to increase the risk for autoimmunity, it might seem as though biology is somehow conspiring against the female sex. But this autoimmune burden can be seen in another way, too: as a reflection of the importance of women for the survival of our species. "Females have to do all kinds of absolutely remarkable things from an immunological perspective that males just aren't called on to do," Danska says. Autoimmunity may be the cost women's bodies pay for their dynamism—but it is at least a burden that science might eventually be able to eliminate.

# DAMAGE CONTROL

Instead of shutting down your body's entire defense system to stop autoimmune disease, scientists are trying more targeted therapies

By Marla Broadfoot

**WHEN MAGDELENE QUINTERO WAS 14 YEARS OLD** her mouth filled with painful ulcers that made eating and drinking unbearable. Her normally tawny skin flamed crimson red across the bridge of her nose and cheeks. The tips of her fingers burst into open sores, as if she had dipped them in acid. She spiked fevers, developed headaches, lost weight and was always tired.

It took a year of visits to various doctors for Quintero to learn that she had lupus, a life-threatening and chronic autoimmune condition that can cause pain, inflammation and damage to any part of the body. It took another two years for her rheumatologist—the only one at the Indian Health Service serving her community of Jones, Okla.—to find medications in the right doses to bring her disease under control.

Quintero, who is now 25, considers herself lucky. Lupus also struck her younger sister, Isabel Hernandez, and has taken a more terrifying form. It began with constant nosebleeds. By the time Isabel was diagnosed, at age 17, her lungs were hemorrhaging blood. She spent 88 days on a ventilator before relearning how to walk, talk and eat. Today, at age 21, her kidneys are failing. Every day she spends hours having her blood filtered by a dialysis machine, waiting for a transplant.

"It is so heartbreaking," says Quintero, who just completed her master's in biomedical science at Oklahoma State University. She worries whether her future holds a similar fate. "But I also feel thankful for my own health and fortunate that the medications that I'm on are doing their job," she says.

Lupus has been called "the great imitator" because its symptoms—including fever, fatigue, joint pain, rashes, headaches, memory problems and organ failure—often mimic many other autoimmune conditions. Those symptoms reveal the many ways our bodies can turn against us as a wayward immune system,



intended to defend us, attacks our own healthy cells.

Traditionally therapies for lupus and other autoimmune diseases have relied on decades-old bluntforce strategies that essentially bludgeon a badly behaving immune system into submission. But these approaches cause collateral damage that sometimes can be worse than the disease itself. Foremost among these treatments are steroids, medications that have unparalleled ability to dampen the entire immune response but in doing so can leave patients vulnerable to dangerous and even deadly infections.

Recent research is fueling a shift in the way autoimmune diseases are treated, based on a more nuanced approach. Distributed throughout the body, the human immune system is a dizzyingly complex network of many different types of cells, organs, tissues and proteins, which communicate with one another through a wide variety of chemical messages. Modern technology, such as gene assays and molecular engineering, is enabling scientists to target individual parts of this network, identifying new targets for treating autoimmunity with much more precision. Some of these new therapies aim to interfere with autoantibodies, rogue antibodies that take aim at healthy cells. Others work by hobbling key chemical messengers that are passed among immune cells.

But these treatments do not work for all patients, and many diseases prove stubbornly resistant, which is why many people with autoimmune problems are drawn to approaches outside of mainstream medicine. Among scientists, the successes and failures are creating a new appreciation for the precarious balance our body maintains between protection and pathology. Half of the immune system-such as cytotoxic or "killer" T cells and antibody-producing B cells-is designed to fight. The other half-mainly regulatory T cells-is designed to keep the peace. When the former goes rogue and the latter fails to keep it in check, autoimmune disease ensues. "All of us, every one of us, has the potential to develop autoimmunity," says V. Michael Holers, a rheumatologist at the University of Colorado School of Medicine, "because our immune system develops with this kind of yin and yang."

#### EARLY WARNINGS

FOR DECADES STEROIDS such as prednisone and dexamethasone have been the mainstay of treatment for patients with autoimmune conditions. These potent anti-inflammatory drugs indiscriminately shut down the production of cytokines, the key messengers that rouse our vast army of immune cells to fight a perceived threat. Although steroids can be extremely effective at reducing the signs and symptoms of autoimmunity, they exact a price so high that some people liken it to making a deal with the devil. Many patients are stuck taking these medications, orally or by injection, for much of their lives, And steroids can create a whole host of other problems, such as cataracts, mood swings, weight gain, trouble sleeping, thinning bones, high blood pressure, high blood glucose and increased risk of infection.

Furthering the problem is that by the time most patients with autoimmune diseases seek treatment, a lot of damage is already done. Autoantibodies have been stealthily coursing through the blood and tissues for months or years, leading to ongoing assaults on a targeted organ—pancreas, kidneys, joints, gut, skin, hair follicles, brain, spinal cord. As a result, treatments such as steroids are defensive in nature, focused on keeping the disease from getting worse or damping down flare-ups.

Now there is a big push among physician-scientists to go on the offense, correcting autoimmune imbalances before they produce their most devastating consequences. Researchers hope focusing on early treatment and prevention could lower the burden of autoimmune disease, much as treating people at high risk of cardiovascular disease with blood pressure medications and cholesterol-lowering drugs has reduced the prevalence of heart attacks and strokes. Several trials investigating this idea are underway for type 1 diabetes, <u>rheumatoid arthritis</u>, <u>lupus</u> and multiple sclerosis.

There are already some <u>early successes</u>. In <u>one</u> <u>study</u>, researchers recruited 76 people with a family history of type 1 diabetes, who also had abnormal blood sugar levels and at least two diabetes-related autoantibodies. Half the participants received an experimental drug, a monoclonal antibody called teplizumab that interferes with the immune system assault on insulin-producing beta cells in the pancreas. The other half received a placebo. More than five years later only 50 percent of people treated with a two-week course of the drug have developed the disease, compared with 78 percent of those who received a placebo. The researchers estimate that in those who did develop the disease, early treatment delayed onset by nearly three years.

"That's a big deal," says Carla Greenbaum, an endocrinologist who chairs the TrialNet Pathway to Prevention, the clinical trial network leading the study and others like it. "This is a disease that affects every moment of every day of your life, so any time without it is clinically important." By fine-tuning this approach, scientists hope they can extend the diseasefree period and perhaps discover ways to block the destruction entirely. And Greenbaum thinks the idea should work for other ailments. "We are really the template for all these other autoimmune diseases that are now also discovering these long preclinical periods," she says.

Multiple sclerosis (MS) is another autoimmune condition where early detection is crucial. It affects the central nervous system, and a telltale sign is white matter lesions, spots on the brain and spinal cord where the disease has stripped the protective covering off the nerves. Over the past decade researchers



Marla Broadfoot is a freelance science writer who lives in Wendell, N.C. She has a Ph.D. in genetics and molecular biology.



## An Immune Signal Blockade against Psoriasis

In psoriasis, skin cells run amok. They grow and proliferate much faster than normal, piling up in red, itchy, scaly, inflamed lesions that can cover large areas of the body. This uncontrolled growth is, essentially, a response to an immune system assault on the skin. A protein called tumor necrosis factor (TNF) activates immune cells against the organ. Anti-TNF drugs that block this protein, such as adalimumab, have proved quite effective. But in a few patients, they trigger a new round of the disease, called paradoxical psoriasis.

#### **Classical Psoriasis**

The initial cause is poorly understood but can be genetic or from some environmental contact. Whatever the reason dendritic cells move into skin layers and evolve into more specialized forms that release TNF. The TNF signal stimulates several types of T cells to start massing in the skin. These in turn release other signals called interleukins, which push skin cells into a hypergrowth state that leads to lesions. The disease is chronic, waning and then appearing again.



#### Breaking the Cycle

Anti-TNF drugs stop this cascade of events early on. Medications such as adalimumab and etanercept block TNF from being made and released by dendritic cells. That blockade prevents the molecule from stimulating T cells. With the inflammatory cycle interrupted, lesions go away or are greatly reduced.

# Anti-TNF drug

#### A Paradoxical Effect

In 2 to 5 percent of patients, anti-TNF drugs can lead to new psoriatic lesions. This paradoxical psoriasis may arise because of the TNF blockade at dendritic cells. Those cells produce another inflammatory signal, called interferon alpha, as well as TNF. Stopping TNF appears to shift the cells into making more interferon, which triggers its own inflammatory cascade in the skin, through an unknown intermediate factor.



have found these abnormalities in hundreds of people with no outward symptoms of MS, who only came to their notice after an unrelated concussion or migraine landed them in a brain-scanning machine. David Hafler, a neurologist at the Yale School of Medicine, believes these cases, known as radiologically isolated syndrome (RIS), could represent the earliestknown stage of MS. He and his colleagues have launched a multicenter study with biotech firm Genentech to treat RIS with ocrelizumab, a drug commonly used to treat later stages of MS. And Hafler would like to find other biological hallmarks that would allow intervention even before the lesions appear. "The ultimate treatment for autoimmunity is to identify [people who are at high risk] and treat them before the disease really begins," he says.

#### SHARPENING THE TARGET

DRUGS SUCH AS MONOCLONAL ANTIBODIES offer the important advantage of being able to go after specific immune system elements that cause a given disease while—unlike steroids—leaving the rest of the

immune system functional. But this new targeted approach comes with its share of difficulties. Although it has expanded the therapeutic options for patients, it has also fizzled or even backfired in some cases, making patients worse. Harmony within the immune system, it turns out, is not easy to achieve.

Several targeted therapies focus on a particularly powerful cytokine called tumor necrosis factor, or TNF. It goes haywire in many autoimmune diseases, setting off waves of damaging inflammation. Monoclonal antibody drugs that block its

action are widely used in the treatment of <u>rheuma-</u>toid arthritis, inflammatory bowel disease and psoriasis. Yet clinical trials in multiple sclerosis showed that TNF inhibitors <u>actually exacerbate</u> the disease. "It is one of the great curiosities of autoimmunity," Hafler says. What's more, targeted therapies that suppress autoimmune disease in one patient <u>have been</u> shown to trigger that same disease in other patients.

The only new medication <u>approved to treat lupus</u> <u>in almost 60 years</u>, belimumab, is a targeted therapy. It blocks a cytokine called B lymphocyte stimulator, or BLyS (pronounced "bliss"), that keeps autoreactive B cells going, extending an autoimmune reaction. Although the treatment has <u>helped</u> many patients, a significant number of them get no benefit, suggesting that different molecular mechanisms may be at play in different people, according to Judith James, a rheumatologist at the Oklahoma Medical Research Foundation.

Luckily, technological advances are enabling researchers to dissect differences—among patients and between diseases—at the genetic level, illuminating patterns that could explain past failures and point the way to future successes. For example, attempts to treat alopecia areata, an autoimmune assault on hair follicles that causes large clumps of hair to fall out, have typically repurposed drugs from the seemingly related skin conditions psoriasis and atopic dermatitis. None of them have worked. When Angela Christiano, a geneticist at Columbia University who has alopecia, completed a study on the genetic basis of the disorder, she suddenly realized why. "You can read it like a road map," she says. "There's a reason they failed: we don't share any genetic pathways with either of those two diseases." Christiano has learned the illness has more in common with rheumatoid arthritis, celiac disease and type 1 diabetes than it does with skin ailments. "I think it is a great example of how genetics can completely realign your thinking," Christiano says.

One of the genes she identified, ULBP3, acts as a distress signal that damaged cells use to tell killer T cells to take them out. Normally the gene turns on only if a cell is cancerous, infected or dying. But in hair follicles affected by alopecia, the gene is stuck in

### What's worse, targeted therapies that suppress autoimmune disease in one patient can trigger the same disease in other patients.

the on position, constantly signaling for the cells' own demise. That signal involves the production of a type of cytokine called a Janus kinase, or JAK. Christiano showed that a class of drugs known as JAK inhibitors, often used to disrupt autoimmune signaling in rheumatoid arthritis, could thwart the killer T cells' attack on hair follicles. Within a few months of treatment, patients who were once bald regrew full heads of hair. When Christiano was diagnosed with alopecia early in her career, no one could tell her whether she would get better or worse, and the only treatments available involved injecting steroids into her scalp. Now her work has led to multiple advanced trials of JAK inhibitors for the illness.

Five JAK inhibitors are already approved for other autoimmune and inflammatory diseases, and <u>numerous others</u> are in the pipeline. Still, there are no guaranteed breakthroughs, and even the latest targeted treatments could have off-target effects. For example, this past February the <u>U.S. Food and Drug</u> <u>Administration warned</u> of an increased risk of heartrelated problems and cancer associated with a JAK inhibitor being used to treat rheumatoid arthritis.



"That's the reality of autoimmune disease therapy right now, so I always say it's worth searching for the lesser of all the evils," says Aimee Payne, a dermatologist at the University of Pennsylvania who is developing gene therapy for a rare autoimmune skin disorder called pemphigus vulgaris. People with this disease have autoantibodies that attack a protein called desmoglein-3 (DSG3), which normally glues skin cells together. When that protein is destroyed, it causes painful blisters to form all over the body, sometimes sending patients into burn units to be treated for lifethreatening infections.

Payne has devised a targeted treatment, tested in mice, that could eliminate the specific population of B cells producing these autoantibodies but leave other B cells alone. The immune system has billions of B cells, which come in many different kinds. The vast majority of them produce antibodies needed to fight viruses and bacteria. Luckily, the anti-DSG3 B cells

For Magdalene Quintero and her sister, their lives feel shaped by their illnesses. Her sister takes 19 medications to manage her lupus symptoms.

> are easy to find because they have a highly distinctive marker—basically a version of the anti-DSG3 autoantibody stuck on their surfaces. "In some ways, these B cells are terrible criminals because they're declaring what they're going to attack before they ever attack it," Payne says.

> To get rid of these disease-causing cells, Payne used a technique invented by her colleague Michael Milone that has successfully eliminated malignant B cells in certain blood cancers. The strategy, called <u>CAR T cell therapy</u>, uses genetically engineered killer T cells that have a kind of homing beacon known as a chimeric antigen receptor (CAR). It steers the T cells to other specific cell types in a search-anddestroy mission. In adapting the technique to treat autoimmune disease, the team gave T cells a beacon derived from bits of the anti-DSG3 autoantibody, which leads the killers straight to anti-DSG3 B cells.

> When the researchers infused the engineered T cells into a mouse model of pemphigus vulgaris, their blisters disappeared. Payne founded a biotech start-up to move the treatment forward to clinical trials, which are currently ongoing. Because the treatment is made of living cells that can replicate and remember their target, she thinks a single infusion

could last decades. "My dream is the one-and-done," she says. "A precision cure of disease."

Other researchers are using a related technique to tip the balance on the other side of the autoimmunity equation. Rather than mobilizing killer T cells, they are amplifying the calming power of regulatory T cells to suppress the overactive immune system. Still in early stages, the approach has shown promise in animal models of ulcerative colitis, multiple sclerosis and rheumatoid arthritis.

#### **BEYOND DRUGS**

ALTHOUGH PHARMACEUTICALS make up the bulk of the growing armamentarium against autoimmune diseases, some of the most intriguing additions explore alternative ways to restore balance in the body.

Many of our basic bodily functions—heart rate, blood pressure, digestion, respiratory rate and sexual arousal—are governed by two opposing forces. The

> sympathetic nervous system initiates the energetic "fight or flight" response, whereas the parasympathetic nervous system halts this activity and prepares the body to "rest and digest." Our ability to shift from one state to the other depends largely on the vagus nerve, a bundle of 100,000 nerve fibers that runs from the brain stem down to the diaphragm before shooting out its tendrils to the heart, gut and other organs. Some research suggests this influential piece of anatomy starts to malfunction before people develop autoimmune diseases. "It would be like the brake failing on your car when you are going down

the mountain," says Kevin Tracey, a neurosurgeon at the Feinstein Institutes for Medical Research, based in Manhasset, N.Y.

Tracey has shown that stimulating the vagus nerve with tiny jolts of electricity can reset the nervous system and actually helps to calm overactive immune cells. He and other researchers have traced the way signals from a small electrical device implanted in the neck travel down the vagus nerve all the way to the spleen, where they shut down the production of TNF and other inflammatory molecules. Initial clinical trials suggest a small zap to the vagus nerve could reduce the severity of rheumatoid arthritis and Crohn's disease, even when delivered through a less invasive device that stimulates a branch of the vagus near the ear when it is pressed against the skin. A company Tracey co-founded recently launched a multicenter randomized, controlled trial of the implantable stimulator. (Similar vagus nerve stimulators are already approved by the FDA for treating epilepsy and depression.)

Another unconventional method looks to correct immune system imbalance with a decidedly lowertech intervention: fecal transplants. The idea of transplanting fecal matter from one person to another originated in ancient Chinese medicine, when a stool slurry called "yellow soup" was used to treat severe food poisoning and diarrhea. In modern times, fecal transplants have become an <u>accepted therapy</u> for a dangerous gut infection caused by *Clostridium difficile*, or *C. diff*.

A few years ago gastroenterologist Jessica Allegretti and other researchers noticed that in patients with C. diff problems, a fecal transplant not only resolved the infection but also helped concurrent cases of inflammatory bowel disease (IBD). The severe digestive distress of IBD stems from inflammation, and some scientists think an autoimmune reaction is involved, although the notion is a matter of some debate. Still, the results "got the community excited about this potential," says Allegretti, who directs the fecal microbiota transplant program at Brigham and Women's Hospital in Boston. Plus, the finding makes sense. There are distinct differences in the populations of gut microorganisms-known as the microbiome-between healthy people and those with ulcerative colitis, a subtype of IBD that does appear to involve autoimmunity. These changes most likely reflect an imbalanced state where pro-inflammatory microbes dominate over anti-inflammatory ones.

Four randomized clinical trials have tested fecal transplants in ulcerative colitis. In all, about a third of patients went into remission, rates similar to those seen with immunosuppressive medications. More studies and clinical trials of the transplants are underway for rheumatoid arthritis, lupus, multiple sclerosis and alopecia areata, further testing the limits of this odd healing modality.

#### OUT OF THE MAINSTREAM

FECAL TRANSPLANTS are not FDA-approved for any medical condition, so don't expect them to emerge as autoimmune treatments anytime soon. Allegretti says the slow track is the right one. "I think there's a misconception that because this is 'natural' it is somehow safer than regular drugs, and I don't think that's true at all," she says. "We are only just starting to understand the long-term consequences of these therapies, and I think they deserve the respect of being studied appropriately in the way we study all drugs." The scientific literature is littered with accounts of home fecal transplants gone wrong, such as the case of a man with ulcerative colitis who attempted the procedure with stool from his infant son and his wife and landed in the hospital with a cytomegalovirus infection.

Yet many people with autoimmune disorders, frustrated with the lack of conventional therapies and impatient with doctors who offer little help and less hope, are willing to take their health into their own hands, using approaches within and outside mainstream medicine to manage their autoimmune symptoms. Joe Person, for instance, is a 37-year-old based in Washington, D.C., who has lupus. When he was diagnosed in his senior year in college, he drafted a decision tree of the possible tests, complications, outcomes and medications. At his first appointment with his rheumatologist, he demanded to be put on the antimalarial drug hydroxychloroquine, which has helped ease lupus symptoms and is the basis of <u>early</u> treatment and prevention trials.

Fifteen years later Person credits that early action with keeping the illness at bay, although he does have physical fatigue and feels his brain works slowly at times. "The takeaway I've gotten from rheumatologists is just sit there and wait for us to invent the pharmaceutical that works," Person says. "Unfortunately, sitting around and doing nothing is antithetical to every survival instinct in my body. I want to do as much as I can proactively, if nothing else to just feel like I'm exploring all options to stay ahead of this." He went into remission after switching to a raw vegan diet, only to have his disease flare when he developed an allergy to raw vegetables. And he installed a tanning bed in his basement to test out a theory that certain wavelengths of ultraviolet light can relieve lupus symptoms, although he has yet to see any positive results.

Some scientists are open to alternatives. Tracey says strategies such as acupuncture could, in theory, reduce stress and inflammation by activating certain branches of the nervous system, although he adds that such approaches sometimes make it "hard to prove cause and effect." To stimulate a healthy gut microbiome without an illegal stool infusion, Allegretti recommends trying fiber-rich foods and plantbased diets. And James advises people with autoimmune problems to avoid smoking and get plenty of sleep, which help the body reduce inflammation: basically "all those things your mother told you," she says.

For Magdelene Quintero and her sister, their lives feel shaped by their illnesses. Her sister currently takes 19 medications to manage her lupus symptoms. Quintero needs to take only two drugs right now and has spent the past few years working under the mentorship of James at the Oklahoma medical foundation, first in the lab and now in the clinic, trying to improve treatments for the disease. She remembers how her great aunt, who also had lupus, spent the last years of her life in a wheelchair, her bones ravaged by steroids. "Back then they didn't have the treatments we have," she says. Quintero is now trying to get into a medical school or a physician assistant program, determined to put herself in a position to alter the course of the disease that has tormented her family.

#### FROM OUR ARCHIVES

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#### THE BODY AGAINST ITSELF

PLANETARY SCIENCE

# Lifting the Venus Curse

Three new space missions are set to reinvigorate studies of Earth's long-neglected neighbor, potentially revealing how and why it became our planet's evil twin

By Robin George Andrews

GLOBAL VIEW of the northern hemisphere of Venus, based on radar data from NASA's Magellan orbiter, which peered underneath the planet's veil of swirling clouds from 1990 to 1994.





IKE MANY KIDS, SUE SMREKAR DREAMED THAT SHE WOULD ONE DAY voyage into space. But instead of becoming an astronaut, she ended up as a planetary geophysicist at NASA's Jet Propulsion Laboratory, where she worked on robotic explorers of other worlds. In some sense, her interplanetary destiny seemed preordained even before she was born: her father hails from a rural community in Pennsylvania named Venus.

Fittingly, the very first mission Smrekar worked on was NASA's Venus orbiter Magellan. Launched in 1989, Magellan was equipped with a radar system that peered underneath the planet's thick clouds to map its entire surface for the first time. Smrekar recalls watching the initial radar images come in, revealing a bizarre world covered in few craters, a surfeit of volcanoes and rolling plains of frozen lava. Magellan's data sharpened what has become one of the greatest unanswered questions in planetary science: What transformed Venus—the second planet from the sun, and a near twin of Earth in size and composition—into such an unearthly and apocalyptic state? Why did these two similar, neighboring planets have such staggeringly divergent stories?

Magellan's explorations ended in 1994, marking the last time NASA sent a dedicated mission to Venus. Just as Smrekar and her peers were beginning to grapple with the planet's freshly unveiled mysteries, sensational claims of life on Mars captured the public imagination. Today, a quarter of a century later, much of the global planetary science community still remains wrapped up in the so far fruitless search for Martian life. All the while, Venus—an acidic, superhot, arid and presumably lifeless wasteland—has languished in the shadows.

A turning point came in June, when NASA announced its latest choices for new interplanetary missions as part of its Discovery exploration program. The space agency had considered four missions: one to visit a moon of Neptune, another to rendezvous with a Jovian moon, and two, named DAVINCI+ and VERITAS, each independently aiming for a return to Venus.

"We are all desperately hoping the 'Venus curse' will be lifted," Smrekar, who is the principal investigator of VERITAS, said before the announcement. She and her colleagues hoped NASA would maybe greenlight a single Venus mission. Instead, to Smrekar's great sur-





#### Robin George Andrews

is a volcanologist and science writer based in London. His upcoming book Super Volcanoes: What They Reveal about Earth and the Worlds Beyond will be released in November 2021. prise, the space agency selected both VERITAS and DAVINCI+ for flight. The two complementary missions are designed to study the planet's bygone habitability. For the first time in three decades, NASA had chosen to go back to Venus—not once but twice.

The good news kept coming. Just a week after NASA's eagerly anticipated announcement, the European Space Agency declared that EnVision, an orbiter that would carry out scientific surveys of select parts of the planet, would be joining the party. A Venusian renaissance had begun.

#### TURNING THEIR BACK ON THE DEVIL

EARLIER THIS YEAR it was not at all clear Venus was set for a comeback. History seemed to suggest that its time in the limelight had already come and gone. During the 1960s and 1970s the planet amounted to an interplanetary front in the cold war as the U.S. and the Soviet Union each sent multiple missions there. But with each foray, it became clearer that the planet was nightmarishly ill suited for future human exploration.

Venus's thick, suffocating atmosphere is about 95 percent carbon dioxide. Its cloud layers are packed with sulfuric acid—enough to chew through skin, bone and metal in moments. If you stood on the surface, you would escape the corrosive acid rain, but only because rain down there is impossible: the ground bakes at more than 900 degrees Fahrenheit, hot enough to broil any astronaut or robot. If you were miraculously heatresistant, you would still have to contend with a surface pressure that is about 90 times that on Earth, making the experience like being a mile or more underwater. No matter which part of the planet you visited, you would die a quick but agonizing death.

Since the end of Magellan, Venus has been rather lonely. Europe's Venus Express spacecraft orbited it from 2006 to 2014. Japan's Akatsuki orbiter, which successfully entered orbit in 2015, remains there to this day, studying the Venusian atmosphere and hunting for its <u>elusive lightning</u>. If it were up to Paul Byrne, a planetary scientist at North Carolina State University and unabashed Venus zealot, there would be plenty of spacecraft flying around or landing there today. Instead, he says, Venus is a planet nobody has cared about for 30 years.

The turning point arrived in 1996, when a cadre of reputable scientists <u>published a paper</u> announcing they had found microscopic fossils in a Martian meteorite named ALH 84001. President Bill Clinton gave a speech on the South Lawn of the White House about the discovery, <u>telling the world</u> that "the American space program will put its full intellectual power and technological prowess behind the search for further evidence of life on Mars."

The discovery did not really pan out—further studies, reported with considerably less fanfare, suggested the "microfossils" could just as well have been entirely abiotic mineral formations. But the dream of finding life proved too enchanting to dismiss. Mission after mission was sent to Mars, each building off the SURFACE IMAGES, such as this panorama from the Soviet Union's Venera 14 lander in 1982, revealed little more than bleak landscapes of volcanic rocks under crushing, corrosive skies.



successes of its predecessors and strengthening the world's allure as a premiere destination for planetary exploration. "I don't want to say that Mars has an inviolable hold over the public," Byrne says, "but it kind of does." He regularly quips that he wishes to blow up Mars, Death-Star-at-Alderaan-style, so everyone would be forced to reconsider Venus instead. He is only half-joking.

Even if Mars was wiped from the heavens, however, the problem remains that Venus is a prolific destroyer of droids. Orbiters survive just fine, but studying the surface requires excellent radar capable of penetrating the dense, overlying clouds. Conversely, with a thinner and transparent atmosphere and a cold, dry surface plagued only occasionally by global dust storms, "Mars is the ideal place to do a lot of planetary surface exploration," Byrne says. But is Mars more valuable to science than Venus? "I do not remotely think so."

One strike against Mars is its size. At only one-sixth the volume of Earth and just one-tenth of our planet's mass, it is not really "Earth-like" at all—at least, not compared with Venus, which by those metrics is practically our planetary twin. There is, of course, the problem of its spacecraft-slaying environment. Heatresistant electronics that can withstand the Venusian <u>inferno</u> are being developed for in situ exploration, but nothing yet exists that could give a surface mission more than a couple of hours of survivability. Even so, Byrne says, Venus's bulk similarity to our own planet makes it a better option for learning about what makes—and breaks—Earth-like worlds. "Venus is going to be hard," Byrne says. "But that's not a reason not to do it."

#### THE TRUTH SEEKER, THE ARTIST AND THE VISIONARY

NASA'S DISCOVERY-CLASS program of interplanetary missions is renowned for being relatively inexpensive (with a circa \$600-million-per-project price tag) but also profoundly heartbreaking. Typically teams of scientists and engineers work together for several years to develop richly detailed proposals that are then judged by senior agency officials. The selection process is as competitive as it is ruthless, producing <u>dozens of</u> <u>losers</u> for every winner—and dictating which swaths of the solar system are destined to be explored by the U.S. VERITAS and DAVINCI+ did not win their coveted Discovery slots through sentimental appeals. Each is a technological tour de force, designed and honed to answer planetary scientists' most burning questions about our inhospitable neighbor.

VERITAS (Latin for "truth," and short for the Venus Emissivity, Radio Science, InSAR, Topography, and Spectroscopy mission) will be in many respects a sequel to Magellan—an orbiter with a state-of-the-art radar system to generate an unprecedentedly detailed map of the planet. It would replace Magellan's old maps with glorious 3-D topographic charts packed with detail, from individual volcanoes and their lavalicked landscapes to fault systems streaking through the land like scars.

VERITAS will also see in infrared, distinguishing specific minerals on the surface by their characteristic thermal glow. But the orbiter's work will not just be skin-deep. Another of its instruments will peer into the planet's guts, mapping the varying strength of its gravitational field to visualize the layer-cake structure of the Venusian interior. This mission, Smrekar says, will finally give scientists a high-fidelity view of Venus akin to the richly detailed data sets they have long possessed for the moon and Mars.

DAVINCI+ (Deep Atmosphere Venus Investigation of Noble Gases, Chemistry, and Imaging Plus) is a mission named after the Renaissance-era master of everything. Its leader is Jim Garvin, chief scientist of NASA's Goddard Space Flight Center, who like Smrekar loves Venus and self-effacingly shirks any limelight: when asked to share some fun facts about himself, Garvin <u>once said</u> that he is "probably too boring for words."

That is not true of his team's mission concept, a bombastic endeavor that would drop an American probe into the Venusian maw for the first time since NASA's Pioneer Venus mission of 1978. The probe would tumble through the atmosphere, gulping and analyzing its constituent chemicals during its intentionally deadly journey. As the clouds parted and the surface approached, it would use its cameras to take the most high-resolution images of the planet's mountainous and geologically complex Alpha Regio region to date, while infrared detectors would parse out the terrain's mineralogy. The probe would expire shortly after landing but not before beaming back the data gathered during its parachute-slowed plunge.

Its descent probe may be the main event, but DAVINCI+ has an orbiter component, too. It will lack a sophisticated radar system, but its cameras will peruse the atmosphere and the surface in ultraviolet and infrared, augmenting the data gathered by VERITAS. The mission's driving goal is to resolve, once and for all, whether Venus's climate has always been so catastrophically awful. "DAVINCI+ was designed to attack this question," Garvin says.

The third member of the Venusian cavalcade, the European Space Agency's EnVision mission, will use its radar systems to map the surface while its ultraviolet and infrared spectrometers analyze the composition of the planet's rocks and atmosphere. It will also carry a radio science experiment that will detect minute variation in the planet's gravitational field, generating a picture of Venus's innards. Like VERITAS, some of EnVision's surveys would be global in nature. But its strength will come from its ability to rapidly target specific sites of interest in response to scientists' evolving needs.

"I was always captivated by Venus," says <u>Richard</u> <u>Ghail</u>, a planetary geologist at the Royal Holloway University of London, who serves as EnVision's lead scientist. Like his American counterparts, he, too, desired to discover how "Earth-size planets work under different conditions." Where better to explore, then, than our accursed neighbor?

#### THE MANY DEATHS OF VENUS

THE MOST TELLING CLUE WE possess about Venus's cataclysmic history is the elevated heavy water content of its atmosphere-a finding that dates to the probe deployed in 1978 by NASA's Pioneer mission. Heavy water is a rarer version of H<sub>2</sub>O in which ordinary hydrogen has been replaced with deuterium-that is, with hydrogen atoms bearing an extra neutron. Because it is heavier than ordinary water, it is harder to boil off into space. Venus's overabundance of heavy water is thought to be the dregs from an ocean's worth of normal water that graced the planet eons ago. To learn what really happened to Venus, we need to find out what happened to all that water. The planet, Garvin says, should not be thought of as a hellish pandemonium but "as an ocean world that lost its oceans." How did it lose them?

Lack of data means that this question, like so many others about Venus, lacks a definitive answer. That hasn't stopped scientists from imagining what those answers might be and how missions such as VERITAS and DAVINCI+ could confirm them. One such dreamer is <u>Michael Way</u>, a research scientist at NASA's Goddard Institute for Space Studies. In recent years he and his colleagues have peered into the <u>possible pasts</u> of Venus using detailed computer simulations.

According to Way's models, the slow but steady brightening of the newborn sun may have doomed Venus in its infancy, cooking the young planet so severely that any water could exist only as steam. All that water vapor, a potent greenhouse gas, would quickly raise the temperature, compounded by the effects of carbon dioxide, another greenhouse gas that bubbled from what was then a planetwide magma ocean. If the sun was the villain in Venus's climate history, then the planet was "dead from day one," Way says.

If the young sun's early brightening was not the culprit, then another antagonist could be to blame. Way suspects volcanoes. Like stars, they influence everything that happens on the surface of a planet, from the evolution of a world's atmosphere to the fate of its oceans.

Several times in Earth's past, continent-size eruptions of lava vented enormous volumes of greenhouse gases into the sky for hundreds of thousands or even millions of years, either <u>contributing to</u> or <u>causing</u> mass extinctions. On Earth, these monster eruptions have (so far) occurred in isolation, each registering as a disruptive blip in our planet's geologic history. But if a few happened on Venus simultaneously, they could have released so much carbon dioxide that the oceans would begin to evaporate, filling the atmosphere with heattrapping water vapor and kicking off an inescapable feedback cycle that would have scorched the world.

So, whodunnit? DAVINCI+ can help determine when Venus lost its water, thanks to its ability to sniff

## Venus's Atmosphere, Unveiled

The inhospitable conditions at Venus are the result of extreme climate change—a world-burning surge of heat-trapping greenhouse gases likely unleashed during huge volcanic eruptions eons ago. But unlike the rest of the planet, one specific region of the Venusian atmosphere is curiously clement, perhaps even suitable for life. After decades of missions there, scientists still have many open questions about Venus and its past and present habitability. And the only way to get answers is to go back.





THREE MISSIONS are set to study Venus in the 2030s, at last putting the mysterious world back in the planetary science spotlight. NASA's VERITAS spacecraft (*lower left*) will create the best yet radar and infrared maps of Venus while studying the planet's interior; the space agency's DAVINCI+ mission will observe the planet in ultraviolet and infrared while delivering an atmospheric probe (*right*). ESA's EnVision spacecraft (*top left*) will scrutinize Venus with radar, infrared and ultraviolet instruments and will excel at rapid, responsive investigations of specific surface targets.

out the noble gases in its atmosphere, including, among others, xenon, argon and helium. Each gas has multiple versions of itself—some heavier, some lighter—and scientists know where each version comes from. For example, helium 3 comes from a planet's deep interior, but helium 4, a heavier isotope, is born from radioactive decay in the crust above. Like this pair, several versions of other noble gases reside in a planet's atmosphere. More important, noble gases do not react with other geophysically relevant compounds, including carbon dioxide and water. That means they are effectively postmarked messages, revealing not only their planetary origins but also when and how they were delivered to Venus's skies.

Measurements of such gases could indicate that

Venus was bone-dry from the very beginning. If so, that would imply the youthful sun was our worldscorching culprit. If, however, the sun did not brighten quite so speedily in its youth, then Venus's carbon dioxide-belching magma ocean should have frozen over, allowing liquid water to form and pool on the surface. Venus could have been a tropical world of rivers, lakes, seas and oceans. <u>Martha Gilmore</u>, a planetary geologist at Wesleyan University, who is part of both the DAVINCI+ and VERITAS teams, brims with excitement over the notion. "There's no reason, according to what we know about the planets, that Venus was not habitable at its onset," she says.

Right now the consensus odds are on mega eruptions exterminating Venus's oceans. This could have happened early on, but perhaps DAVINCI+ will reveal that Venus was a water world well into its planetary adolescence. "I think *the* question about Venus is: Were there oceans for billions of years on the surface?" says <u>Joseph O'Rourke</u>, a planetary scientist at Arizona State University. It could be that for much of its lifetime, Venus, too, was another pale blue dot orbiting the sun—a paradise lost.

If Venus was indeed a water world for eons, then it also must have had plate tectonics. This mountainmaking, basin-carving, volcano-building process also serves as a planetary thermostat. Atmospheric carbon dioxide dissolves in the oceans, where it gets trapped in tectonic plates that dive into the hot mantle undergirding the crust. Eventually that greenhouse gas will be liberated again, flowing to the surface and then the sky in an assortment of volcanic eruptions fueled by deep-seated magma. Much of a terrestrial planet's longterm climatic stability comes down to this carbon-cycling process. On Venus, both EnVision's and VERITAS's radar systems could spy ancient or active faulting, signs that this habitability-defining cycle once took place.

Both missions will also examine the tesserae, odd continentlike plateaus that dot the Venusian surface. Most of the planet is covered in lava flows (which must have erupted long after the epic climate-changing volcanism that may have boiled off its water). Rising high above these lava flows, the tesserae are thought to represent the oldest rocks on Venus. "They could be half a billion years old, they could be four billion years old we don't know," Gilmore says.

Not only do scientists not know how old the tesserae are, they do not know *what* they are. If the tesserae truly are continental rocks akin to those on Earth, it would have taken a lot of water to make them. This would be concrete evidence that Venus was once a water world. "That would blow people's minds," O'Rourke says. If they contain layers, as Byrne and his colleagues have recently <u>suggested</u>, they may be sedimentary features, preserving evidence of ancient rivers and lakes. Alternatively they may be pancakelike layers of lava, perhaps remnants of the ancient global volcanism that destroyed the sky.

DAVINCI+'s probe, O'Rourke says, would get an extremely close-up and detailed view of just one tessera. "We don't even know that all the tesserae are the same, so just picking one is a bit of a gamble," he says. "But DAVINCI+ will get superb, human-scale geology images that you just can't really do from orbit." On the other hand, VERITAS would provide a map of every tessera, though with less detail. Meanwhile EnVision would pick several tesserae to carefully study from on high.

VERITAS's dynamic map of Venus, which could discern changes by imaging one spot on the surface several times, may also show that the planet is still volcanically active today. This is a long-held belief supported by plenty of circumstantial evidence, but scientists have yet to witness the smoking-gun proof of a live eruption. "It would be just plain cool to find an active volcano," Smrekar says. EnVision, too, could help complete this quest by detecting the scent of a gassy plume belched out of an erupting volcano or spotting the heat leaking out of any magma-filled mountain.

Confirming that such a key planetary process is still churning away is more than merely ticking a box. Like all tumultuous, transformative tectonic activity, volcanoes are powered by what goes on in the deep interior of worlds. Catching erupting volcanoes in the act would provide an open window into Venus's dark geologic heart, allowing scientists to compare the vigor of its rhythm with that of Earth's.

And while DAVINCI+ would determine how much water Venus has lost, EnVision would ascertain how much water Venus still holds. "Is there still water inside the planet?" Ghail says. By sniffing the H<sub>2</sub>O-containing gas plumes gushing out of its volcanoes, scientists would learn whether its interior is as desiccated as its exterior.

#### A TIME OF HOPE AND FEAR

LIKE ENVISION, VERITAS and DAVINCI+ are far from hastily hashed-out proposals. Sketches of both mission designs began cropping up more than a decade ago. (Versions of both were finalists in <u>the last Discovery</u> <u>competition in 2017</u>, but they lost out to <u>Psyche and Lucy</u>, two asteroid investigation missions.) Each proposal is built on more than 50 years of scientific comprehension. It has been a long, stressful journey for everyone.

As the latest Discovery announcement approached, tension levels peaked. The first few months of 2021 were an especially taxing experience for both mission teams, who worked around the clock to impress the arbiters of their future. "To really describe the effort over the past year would take a novel," Smrekar says. The concept study report her team submitted to the judges last November was "just shy of the number of pages in *War and Peace*."

Persisting through the pandemic also took its psychological toll. "Teams work intensely together. Perhaps, especially under COVID, the team becomes a little family," Smrekar says. "I'm immensely grateful to, and in total awe of, the people who had to manage small children at home or take care of elders during this past year."

VERITAS and DAVINCI+ were up against two indisputably outstanding mission concepts. The first was the Io Volcano Observer, or IVO, which would have visited the eponymous Jovian moon—the most volcanic object known to science and the best place to understand how gravitational tides can keep worlds geologically active long after our naive estimates of their expiration dates. The second mission concept was Trident, which would have headed to Neptune's moon Triton, a relic of the outermost solar system kept puzzlingly youthful by some scarcely glimpsed form of icy volcanism.

Judged solely on their merits, each of the quartet stood an excellent chance of winning. But for one or some to win this contest, others must lose. And in weighing the odds, it is impossible to ignore the fact that on September 14, 2020, a wild card was drawn that may have tipped the scales in Venus's favor: a team of scientists announced that, using two telescopes, they had detected phosphine around a particular altitude in the Venusian clouds where temperatures and pressures could allow droplets of liquid water to exist.

Phosphine can be made by volcanism and lightning, but it can also be made by microbes, which



#### ALPHA REGIO,

a 1,500-kilometerwide swath of Venus's surface, is defined by strangely deformed mountains and volcanic plains. This is the intended landing site of the DAVINCI+ probe. raised the possibility that this discovery was <u>indirect</u> <u>evidence of alien life</u>. In the blink of an eye, interest in both phosphine and Venus—from the public, media and scientific community—exploded.

The detection has been called into question in the months since, with <u>analyses</u> either corroborating or refuting it. Ultimately whether or not there is phosphine and whether or not it is being manufactured by microbes were not all that counted in the competition. This controversy also underscored an important fact: there is a global region of Venus's clouds that is neither too hot nor too acidic to fundamentally preclude the possibility of indigenous microbes flourishing there, having adapted to dwell in those conditions.

On Earth, scientists cannot seem to stop finding microbes—thriving, surviving or dormant—in <u>places</u> that would <u>promptly kill</u> plants and animals. Mars's surface is an irradiated, frigid desert hostile to life, but microbes may find a home in the potentially <u>warmer</u>, <u>wetter</u> subsurface. Like Mars, Venus helps to redefine the meaning of habitability. "A hellish planet isn't necessarily inhospitable in every way," says Clara Sousa-

Silva, an astrochemist at the Center for Astrophysics | Harvard & Smithsonian in Cambridge, Mass., and a member of the original phosphine discovery team.

Although it has been suggested that DAVINCI+ could detect phosphine as it makes its plunge, neither it nor VERITAS nor EnVision was designed to study this suddenly fashionable chemical compound. But all three could help constrain the other planetary processes that can make phosphine, from volcanism to atmospheric alchemy. In any event, perhaps what matters most is that phosphine gave Venus a PR boost much like the suspicious-looking meteorite gave Mars in 1996. "I think [phosphine] is the icing on the cake for us," Gilmore says, "because Venus is compelling irrespective of life."

Smrekar and Garvin know this better than anyone. Both are Venus veterans who have been in the field since before the Magellan era. Both wanted answers to their long-held questions, to snatch the low-hanging fruit that has simply hung there, frustratingly unplucked, for decades. Whereas Mars-centric scientists have frequented mission-control rooms, erupting into cheers as the latest robot joined its friends on that rusted world, Venus proponents have worked and waited, torturing themselves over the thought that, this time, *this time*, NASA may pick a mission to head back to Venus. "I have been nervous for the past 41 years," Garvin said shortly before the Discovery selection.

"To say we were nervous is an understatement," Smrekar admits, speaking of her own team. "Those of us who are very close to the mission have poured our hearts, our weekends, our ingenuity into making this happen."

The lack of a win for either team would have come as a huge blow. If neither mission had been selected, many would have perceived the decision as absurd, perhaps even insulting. The spacecraft designs were the best they could be. The momentum of the community was impossible to ignore. And now it had phosphine in its corner.

Even so, if both VERITAS and DAVINCI+ had been rejected, there were still some reasons to be optimistic. As well as Europe's promising EnVision prospects, other space agencies, including those of <u>Russia</u> and <u>India</u>, have been seriously pondering a return to Venus and may have carried the torch if NASA had failed to pick it up.

Younger Venusian scientists, such as O'Rourke, were determined to keep the fire burning, too, even as the American-based Venusian community's venerable legends retired. "The last time a U.S. spacecraft entered orbit around Venus, I was 10 days old," O'Rourke says. Despite the lack of mission opportunities, "I just got into it, like a lot of people my age, because it's obviously so interesting." He suspects that the appetite for Venus science would have been unquenched, no matter what happened with NASA's latest Discovery competition.

In the days before NASA's fateful decision, fear lingered in the words of the Venusians. But thanks to worlds orbiting alien stars, so did another note of hope.

Exoplanet hunters have caught sight of a multitude of Earth- and Venus-size worlds far from our galaxy. Yet current telescopic technology makes it almost impossible to tell whether they are as welcoming as our planet or hellish as Venus. For now studying Venus up close may be the only route to reliable estimates of which is more common in the cosmos: Earths or Venuses. Exoplanet hunters are starting to acknowledge this fact, reckoning that maybe they should know the solar system itself a little better, Sousa-Silva says, "if nothing else, because it's such a good lab for exoplanet research."

Cracking the case of Venus would clearly be to the benefit of not just a select few but everyone in the planetary science community. "Only Venus can tell us why our home planet is unique in our solar system and the likelihood of actually finding Earth 2.0 around another star," Smrekar says. Awaiting the announcement, the VERITAS and DAVINCI+ teams had hoped that this widely shared conviction, along with many lifetimes' worth of work, would finally push at least one of them across the finish line—and that an emissary would once again visit the beguiling world that has dominated their dreams.

#### THE FLEET ARRIVES

FOR A TIME following NASA's declaration that Venus emerged victorious in its latest Discovery-class selections, the proponents of VERITAS and DAVINCI+ basked in the afterglow. "I jumped up and down more than I have in quite a few years," Gilmore recalls. "We are off to *Venus!*" Garvin gushes. "I don't know what else we could have done better to make this the right mission for the moment," Smrekar says. "I feel like we did that. And I feel like NASA noticed."

Magellan was the very first mission Smrekar worked on. Now, she says, VERITAS will be her last and the crowning achievement of her life in science. "This is going to be the capstone of my career," she says. "I can't wait to see what we discover."

These two teams did not just lift the curse; they obliterated it. And the very next week, EnVision was chosen by the European powers that be. In the 2030s Venus will be getting its own fleet of scientific sleuths.

For the vanquished, an inevitable disappointment was tinged with optimism. Proponents of an Io mission <u>hope</u> that they will clinch victory in the next Discovery competition—or perhaps even in the next tier up: a competition for the pricier and more technically ambitious missions in NASA's New Frontiers program. Those wishing for a return to the oft-forgotten worlds of Uranus and Neptune, each of which last saw a spacecraft <u>in the late 1980s</u>, are <u>eyeing</u> a future "flagship" mission, one of the \$1-billion-plus behemoths that constitute the pinnacle of NASA's robotic space exploration fleet in terms of size, cost and capability.

The Venusians, on the other hand, found themselves getting used to their new status as triumphant victors. Thanks to their tireless efforts, the next decade will now belong to the second planet. At last, Ghail says, "there's a recognition that we need to do at Venus what we've done at Mars."

Like their DAVINCI+ and EnVision colleagues, Smrekar and her VERITAS collaborators are thrilled, exhausted and incredulous all at once. The night before NASA's announcement, she had snapped a photograph of Venus, pointlike and gleaming in the dark sky above. In the aftermath of the announcement—in the light of a new day—that diamantine speck suddenly looked quite different. It was no longer an unreachable isle but the destination for NASA's next giant leap in interplanetary exploration.

#### FROM OUR ARCHIVES

scientificamerican.com/magazine/sa

Is There Life on Venus? These Missions Could Find It. Leonard David; ScientificAmerican.com, September 23, 2020.

NATURAL GAS, primarily methane, is burned, or "flared," into the atmosphere at a Texas oil well. ENVIRONMENT

## Methane Methane Methane Methane Methane Methane

Emerging technology can pinpoint methane emissions, but will oil and gas companies and their regulators respond?

By Anna Kuchment

# Paolo Wilczak banked his two-seat airplane above a grid of flat, industrial land in

West Texas. About 60 meters below, I saw a bright flash of orange. It was a "flare"—a tall, vertical pipe beside a commercial oil well and storage tanks that was spitting flames into the windy afternoon air. The pipe was burning off unwanted gases, largely methane, that had risen from belowground with the oil. "Let's see if this

> flare is doing its job," Wilczak said, his voice barely audible above the plane's loud single engine.

> Wilczak is a 23-year-old pilot and researcher for Scientific Aviation, a Boulder, Colo., company that tracks air quality for clients such as the United Nations, government agencies, environmental groups and private companies. We were flying about 48 kilometers north of Odessa, a city in the heart of the Permian Basin, a Kansas-size expanse that straddles West Texas and southeastern New Mexico. Hundreds of millions of years ago this region was covered by a wide, shallow sea populated by tiny organisms that built vast reefs. The decomposing remains of those creatures collected in oil-forming deposits now as deep as 3,000 meters or more. Today the Permian is home to one of the world's biggest oil fields-the largest and fastest-growing in the U.S., the source of 38 percent of the country's oil and 17 percent of its natural gas. After the U.S. ban on oil exports was lifted in late 2015, oil and gas production here exploded. There are now some 150,000 active wells in the Permian; oil production is more than four times what it was a decade ago.

> The Permian is also one of the country's largest emitters of methane—a potent greenhouse gas that is increasingly being recognized as an important driver of the climate emergency. Since 2019 Scientific Aviation's planes have been in high demand as scientists have tried to get a handle on the amount of greenhouse gases leaking from Permian oil tanks, processing plants and other infrastructure.

> Wilczak eased the plane downward toward the flare and started to circle it in a tight spiral. Below



us a circuit-board pattern of straight dirt roads and flat squares of bare soil stretched toward the horizon. Pumpjacks in the squares nodded up and down as they sucked up oil from inside the earth. As we looped around the column of atmosphere above the flare, tubes mounted under the right wing pulled air into a spectrometer behind our seats. The instrument analyzed the air samples and displayed green, red and blue graph lines on a laptop screen between us. The green line—carbon dioxide—spiked, but the blue line, for methane, remained low. The flare was burning cleanly, converting methane into less potent, though still problematic, carbon dioxide.



Anna Kuchment is a contributing editor at Scientific American and a staff science reporter at the Dallas Moming News. She is also co-author of a forthcoming book about earthquakes triggered by energy production.



Many operators flare their gas, often because they are interested only in the oil. When flares work properly, they convert methane to carbon dioxide and water vapor while reducing the amount of volatile organic compounds released into the atmosphere, which can create smog and are linked to respiratory and cardiovascular problems. But flares can malfunction, pipelines can leak, and operators can vent methane without burning it to relieve pressure and prevent explosions. Other large sources include emissions from gas-powered controllers that open and shut valves on wellheads, tanks and other hardware. Last September, Wilczak recorded a leak so large it strained the spectrometer's limits. "It was way higher than anything I had ever seen in my over 1,000 hours of taking measurements," he told me later. An engine at a compressor station had failed, causing the plant to emit more than 12,000 kilograms of methane per hour—the global warming equivalent of driving 65 cars for a year. He made sure the operator was notified, and when he surveyed the area the next day, he found that the leak had been fixed.

Aging infrastructure compounds the problem. The Permian's first boom dates to the early 1920s, when a small group of investors placed an improbable bet on an oil well called Santa Rita No. 1. When

#### WEST TEXAS

and southeastern New Mexico have enormous oil and gas deposits, tapped at tens of thousands of sites (earthen squares).
it came in as a gusher, it triggered a land rush that helped to build Texas's legendary fossil-fuel industry. Many wells are decades old—far older than those in comparable fields, or plays, such as North Dakota's Bakken and Texas's Eagle Ford, where infrastructure is more reliable, says Artem Abramov, head of shale research at consulting company Rystad Energy. Hundreds of thousands of wells and pipeline sections have simply been abandoned, their decaying seals and fittings leaking methane that rises from belowground.

Since at least 2010, university scientists, energy companies and other experts, many brought together by the Environmental Defense Fund (EDF), have worked to understand the impact of new extraction techniques such as modern hydraulic fracturing, or fracking, and horizontal drilling on methane emissions. A major obstacle to this project has been the difficulty of finding individual emissions sources. Methane is colorless and odorless; it cannot be spotted with the naked eye. And before anyone can fix a leak, they have to locate it.

Recently the Permian has become a laboratory for scientists to experiment with new ways of identifying emissions. Much of the impetus came from new Environmental Protection Agency and state regulations, enacted beginning in 2015 that mandated tougher air emissions and monitoring requirements for oil and gas companies. Researchers are piloting planes, flying drones, directing satellites and installing complex ground-sensor networks. New satellites scheduled to launch soon will track methane at global and local scales, making data freely available to anyone.

PERMIAN BASIN was a shallow sea with extensive reefs hundreds of millions of years ago.



There is a large gap, however, between measuring something and controlling it. New technology will have to be matched with stronger regulations and cooperation from a powerful oil and gas industry that prefers to police itself. ExxonMobil, BP and a few other major producers have pledged to cut their Permian emissions over the next two decades, but not all companies are making such promises, which are not binding anyway. A December 2020 survey by the Dallas Federal Reserve Bank found that only about one third of companies operating in the Permian had plans to reduce emissions or flaring. All of which is why people such as Robert Howarth, a biogeochemist and ecosystem scientist at Cornell University, argue that measuring methane emissions from individual sources and making that information public could be the best way to hold polluters to account.

#### LAND OF LEAKS

METHANE COMES FROM A VAST ARRAY of natural and anthropogenic sources: wetlands, shallow lakes and rivers, livestock farming, landfills, agriculture, wastewater treatment plants. Daniel J. Jacob, an atmospheric chemistry professor at Harvard University, estimates that anthropogenic methane sources are evenly divided among oil and gas infrastructure, coal operations, landfills, livestock farming and agriculture.

It is much harder to control emissions from livestock than from a leaky oil well. Combine that fact with the rapid growth in fossil-fuel industries, and it is clear why they are the primary target in the push to control the greenhouse gas. Howarth says oil and gas are probably the largest and fastestgrowing contributors; the post-2006 methane increase coincides with the U.S. fracking surge.

Methane accounts for only about 10 percent of U.S. greenhouse gas emissions, but it is much more powerful than carbon dioxide in trapping heat over a 10-year period. Atmospheric methane levels have risen relentlessly since 2007. This past April the National Oceanic and Atmospheric Administration reported that the one-year increase in methane concentrations for 2020 was an all-time high of 14.7 parts per billion, despite the economic slowdown caused by the coronavirus pandemic.

Yet stopping methane emissions from oil fields is relatively straightforward once they have been located. Jacob and other experts say the fixes are inexpensive and can even make money: companies could sell that methane instead of flaring it or allowing it to leak. And the benefits of cutting the pollution are huge and rapid. "If we reduce methane emissions now, we slow the rate of global warming almost immediately," Howarth says. A United Nations report released in May of this year concluded that a 45 percent reduction in human-caused methane emissions by 2030 would help keep warming to 1.5 degrees Celsius this century, in accordance with the goals of the Paris climate agreement. Such a reduction could limit the impact of deadly heat waves, droughts, flooding and mosquito-borne diseases, potentially saving thousands of lives.

If methane emissions from oil fields are low-hanging fruit, the Permian is a fertile orchard. An April 2020 study led by researchers at Harvard found that the basin emits enough methane to power seven million homes. The work concluded that the rate of methane leakage from the Permian is about 60 percent higher than the national average for oil and gas production sites. As many as one in 10 flares in the Permian malfunction, according to various estimates. And a recent EDF study found that Permian flares operate at only about 93 percent efficiency on average. Even that seemingly small shortfall has a large impact on the climate, EDF scientist David Lyon says.

Permian releases are also much larger, on average, than those in other basins, according to a June 2021 study in *Environmental Science & Technology Letters*. The basin "is qualitatively different from the other major methane-emitting regions we've surveyed around the U.S.," says Riley Duren, a co-author of the study and a research scientist at the University of Arizona and NASA's Jet Propulsion Laboratory. Growth rate is a factor; at the height of production in 2019, companies were drilling 600 new wells per month. "There are many more pressure

points along that supply chain," Duren says.

Nearly every component in that supply chain can leak methane. After a well is drilled and fracked, the liquids and gases that come up go through a separator that divides oil, gas and water. Oil goes to tanks, where it waits for trucks, or to a pipeline. Water flows to other tanks or pipelines for disposal. The gas is either flared at the well pad or piped to a network of gathering stations, compressors and processing plants that refine it into the natural gas that heats homes, as well as butane, ethane and propane.

Small flares can be found beside tanks and wells; large ones are found at processing plants, says chemical engineer David T. Allen, director of the University of Texas at Austin's Center for Energy and Environmental Resources. Gas-powered controllers and valves are found on nearly every piece of equipment across the byzantine infrastructure. "Each controller

### Atmospheric Methane Continues to Climb

The atmosphere contains more than 2.5 times as much methane as it did before the industrial revolution. The amount, or abundance, rose steeply from 1984 to about 2000, went up slightly from 2000 to 2007, then rose quickly from 2007 through 2020. Each year the level follows a cycle, lowest during the Northern Hemisphere's summer and highest during late autumn (*jagged edges of chart*).

Globally Averaged, Atmospheric Methane Abundance over Time, in Parts per Billion (ppb)



emits a relatively small amount of methane," Allen says. "But there are hundreds of thousands of them."

#### ACCURATE DETECTION

THIS UNFATHOMABLY LARGE SET of potential methane leaks is why scientists, environmental groups and some large fossil-fuel companies are pushing for ever sharper surveillance of the Permian. So far aerial surveyors such as Scientific Aviation can trace emissions only to a general area and not to a specific piece of equipment, unless it is an obvious and isolated flare pipe like the one I saw. "We can circle a one-kilometer radius of land and tell you something is definitely happening there," says Mackenzie Smith, a senior scientist at Scientific Aviation, "but everything in the Permian is so dense that there might be 20 sites in that circle."

The ubiquity of compact devices makes it that much more important to have high-resolution moni-



OIL PUMPJACKS, powered by an electric motor or combustion engine, typically nod up and down roughly 20 times a minute, drawing one to 10 gallons of fluid with each stroke. tors. In a recent demonstration on a Zoom call, Duren showed me a video of the Permian shot from about 5,200 meters up by planes equipped with NASA-built imaging spectrometers, which detect methane and other gases based on the way they interact with light. The familiar circuit-board-like landscape appeared, but it was overlaid with bright red plumes where methane was leaking. "It looks like there are wildfires everywhere," he said.

The resolution is about three to eight meters, far sharper than most current satellites and low-flying aircraft. But even that precision is not quite enough to isolate point sources. "It can be difficult to determine the root cause without additional, higher-resolution data," Duren says. Also, infrastructure is constantly being added, which can make images even a few months old obsolete. Some of the planes now carry high-resolution cameras that map equipment when the spectrometers detect gas. Another challenge is that many sources are intermittent and unpredictable. Half of the emitters are active only one quarter of the time, Duren says. EDF, which has sponsored research by Jacob, Allen, and others, has also found a concerning number of superemitters that vent significant amounts of gas. To be effective, methane monitoring really needs to operate continuously, at least on a daily basis, over large areas.

That is where satellites come in. Today's satellites can capture emissions only across broad regions. In 2018 and 2019, for example, Jacob used the European Space Agency's TROPOMI satellite to make some of the best large-scale measurements of leaks from the Permian. But TROPOMI's resolution is only about 5.5 by seven kilometers, an area that could hold dozens of oil and gas sites.

Scientists will soon launch a new generation of sensors that can pinpoint individual facilities. Car-

bon Mapper, a collaboration by NASA, satellite company Planet, the University of Arizona, Arizona State University, the state of California, and others, will launch two satellites in 2023. Several more will follow in 2025 and beyond until Carbon Mapper has at least 18 craft flying through space. Eventually the constellation will provide daily sampling of 80 percent of the largest-known methane and carbon dioxide emissions areas around the globe, which occupy 7 to 10 percent of Earth's populated land area.

Each image pixel will cover a square 30 meters on a side. The consortium will make data open so regulators, companies, environmental groups and the general public can search a Web site and track emitters. NASA and Planet are procuring components, and assembly and testing will begin next year. Meanwhile the consortium continues to conduct aerial surveys.

EDF also plans to launch its own satellite, MethaneSAT, in 2023, supported in part by \$100 million from Amazon founder Jeff Bezos's Earth Fund. The hardware, now in production, will precisely quantify the volume of emissions over regions worldwide. EDF will make the data publicly available online.

Once both groups of satellites are operating, they will complement each other. "Imagine you're looking down from space and taking pictures of the Permian with two cameras: a camera with a medium- to wide-angle lens and a camera with a telephoto lens," Duren says.

Some oil and gas companies are testing new technologies on their own. Houston-based TRP Energy is experimenting with aircraft, drones and groundbased sensors to monitor its emissions. Co-founder Randy Dolan says preventing and repairing leaks is a priority because "by reducing methane intensity, natural gas will remain the most attractive bridge fuel as we go through this global energy transition."

In recent years environmental advocates have questioned the idea that natural gas has only a modest climate impact. Cleaning up operations might also be a response to investors who are demanding that companies focus on green energy; in May 2021 ExxonMobil shareholders elected three board members who pledged to steer the company away from oil and gas.

Dolan predicts that companies will end up using their own combinations of technologies to stay on top of leaks. Dallas-based Pioneer Natural Resources conducts annual flyovers of its largest Permian facilities, and if spectrometers show high readings, the company sends in a ground crew with special cameras to pinpoint trouble spots.

ExxonMobil, Pioneer, Chevron and others are working with Allen to test a ground-based, continuous-monitoring system called Project Astra. The goal "is to find superemitters—find them fast, and then you can get them fixed fast," Allen says. This fall the group will deploy about 50 to 100 groundbased sensors across up to 50 square kilometers of the Permian that contain roughly 100 oil and gas sites. The focus is unmanned installations such as well pads that have unintended emissions. Processing plants have employees who can catch such malfunctions, Allen explains, but "a well site may see a person only infrequently."

A typical sensor will be small, solar-powered and attached to a pole, sending real-time measurements via cellular networks. Every day operators will see whether a site is operating properly, possibly malfunctioning or abnormally emitting methane. Researchers will test several types of sensors, including an inexpensive metal-oxide sensor developed by Scientific Aviation, which is also testing its own

Well pads multiply so fast that regulators "don't know what's going on. They can't even begin to regulate the mess out here." —Sharon Wilson, *Earthworks* 

continuous-monitoring system called Project Falcon. "We're really excited to see if the technology gets off the ground," says Mark S. Berg, executive vice president of corporate operations at Pioneer. "It'll be a lot more effective and a lot more costeffective" than aerial surveys and private satellite data that some companies are now using, he says.

#### **KEEPING EMITTERS HONEST**

WHETHER COMPANIES FOLLOW THROUGH remains to be seen. And not all fossil-fuel companies are motivated to reduce emissions. Small firms that operate only a few wells might not have the resources. Sharon Wilson, a senior organizer for environmental group Earthworks, knows the vagaries firsthand. Every few months she loads her rented SUV with camera equipment and drives six hours from her home in Dallas to the Permian. She has worked for years to show that emissions are higher than official government measurements indicate.

Last March, I joined Wilson and two of her colleagues for several days of fieldwork near Pecos, Tex., a city roughly 120 kilometers southwest of Odessa that claims to be the site of the world's first rodeo. "Do you smell that?" Wilson asked on our first evening as she pulled her white vehicle off a dusty dirt road. We were slowly cruising in twilight along oil and gas pads not far from our hotel. The wind brought in a strong sulfurous odor that quickly made our eyes water. Methane is odorless, but it is often accompanied by foul compounds such as hydrogen sulfide.

Wilson, in her 60s, with flowing gray hair, grabbed her gas-imaging video camera, which looks like a camcorder. She got out of the car and aimed it at a flare about 200 meters away. At that distance the pipe resembled an oversized match standing on end, with orange flames streaming from the top. It roared and whistled as loudly as a low-flying 747. Peering through her camera, which records infrared wavelengths humans cannot see, Wilson assessed that the flare was burning cleanly and that nearby tanks were not leaking. We got back into the SUV and inched down the empty road while she kept her camera on, searching for the smelly culprit. Soon she spotted a pipe that to us looked unlit, but the camera revealed a ghostlike cloud rippling into the air from the top: emissions that should not have been there.

### Hidden Culprits: Old and Abandoned Wells

When producers suck most of the oil or gas out of a well, they move on. They are supposed to plug the old well and reclaim the land, but many are far behind. And because wells have been drilled for more than a century, there are numerous unplugged "orphan" wells whose owners are long gone. Various studies find that a large amount of methane is leaking from all these portals into the atmosphere. An Interstate Oil and Gas Compact Commission report indicates that the U.S. has more than 1.6 million unplugged wells and more than 56,000 orphan wells (*numbers below*). It also says there may be hundreds of thousands more undocumented orphan wells in the U.S. In 2018 only 2,377 wells were plugged nationwide.



We returned the next day. Again, the pipe appeared inactive, but the camera captured clouds of billowing gas. Wilson marked it on a digital map.

Wilson hunts for and tracks sites that regularly emit large amounts of methane. She reports them to companies, often including video as documentation. She also sends her findings to the Texas Commission on Environmental Quality, which regulates the air Texans breathe, and the Railroad Commission of Texas, formed in 1891 to regulate railroads but which today oversees oil, gas and mining industries. Well pads, she says, multiply so quickly that regulators cannot keep up. Sometimes when she calls, "they can't find the site in their records," she says. "That's a problem. They don't know what's going on. They can't even begin to regulate this mess out here." She often has to make multiple complaints and notify local news outlets before companies take action.

Operators are always unhappy to see her. One afternoon I was driving, and we pulled off the road so Wilson could film some tanks. A man in a crimson pickup truck pulled up behind us, jumped out of his cab and began waving his arms wildly, motioning for us to leave. "Get out of here, Earthworks," he said, walking up to Wilson's window and blocking her camera lens with his hand.

"That's very mature," Wilson told him. She reached for her iPhone and began to record him. "What are you trying to hide?" she asked.

The man, in his 20s, bearded and with pale blue eyes, backed off but warned her that she was on private property. Wilson reminded him that we were parked on a public Texas road and that she was a Texan. "Texans believe in oil and gas," the man scolded as he climbed back into his truck and drove off.

Despite her work, Wilson has given up hope that the industry will operate cleanly. To her, the upcoming monitoring technologies are a waste of resources that will only delay the world's transition to renewable energy. By the time the new satellites go up, she says, methane emissions will be even greater. Wilson thinks fracking, new drilling permits and other fossil-fuel development should stop altogether. She says President Joe Biden should declare that climate change is a national emergency so he can use expanded powers to reinstate a ban on crude oil exports, imposed in 1975 after the first U.S. oil crisis. "When that ban was overturned in 2015, it charged the Permian Basin fracking boom," she says.

#### **TOUGHER CONTROLS**

NEW MONITORING METHODS and the data they can generate may be pushing companies and regulators to act. For example, ExxonMobil and Chevron have promised to cut emissions in half by 2025 and 2028, respectively, and to end routine flaring by 2030. But a recent analysis by two nonprofit sustainable energy organizations, Ceres and the Clean Air Task Force, revealed a surprising pattern: some major oil and gas companies are selling their most highly polluting assets to smaller, lesser-known firms that continue operations. Ceres and the task force found that 195 of the smallest producers account for 22 percent of U.S. emissions but only 9 percent of production.

Last November the Railroad Commission began requiring operators to submit more specific information to justify flaring or venting. It also launched its own drone program during the pandemic to track emissions from well blowouts and from other emergencies.

New Mexico, home to a large chunk of the Permian, issued new rules in May 2021 that require oil and gas companies to capture 98 percent of natural gas emissions and bar the firms from venting or flaring except during emergencies. It is unclear whether the state has enough inspectors to keep tabs on bad actors, however.

Federal rules are in flux. Under President Barack Obama, the EPA passed a regulation requiring oil and gas operators to perform leak detection and repair twice a year for equipment installed after 2015. President Donald Trump rescinded those rules at the end of his term, but in late June, Biden signed a bill from Congress that reinstated them. Policy watchers think the Biden administration may extend the rules to older equipment, too.

Scientists hope that the satellites and open data will not only clean up the Permian but also show the rest of the world how to better maintain its fossil-fuel infrastructure. Methane emissions are a global problem that needs a global solution. In 2020, for example, European Space Agency satellites found large plumes of methane coming from Russia's Yamal pipeline that supplies Europe with gas from Siberia. The Carbon Mapper and Methane-SAT technology will eventually provide regular measurements of greenhouse gas emissions in major fields worldwide.

Howarth says a big problem with the Obama-era regulations was that there was no built-in verification mechanism. The government left it up to companies to report how much flaring and venting they were doing. Soon "anyone who has that [satellite] information can go and determine whether or not the industry self-reporting is accurate. I think that's a huge game changer," he declares. "When company X says it never vents, you can say, 'Well, that's not true. Here are the satellite data.' And that, presumably, would lead to action."

#### FROM OUR ARCHIVES

When Methane Made Climate. James F. Kasting; July 2004.

SAVING the Santa Monica mountain lions will require connecting them to larger mountain lion populations north of L.A., such as the Santa Susana group to which this puma belongs.

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# IONS ANGERS

CONSERVATION

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The Santa Monica mountain lions are so inbred that they are starting to show genetic defects. An ambitious plan to build the largest wildlife crossing in the world could save them

By Craig Pittman

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**Craig Pittman** is an environmental writer based in Florida. He is author of *Cat Tale: The Wild, Weird Battle to Save the Florida Panther* (Hanover Square Press, 2020).





IOLOGIST JEFF SIKICH HAS WORKED AT THE SANTA MONICA MOUNTAINS National Recreation Area since 2002. He has dealt with a lot of odd things, including, on one memorable occasion, a call to bring his dart gun to tranquilize what turned out to be a three-foottall statue of a mountain lion rather than an actual mountain lion. But what he was seeing one March day in 2020 was unusual and ominous. It was also not that surprising. "It had always

been in the back of my mind" that this might happen, he says, although he had hoped it never would.

Sikich had set out a cage trap with a roadkilled deer inside, hoping to catch a young male mountain lion. When it worked, he used a tranquilizer dart to knock the cat out. But upon examining the animal closely, "something looked funky with his tail," Sikich recalls. The tail, he realized, ended with a 90-degree turn—a distinctive kink with an angle as precise as that of a drawing in a geometry text. In addition, the young male had only one testicle. The second one had not descended as it should have. Sikich placed a radio-tracking collar around the cat's neck and named him P-81 because he was the 81st puma in that region to be captured and collared.

P-81 wouldn't be the last mountain lion to show such genetic defects. After P-81's capture, as Sikich was doing routine reviews of footage from several different trail cams, two more cats with kinked tails turned up. He couldn't tell about their testicles, but the kinked tail was bad enough. It is a troubling omen for this small colony of apex predators that belong to a subspecies of *Puma concolor*, commonly known as the puma, panther, cougar or mountain lion.

More than 30 years have passed since the last time scientists discovered genetic defects like these in pumas. Back then they happened across the country to a different puma subspecies, the Florida panther. Despite the gap in time and space, the mountain lions are reproducing two of the exact defects that the panthers manifested—defects that were forecast to doom them to extinction. "It's certainly a bad sign," says Stephen J. O'Brien, a genetic epidemiologist at Nova Southeastern University, who worked with Florida officials to save the panthers. "It's a wake-up call."

Rescuing the Florida panther required an extraordinary intervention by humans. Rescuing the Santa Monica mountain lions will require another extraordinary human effort—but a different kind. Fortunately, there's a cat up in Hollywood who's helping, prowling around near the iconic sign overlooking the Hollywood Hills.

AS RECENTLY AS THE 1700S, pumas roamed all across North and South America. Today their distribution is patchy, but their population still stretches from Canada to Argentina. *P. concolor* is not exactly the same cat wherever it is found—there are slight genetic differences—but all its members are silent hunters, swift assassins and tenacious fighters, with long, lean bodies built for speed. The males measure six to eight feet from the nose to the tip of their long, heavy tail; females stretch five to seven feet. In a sprint, they can reach 50 miles an hour. Mountain lions are solitary animals. They hunt alone, sleeping by day and emerging at dusk to search for prey. In the wild, they can live for around a dozen years, assuming they don't get run over or killed by another mountain lion.

When mountain lions are born, they are adorable little balls of fluffy spotted fur. Once fully grown, though, everything about them screams "predator." A mountain lion's body is adapted to hunting, with a light but strong skeleton that anchors heavy muscles. Mountain lions have longer rear legs than other large cats, which makes them capable of vertical leaps of up to 15 feet and horizontal leaps of up to 45 feet. This phenomenal jumping ability enables them to surprise their prey by flying in from above, seemingly out of nowhere. The mountain lion's heavy tail enables it to keep its balance during such long jumps. If the hunted animal tries to run, the cat's large pawsnearly five inches wide-provide good traction for turns, a definite advantage during a pursuit. When the cat is ready to kill, its retracted claws pop out to grab onto whatever it has caught. It chomps down hard with its powerful jaws, which are lined with 16 teeth on the top and 14 on the bottom.

Pumas play a crucial role in the health of their ecosystems. They keep prey populations in check. And because they seldom devour a kill in one sitting, preferring to eat their fill and hide the rest for later, their leftovers become ready-made meals for more than 200 species of birds and mammals. Then the insects move in, some spending their entire lives in those left-behind carcasses. The insects break down what remains, releasing nutrients into the soil.

To make this elaborate chain work, though, the cats need a lot of room to roam. Male mountain lions have a range of around 150 square miles; females, 65 square miles. And that is where the mountain lions of the Santa Monica Mountains have run into trouble.

Because it borders sprawling Los Angeles, the 153,000-acre Santa Monica Mountains National Recreation Area is considered the largest urban national park in the U.S. Its valleys have been covered in concrete to create some of the busiest highways in the nation, which serve a still-growing mishmash of residential and commercial buildings. Every new housing development or shopping center whittles away five or 10 acres here, maybe 15 there, fragmenting the landscape and the population of pumas. At its worst, this fragmentation separates males from reproductively available females. As a result, the mountain lion dating pool has become perilously small—something like what happened with the Florida panther.



MOST FLORIDA PANTHERS live in a low-lying, soggy landscape adjacent to the Everglades known as Big Cypress National Preserve. They are the last remnant of the pumas that Spanish explorers and early settlers called "lions" or "catamounts." They once roamed the whole Southeast, but by the 1980s Florida panthers were the only pumas east of the Mississippi. As the panthers lost habitat and their preferred prev fled. their numbers dwindled until there were no more than 30. Some estimates put the number in single digits. With such a small population, inbreeding was inevitable. Fathers mated with daughters, brothers with sisters, and mothers with sons. Soon they were producing offspring with kinked tails and undescended testicles. Some even had atrial septal defects-holes in their hearts. It was as if they had hit a biological brick wall.

Genetic diversity ensures that a species can survive and adapt to changing conditions. Without it, an infectious disease can easily wipe out the entire group. The genetic defects among panthers were the visible marks of an invisible degradation. Male panther sperm had a ratio of 6 percent normal to 94 percent developmentally malformed, according to O'Brien. Some experts proposed a captive-breeding program to fortify the panther population. The idea was to cap-

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SANTA MONICA

P-81 has genetic

mountain lion

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ciated with

inbreeding,

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ture wild panther kittens to raise in a special facility, where they could be selectively bred to create a genetically diverse source population that could be reintroduced to the wild. But the plan never got off the ground, because all the kittens that were supposed to be used for breeding turned out to suffer from the defects.

Ultimately state officials persuaded the U.S. Fish and Wildlife Service to approve an unprecedented experiment. In 1995 they dispatched an expert tracker named Roy McBride to capture eight female cougars from Texas and bring them back to Florida, releasing them into the wild to breed with the male panthers. They believed this plan might work because the two subspecies probably interbred in the past, back when their ranges overlapped. Sure enough, five of the eight females produced hybrid offspring that were free of defects. The healthy offspring sparked a baby boom among the panthers. Now an estimated 130 to 200 adults prowl what is left of Florida's wilderness.

One reason no experiment like this had ever been attempted before was a fear it would end the legal protection provided by the Endangered Species Act. Critics worried that offspring arising from interbreeding between Florida panthers and Texas cougars might not be considered Florida panthers and thus would not qualify for protection.

The Fish and Wildlife Service issued a provisional rule so the experiment could proceed. The other fear: The cougars' distinctive genes would swamp the panthers' genetic material. Although they are from the same species of cat, scientists say they have genetic markers that show they are subspecies distinct from each other.

Afterward, though, two different studies determined that genetic swamping did not occur. One study examined genetic samples taken from nearly 600 individual Florida panthers that had been collected since 1981 and traced the bloodlines of all the panthers then alive, comparing them with panthers born after the Texas cats were brought in. The study found that the panther population increased threefold, genetic diversity doubled, survival and fitness measures improved, and correlates of inbreeding declined. In the future, the panthers will need to have five Texas cougars introduced every 20 years to prevent inbreeding and reduce the risk of extinction, assuming there is room for them as people rapidly develop the landscape.

But as successful as the Florida panther's "genetic

### Plight of the Pumas

California's mountain lions are highly restricted by habitat fragmentation that has occurred as a result of people developing the landscape. The fragmentation has isolated males from reproductively available females, leading to inbreeding that has reduced the genetic diversity of some populations—including those in the Santa Monica Mountains and the Santa Ana Mountains—to perilously low levels.

Area enlarged

rescue" program has been, California's mountain lions require a wholly different intervention because they are that much more restricted by habitat fragmentation. The solution to their genetic defect problem, experts say, lies much closer to home. And it involves more concrete, not less.

Vadre

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OHN BENSON WAS THINKING about what happened to the Florida panthers while writing up a study on the future of two populations of Santa Monica mountain lions that humans have cut off from the larger group in nearby natural areas. Specifically, the study was trying to forecast the possibility of their extinction within 50 years. Benson, then a wildlife ecologist with the La Kretz Center for California Conservation Science at the University of California, Los Angeles, had previously studied panthers while working for the Florida Fish and Wildlife Conservation Commission, so he knew the story. He viewed what happened with the panthers as a cautionary tale for the mountain lions. Researchers who work with various types of pumas know they're dealing with charismatic megafauna that laypeople often view as over-

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**California's** 

**Populations** 

The state has nine

genetically distinct

groups of mountain lions.

The six encompassed by the dotted line—including the

Santa Monica mountain lions-

significant subunit that could be

considered threatened under

constitute a so-called evolutionarily

California's Endangered Species Act.

Puma



grown house cats. In fact, they are attempting to manage large apex predators, each one with its own distinct personality and specific needs. Pumas tend to be elusive and averse to being around humans, further complicating efforts to understand them. Because of the animals' size, they are sometimes feared by the public, which contributes to political pressure on biologists to minimize risks of a confrontation that might arise from conservation efforts that increase the population.

When Benson, Sikich, Sikich's National Park Service colleague Seth Riley and their colleagues published their paper, they described a couple of different scenarios. According to the computer model, "their reproduction was pretty good ... and the population would remain stable," Benson says. The study found only a 16 to 21 percent probability of extinction, mitigated by their scrubland habitat and the availability of prey. "Although there is lots of development and roads all around, within the Santa Monicas themselves about 90 percent of the area is still natural, or relatively so, and half of it is actually publicly owned," Riley says.

The problem, Riley notes, is that "the Santa Monicas are not big enough by themselves for a viable population genetically or demographically and that they are also not well enough connected to the other nearby natural areas." When the authors factored in the lack of genetic diversity among the mountain lions, the modeling outcome changed dramatically because of what scientists refer to as "inbreeding depression." The Santa Monica Mountains population and the one in the Santa Ana Mountains in Orange County already had the lowest genetic diversity documented for mountain lions-aside from that of the 1995 Florida panthers. After accounting for the lack of genetic diversity, Benson says, every run of the model found that once the inbreeding depression began, the cats would probably go extinct in 50 years.

Benson and his co-authors had no idea when the paper came out that the first signs of genetic defects would crop up so soon. But they knew it was likely to happen eventually because the biggest obstacle to improving the mountain lions' genetic diversity had been blocking their path since 1950.

Los Angeles is a city of highways, and the biggest



A WILDLIFE BRIDGE to be built across Highway 101, shown in an artist's rendition, would be the world's largest.

one of all is U.S. 101, a major north-south route linking L.A. to San Francisco and the Pacific Northwest. The road varies between eight and 10 lanes of traffic and sees around 300,000 vehicles a day. That highway prevents the Santa Monica mountain lions from getting across to mate with the larger population of mountain lions in the 2,970-square-mile Los Padres National Forest. Once biologists began putting radio collars on the dozen or so mountain lions that they were monitoring in the Santa Monica Mountains, Riley says, they would track the males as they traveled to the 101, saw the river of traffic and then turned back. "The habitat we have there for them seems good," Riley says of the cats in the Santa Monica Mountains. "They find plenty of deer." But because of the 101, their only potential mates are close relatives, which leads to inbreeding.

Then, in 2009, a miracle happened. The 12th puma they had captured and collared, P-12, found a way to cross the road, in an area called Liberty Canyon where there is natural habitat on both sides of the highway. "That was a pretty big deal," Riley recalls, "because he not only crossed and survived, but he also reproduced."

A handful of other mountain lions have since followed P-12's lead, mostly at night when traffic is lighter. One figured out how to cross using a six-footwide culvert under the 101 and made 42 crossings in less than a year, Riley says. But then that cat died from injuries suffered in a forest fire, and no other cats have set foot in that long, dark culvert since.

To California biologists, attempting to help the Santa Monica mountain lions by trucking them to a place with a more diverse puma population or hauling individuals from a more diverse population to breed with the Santa Monica cats like the Florida officials did seemed like too much human intervention, with too much risk for trauma to the wild creatures. Still, the repeated crossings gave the scientists an idea for how to help the Santa Monica mountain lions: Build them a safe place to cross the 101. That way the cats would be reconnected to the larger population of pumas in the Sierra Madre range to the north, which would allow them to find mates capable of boosting the smaller group's genetic diversity.

The Fish and Wildlife Service and transportation officials considered the idea of a tunnel but rejected it. It would cost too much and be too disruptive to the drivers using the highway, and there was no guarantee the animals would use it. That left only one option: An overpass that would soar above the 101 and allow the mountain lions on both sides of the highway to come and go as they please. Fencing built on either end would funnel the lions toward the overpass so they would not wander into traffic. That way there would be no need for humans to capture the cats and move them. "Ideally, if we get them this vegetated overpass built, they'll do it on their own," Sikich says.

National Park Service officials, after consulting with wildlife-crossing experts and the California Department of Transportation, nicknamed Caltrans, came up with plans for a 165-foot-wide overpass positioned 16 feet above the pavement of the 101. The north end connects to a hillside, and as the overpass reaches the south side it slopes down a bit, Sikich says. If built, it will be the world's largest wildlife bridge, with an estimated price tag of \$87 million. The crossing would be constructed and landscaped to resemble the surrounding countryside, with sound-blocking barriers to quiet the noisy traffic below. The best spot for the overpass, the biologists concluded, would be the place where P-12 first crossed, the spot in Liberty Canyon with natural underbrush on both sides of the road. The lions could use it any time of the day or night without fear of becoming roadkill. The land on both sides of this segment of the highway had already been protected. Even better, it is contiguous with large swaths of protected habitat to the north and south of this connection, thus making it a viable solution for connectivity within the Santa Monica Mountains. Ideally the cats wouldn't even realize they were on a human-made structure.

Conservationists first tried such wildlife overpasses in France in the 1950s, and they have grown in popularity in Europe. They are beginning to catch on in the U.S., too. For instance, in 2018 Utah opened a 320-by-50-foot bridge to allow moose, elk, deer and other wildlife to cross over the six-lane Interstate 80 near Salt Lake City. There is just one problem with the Liberty Canyon bridge: Caltrans had no money set aside for building a highway in the skies whose primary users would be feline predators. That's where the cardboard cat comes in.

Beth PRATT of the National Wildlife Federation had worked in Yosemite and Yellowstone, so she was used to lonesome wilderness areas and their wildlife. Learning that the mountains adjacent to sprawling Los Angeles contained mountain lions was "mind-blowing," she recalls. "It changed the way I looked at wildlife." After Pratt became the regional executive director of the environmental group's California Regional Center, she got in touch with the biologists at the Santa Monica Mountains National Recreation Area and asked if there was anything that her organization could do to help: "And they said, 'Well, there's this little corridor we're trying to build.'"

She met with Caltrans officials to talk about it. "Caltrans has been phenomenally supportive," she says. "They told me, 'We don't have the money, but if you get us the money, we'll build it." They worked out a deal in which 80 percent of the money—more than \$69 million—would come from private donors and the other 20 percent from public funds for conservation projects. They do not need to raise all the money before starting work.

The National Wildlife Federation launched a fundraising drive for the 80 percent, calling it "Save LA Cougars," and it picked a mascot sure to attract public sympathy: A male mountain lion, P-22, that in 2012, against all odds, took up residence in Griffith Park near the famous Hollywood sign. Genetic tests determined that the cat came from the Santa Monica Mountains population, which means it crossed both the 101 and another major highway, I-405, to reach its current home. Despite the urban setting, Griffith Park offers P-22 plenty to eat and places to hide during the day. But it is the only mountain lion in the sixsquare-mile urban park, which makes P-22 ideal for the campaign. "We're talking about a lonely bachelor doomed to never have a girlfriend," Pratt says. "He has been embraced by the public. We have the perfect relatable victim."

Pratt had a life-size cardboard cutout of P-22 made, which she carries around to fundraising events all over Los Angeles and elsewhere. She has persuaded well-known figures such as actor Sean Penn and Representative Adam Schiff of California to pose with it, drawing even more attention to the puma's plight. Word of the project has gone viral, she says: "We've gotten donations from London, Florida. One Kansas couple who have never been to California have given us \$500,000." Los Angeles even celebrates a "P-22 Day" every October featuring lots of festivities to raise money and awareness of the mountain lions' plight. Last fall the festival went virtual, as so many events have been forced to do. That required taking a more creative approach to the event, Pratt says. "We got some game developers to create a game interface." One of the games features P-22 using a jet pack to get out of the park.

Some people have questioned the worth of the overpass, though not many. During the environmental review "there were more than 8,000 comments for the project and only 15 against," Pratt recalls. People have rallied to the cause from all sides of the political spectrum because people love animals, and "this is a tangible problem to solve," she says.

As of May, the fundraising had hit the \$44-million mark, more than enough to get the project to the final design and engineering phase. Then, in July, Governor Gavin Newsom approved a state budget that includes \$7 million for the Liberty Canyon Wildlife Crossing. Caltrans expects to break ground as early as November. The goal is to have the overpass open for the mountain lions to use by 2024.

Pratt says they have no plan B for the cats and don't believe they will need one. Not hitting their funding targets "would only delay groundbreaking, not cancel the project, but we're not even anticipating any delays at this point," she says.

But now that P-81 and the other two cats with kinked tails have shown up, the fundraising campaign has become a race to rescue the Santa Monica mountain lions before they are too far gone. "Their genetic diversity is likely to continue to erode," Benson says. "What no one can say is when it's likely to lead to extinction. You don't want to wait until it's too late." On the other hand, he reflects, "if we can conserve large carnivores near Los Angeles, I think that bodes well for us being able to do the same thing elsewhere in the country."

#### FROM OUR ARCHIVES

Tracking Tigers. Ullas Karanth; July 2016.

#### NONFICTION

# **Planetary Plot Twist**

To encourage climate action, we need better stories

Review by Kate Marvel

Once upon a time there was a world in mortal danger. Some people tried to stop it; others claimed it was ≈all a hoax. They squabbled on the Internet, calling one another terrible names, until they were swallowed up by the rising sea.

Once upon a time there was a polar bear. It died. And it was all your fault. You are to blame for the drought in California and the impending disintegration of the Greenland ice sheet.

Once upon a time there was a world, but who cares? It was doomed. Nothing could be done, and everyone was destined to be miserable.

I don't like any of these stories, and I bet you don't either. Much of the world's failure to address climate change stems from a failure to tell different ones. I want to read climate science fiction that isn't set in a dystopia. I want to see heist movies where charismatic teams pull off audacious robberies of fossil-fuel companies. I want time-traveling paleoclimate action scenes where the heroes fight Siberian volcanoes. I want personal narratives about anger crystallized into action and eulogies for the things we're losing. I want a story that begins with scientists issuing desperate warnings, and then everybody listens and takes appropriate action, and it turns into a nice romantic comedy. If we're going to save the planet from extreme weather and social chaos, we need more stories with heroes who make a better future possible.

As far as heroic characters go, I'm not sure you could do better than Katharine Hayhoe. She is an accomplished climate scientist and charismatic communicator as well as an evangelical Christian living in Lubbock, Tex. And she's *much* nicer than most of us. This is evident on her social media feeds, where she tirelessly responds to bad-faith questions with grace. I don't know how she summons the will to say for the umpteenth time that yes, it's warming; no, it's not a natural cycle; yes, it matters. But in doing so, she's trying to make a



Saving Us: A Climate Scientist's Case for Hope and Healing in a Divided World by Katharine Hayhoe. Atria/ One Signal, 2021 (\$27) point. The easiest climate solution, she says, is to talk about it. Not necessarily to the "dismissives," the small but loud minority who are convinced it's all a hoax, but to their audiences, the lurkers who read but don't engage. Hayhoe knows that on the Internet, someone is always watching.

In Hayhoe's excellent new book, *Saving Us*, she argues that everyone can take a role in this performance. After a deliber-

ately perfunctory summary of the facts (it's real; it's us), she gets right to the point: they're not enough. We're swimming in more facts than any human brain can process. We're prone to information overload and motivated reasoning, especially when something threatens our identity, feelings or sense of morality. What if, Hayhoe suggests, we talked about *that*?

The central argument of Hayhoe's book is that we can counter bad narratives with better ones. For instance: Is climate change an abstract concept? No, it is already strengthening hurricanes, causing droughts and amplifying heat waves. Is the cure worse than the disease? No, climate solutions have massive health benefits. Can we afford climate action? We can't



afford the effects of climate change. For more productive conversations. Havhoe suggests focusing on shared values. Her stories go something like this: Once upon a time, a climate scientist gave a talk to a hostile audience. They were prepared to tune her out or shout her down. But she spoke their language, cared about the things they loved and understood their fears. So they listened. And that, for her, was a good start.

Saving Us also confronts some of the most unhelpful climate stories. Havhoe has no patience for public shaming and purity tests. She admirably debunks the myth that we're doomed. I've always thought that people who say climate action is impossible because of "human nature" don't understand humans or nature. I agree with Hayhoe that not only is a better future physically possible, but we have most of the tools we need to bring it about.

That's not to say the book is perfect. Hayhoe can seem too credulous at times. I found it hard to believe that an oil-drilling executive might change his career trajectory after one of her talks, and I'm wary of accepting the climate commitments of fossil-fuel companies at face value. Climate action is pro-life, she says, and I agree completely. But a cynic might suggest that

branding other objectively pro-life policies (gun control, humanitarian aid, deathpenalty abolition) as such has not increased their traction in conservative circles. Climate action requires not just narrative but amassing and exercising raw political power. Many wealthy people stand to lose influence and easy money when the rest of the planet gains. They have vested interests in stopping climate

we can limit global warming to avoid the worst-case scenarios. We may not all live on the same planet as Katharine Hayhoe, but I hope we can get there soon.

Because whatever our world looks like right now, the science says it's rapidly becoming something else. That means another story is possible, and it goes something like this: Once upon a time, there was a world full of wondrous creatures who

It can be tempting to read her book and think: What planet is Katharine Hayhoe living on? The answer, of course, is one in which greenhouse gas emissions do not continue their unabated rise, where we can limit global warming to avoid the worst-case scenarios.

action. And they know how to talk, too.

Can the voices of millions counter the megaphones of the rich? Is the power of empathy, character and storytelling enough to overcome the power of, well, power? Hayhoe thinks so-at least she is convinced that good stories can change the world. It can be tempting to read her book and think: What planet is Katharine Hayhoe living on? The answer, of course, is one in which greenhouse gas emissions do not continue their unabated rise, where built roads and cities. canals and fields. All of this was powered by cheap energy that they dug out of the ground. When they learned how that energy was poisoning the world, they embraced their agency rather than denying their impact on the planet. Everyone played their part to restore balance: some harvested the wind and sun. some worked to draw the poison out. some demanded their leaders take things seriously. They rebuilt it all, grieving what they lost and saving what they could.

#### IN BRIEF -

#### Life Is Simple: How Occam's Razor Set Science Free and Shapes the Universe by Johnjoe McFadden. Basic Books, 2021 (\$32)



#### Named for 14th-century

philosopher William of Ockham, Occam's razor is the scientific principle that "entities should not be multiplied beyond necessity."

In Life Is Simple, geneticist Johnjoe McFadden offers a breezy but well-researched look at how the razor has inspired some of science's biggest ideas, from Copernicus's view of the universe to the Standard Model of particle physics. Taken together, his examples illustrate with persuasive power how "simplicity continues to present us with the most profound, enigmatic and sometimes unsettling insights" into how the universe works. —Amy Brady

#### Talk to Me

by T. C. Boyle. Ecco, 2021 (\$27.99)



In T. C. Boyle's latest novel, clearly inspired by the infamous Nim Chimpsky experiment—an attempt to prove, contra Chomsky, that hu-MLK TO MC mans weren't the only animals able to acquire language-fictional animal behaviorist

Guy Schermerhorn is raising a Chimpskyesque ape named Sam in a house outside his California college town, teaching him to "speak" American Sign Language. Schermerhorn wants to "lift the roof right off of everything we've ever known about animal consciousness"; he also wants to go on Johnny Carson. What starts as a comedy about an interspecies love triangle quickly moves into darker territory. The book's real subject is human selfishness and cruelty, particularly as practiced by the male of the species. -Seth Fletcher

#### The Truth and Other Stories

by Stanisław Lem, translated by Antonia Lloyd-Jones. MIT Press, 2021 (\$39.95)



This collection by the late Polish writer Stanislaw Lem is made up of mostly mid-20th-century stories that have been translated and published in English for the first time. Lem's

protagonists embody both "inflamed curiosity" and resigned unease as they encounter the runaway consequences of new technologies. Sci-fi writer Kim Stanley Robinson, who wrote the foreword, calls Lem's voice "passionately rational." Novelist and critic John Updike once described Lem's writing as engaging, "especially for those whose hearts beat faster when the Scientific American arrives each month." Indeed, as our world changes faster than we can make sense of it. Lem's prescient imagination shows the power of science fiction for peering into the future. —Jen Schwartz

# Lab Leak?

# It's not totally irrational; unfortunately, its loudest proponent was

By Naomi Oreskes

In June a well-known climate scientist opined on Twitter that "I'd be more likely to believe the COVID lab-leak hypothesis if the people pushing it weren't largely the same people pushing [bogus] conspiracy theories about the 2020 presidential election and climate change." He has a point. Early in the pandemic, the lab-leak theory was promoted by then president Donald Trump, who was dismissive of masks and social distancing. He speculated that COVID-19 infections might be effectively treated by irradiating sensitive lung tissues with ultraviolet light, using untested and possibly unsafe drugs, or injecting dangerous household cleansers. Trump also knowingly put his own Secret Service detail at risk by riding with them in a closed car while he was fighting an active infection, misrepresented hurricane forecasts and advanced misleading ideas about vaccine safety. And—most egre-



giously for climate scientists—he repeated the ridiculous claim that climate change was a hoax.

We all judge messages by the messenger. If our trust (or lack of it) is grounded in experience, this pattern is rational: we would be foolish to trust someone who in the past has repeatedly misled us, been mistaken or given us bad advice. We wouldn't go back to a doctor who had misdiagnosed a serious disease or a car mechanic who had cheated us. We wouldn't stick with a financial adviser whose stock tips had consistently proved wrong.

To be clear, <u>most scientists</u> think animal spillover is the most likely explanation because that's where most new diseases come from. True, the source animal has not yet been identified, but it



Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *Discerning Experts* (University of Chicago, 2019).

took decades to determine that <u>HIV was</u> derived from primates. True, there is a lab in Wuhan that studies bat viruses, but it's typical for scientists to study viruses endemic to their regions. And blaming humans for disease is as old as disease itself.

But what do we do when evidence suggests that a claim might be right, even if the person making it has been repeatedly wrong? Here it's helpful to distinguish between two forms of the lab-leak theory: the malevolent and the accidental. The malevolent version holds that China deliberately released the virus. I know of no credible scientists who embrace that idea, and it strikes me as unlikely because politicians with even the most meager understanding of pandemics would realize that any deliberately released virus would affect China as much as or more than the countries to which they hoped to spread it.

The accidental version holds that the virus got out by mistake. Here things get trickier but more plausible. Even institutions that take great safety precautions still sometimes fail. Just think about the nuclear power industry, where <u>serious accidents</u> have occurred in Japan, the Soviet Union, the U.K., the U.S., Canada, France, Belgium, Sweden and Argentina and minor or moderate accidents in most countries where nuclear power is used. Or consid-

> er railroads, where major accidents still occur every year; the most deadly accident in U.S. railroad history occurred in Tennessee in 1918, almost 100 years after the industry got started.

> The late Yale University sociologist Charles Perrow developed the theory of "normal accidents" to explain this phenomenon. People are human. We all make mistakes. Fortunately, our mistakes are often minor and can be easily corrected. But in complex technological systems, small mistakes may rapidly ramify and compound into large problems. When people don't know how to fix their mistakes—and are perhaps embarrassed or ashamed—they may try to cover them up, impeding the ability of those around them to fix the problem, too.

> It's not hard to imagine that a COVID researcher made a small mistake and tried to hide it, and things then spiraled out of control. It doesn't mean this is what happened, but it does mean we should keep an open mind until we know more. The lab-leak theory *is* plausible, and it is rational for scientific institutions to investigate closely, even if some of the people promottim are irrational.

ing the claim are irrational.

Life is short, research is expensive and not every theory is worth pursuing. But when the stakes are high, it generally behooves scientists to look closely at any idea that has not yet been properly evaluated. If there is credible evidence that the SARS-CoV-2 virus may have escaped from a lab—in China or anywhere else—that evidence should be evaluated, even if we first heard the message from an untrustworthy messenger.

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### 50, 100 & 150 YEARS AGO INNOVATION AND DISCOVERY AS CHRONICLED IN SCIENTIFIC AMERICAN

Compiled by Mark Fischetti

#### A Metric Daydream

"A proposal that the U.S. switch to the metric system has been sent to Congress by Secretary of Commerce Maurice H. Stans. The proposal adopts recommendations made in a National Bureau of Standards report, which describes metrication as 'a decision whose time has come.' The U.S. is the only maior nation not on the metric system or committed to change to it. 'A metric America,' the report says, 'would seem to be desirable in terms of our stake in world trade.' If Congress follows the proposal, it will set a target date 10 years ahead. A high priority would be teaching children and the public to think in metric terms. By the target date the U.S. would have become 'predominantly, though not exclusively, metric.' Presumably gains and losses in football would still be described in yards, and sayings such as 'A miss is as good as a mile' would remain in the language."

#### **Galactic Radicals**

"The same simple molecule that was first discovered in the interstellar reaches of our galaxy eight years ago has been detected within two other galaxies some 10 million lightyears away. It is the hydroxyl radical, OH. Radio interferometry shows it is present in M82, an exploding galaxy in the constellation Ursa Major, and in Nee 253, a small spiral galaxy in Sculptor. Evidently hydroxyl radicals number about one to every million hydrogen atoms in the interstellar clouds-about the same proportion as in our galaxy."

#### **Radio Signals** $\sim$ from Mars "The Martian radio-signal cycle

comes around every few years. The newspapers 'play up' the announcement that mysterious signals have been intercepted. J. H. C. Macbeth, London manager of the Marconi Wireless Telegraph Company, Ltd.,

#### SEPTEMBER







recently stated in a speech that William Marconi was now convinced that he had intercepted signals, reported to have an extremely long wavelength. Somehow it is difficult to believe. Radio communication is such an intricate development that it would be very rare indeed if two peoples, located on different planets, should have worked out precisely the same method of communication. We can more readily believe in the Martians making use of huge mirrors for reflecting light, or even huge searchlights, as a means of attracting our attention."

#### Scientific American **Goes Monthly**

"Announcement: The weekly Scientific American and the Scientific American Monthly are to be combined into a single monthly Scientific American. The first issue will be dated November 1921. The new monthly will have increased reading matter, more illustrations and a broader range of subjects. We confess that after bringing out the

Scientific American week by week for over three quarters of a century, we feel a twinge of regret. It is done, however, so we can present the same material in a better balanced and more fully digested form, and at a far lower cost to the reader. The new magazine will embrace all branches of science, research, engineering and industrial advance. The subscription price will be \$4.00 a year. The price per copy will be 35 cents."

Vicious Fish **IO I** "Among beings that inhabit the globe's waters are things beautiful, ludicrous and fearful. The latter class includes the scorpion fish. It inflicts its injuries by its dorsal fin, which is serrated, and until this is broken by a club or stick, no one will venture to touch it with the hand. A fish named 'candirou' is said to infest the mouth of the Amazon: although scarcely larger than the minnow, when this little fiend seizes hold of the flesh it holds on with such tenacity that it cannot be removed without tearing out a mouthful of flesh. Another



1921: Vehicle ferry. The expansion of automobiles for touring and of motor trucks for freight transportation has resulted in a new type of ferryboat, the Hullfin. Only 140 feet long, it will have 472 feet of driveways.

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### **GRAPHIC SCIENCE**

Text by Tanya Lewis | Graphic by Amanda Montañez



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