Venus' Mysterious Lights | Amped-Up Hurricanes

ScienceNews

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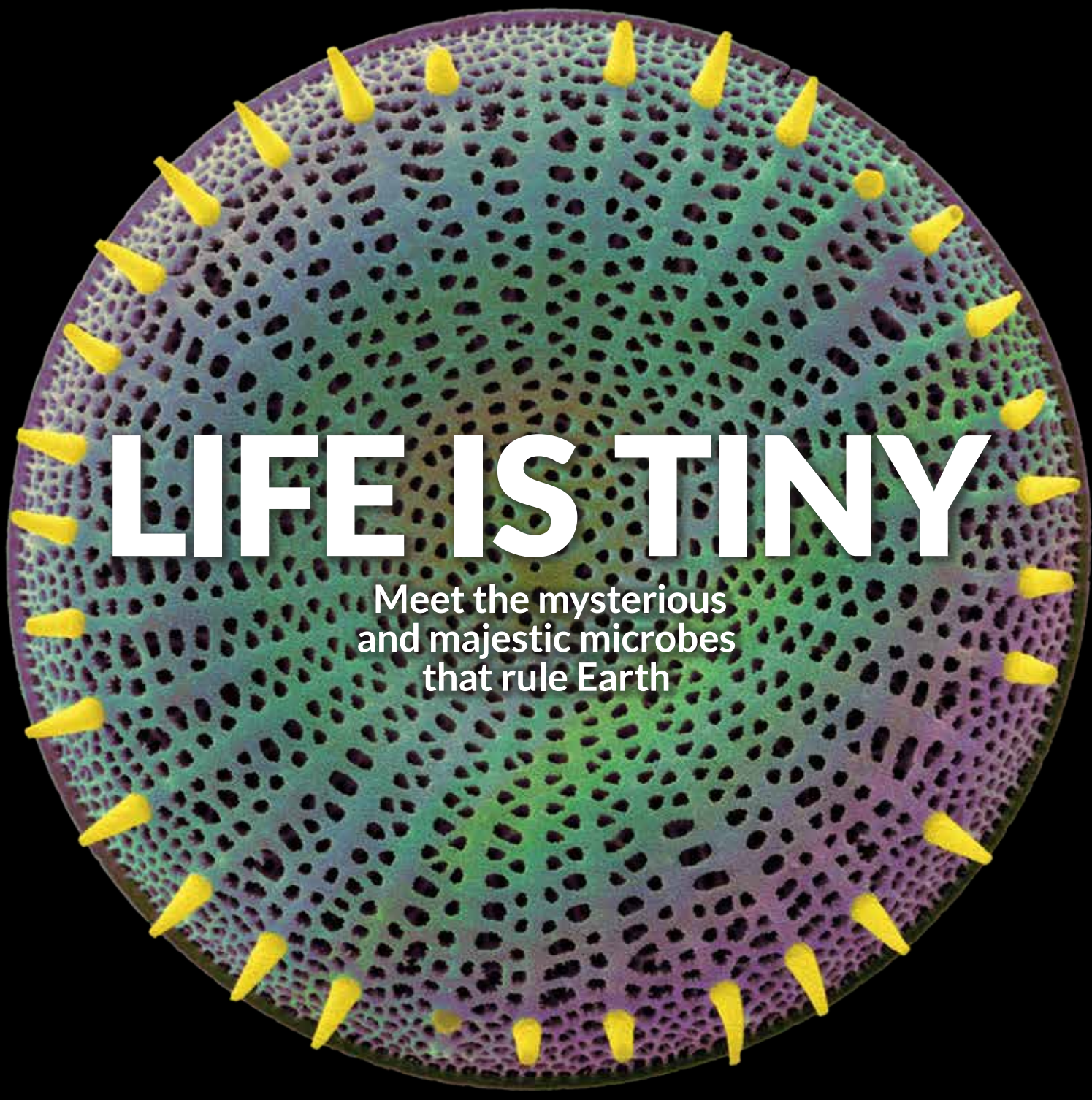

LIFE IS TINY

Meet the mysterious and majestic microbes that rule Earth

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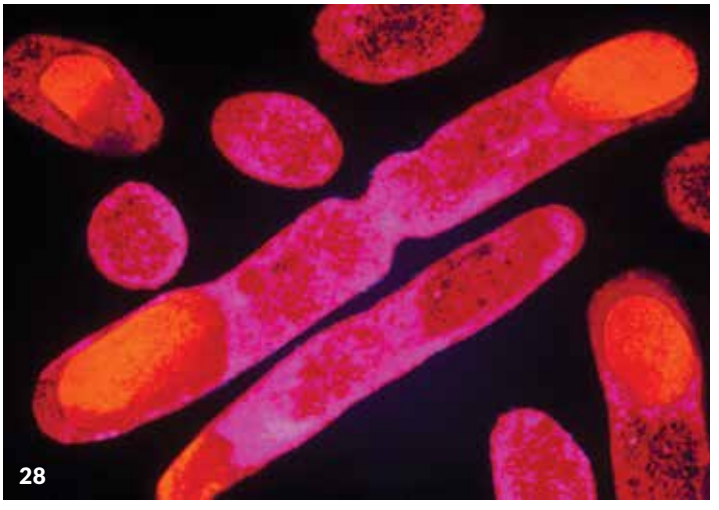
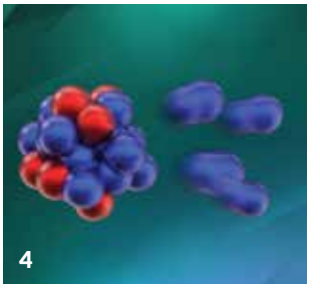


Features

News

FROM TOP: VOLKER STEGER/SCIENCE SOURCE; ANDY SPROLES/OAK RIDGE NATIONAL LAB; ANDREAS SACHSE



Departments

COVER This microscopic diatom, a type of protist, has a hard, porous cell wall. *Dennis Kunkel Microscopy/Science Photo Library/Alamy Stock Photo*

The challenges of seeing the profusion of tiny life

When I imagine life on Earth, I think of grand images: springboks bouncing across the African savanna, penguins waddling in the snow, dolphins leaping into the air, redwood trees soaring above the forest. But scientists are exploring a profusion of creatures with equally fascinating behavior that aren't seen in David Attenborough–style documentaries. In fact, our eyes can't see them at all.

Minuscule life-forms known as protists have been known for centuries. But powerful microscopes, advances in genetic and computational technologies, and old-fashioned fieldwork are now revealing extensive diversity among these single-celled life-forms. Many are bizarre enough to star in a science fiction series. As life sciences writer Susan Milius reports, one critter has a "head" that spins, a skill creepy enough that its discoverers gave it the name *Daimonympha friedkini*, inspired by the demonically possessed child in the 1973 film *The Exorcist* and its director, William Friedkin (Page 18). Another creature, shaped like a flying saucer, glides into the bodies of its prey, devouring them from the inside.

These two discoveries and many other recent ones are forcing scientists to rethink their concepts of how microbes are related to other organisms, as well as to rethink the whole tree of life. "What struck me most as I worked on the story was how little of it I can see," Milius said of the tree of life and its many microbial branches. That and the fact that it's not so much a tree as invisible bramble tangles of life, Milius says.

Trying to figure out how to illustrate the protists in the bramble tangles proved a challenge. *Science News* design director Tracee Tibbitts spent many hours digging through electron microscope images in search of the right tiny, crazy-looking things. "Species ID is a recurring theme at *Science News*," Tibbitts told me. "This took it to another level."

And even when she found the right species, the images often didn't capture what makes these creatures special; their physiology is so alien to ours that they all tend to look alike. We wondered if drawings might work better. Many historical depictions of long-known protists were penned by Ernst Haeckel, a supporter of the discredited "science" of eugenics, and used as design motifs by René Binet, a Trotskyite turned Nazi. We felt uncomfortable giving those people more attention. So back to the hunt for other options.

Ultimately, we were able to find images that we think do these creatures justice, revealing their remarkable forms and behavior, like that spinning demon "head."

The experience has left us marveling at the diversity of life, not only these tiny life-forms but also much larger creatures featured in this issue, including a parasitic worm that made a home for itself in a woman's brain (Page 4), pirate spiders that trick their prey into walking the plank (Page 11), songbirds that are excellent problem-solvers (Page 14) and small snakes that take supersize gulps (Page 36).

There's so much more to discover about Earth's inhabitants, the majority of which dwell in the microbial world. The tree of life is vast, and the part that looks like us is incredibly small. —*Nancy Shute, Editor in Chief*

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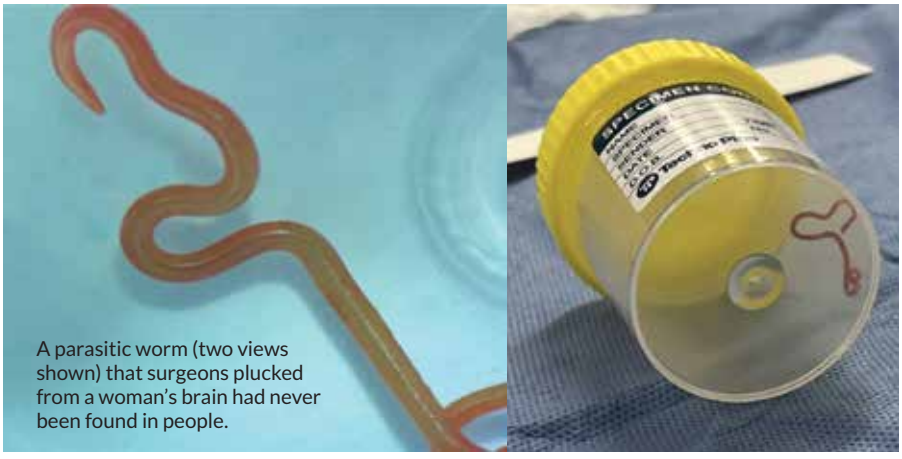
Excerpt from the October 20, 1973 issue of *Science News*

50 YEARS AGO

Dangers of thermal pollution

Most urban dwellers have experienced the swelter of a summer night in the city, but higher temperatures in the atmosphere over such "heat islands" may have more insidious effects, which urban planners seldom consider.... Urban-rural temperature differences can be as high as 18 degrees [Fahrenheit].

UPDATE: Today, excess heat from pavement and buildings cause U.S. cities to run half a degree to 4 degrees Celsius (1 to 7 degrees F) higher on average than outlying areas. This heat island effect is expected to worsen as a side effect of climate change. Because urban areas are expanding, that means their growing populations are at risk for heat-related illness or death, scientists reported in 2019 in *Environmental Research Letters*. To stay cool, some cities are switching to roofs and surfaces that reflect a lot of sunlight and heat. Adding trees helps too: Trees provide shade and emit water vapor that lowers air temperature, almost like if a city could sweat (*SN: 4/14/18, p. 18*).



A parasitic worm (two views shown) that surgeons plucked from a woman's brain had never been found in people.

HOW BIZARRE

Python parasite worms its way into the human brain

The woman's mysterious symptoms started in her stomach.

Weeks of abdominal pain and diarrhea led to night sweats and a dry cough. Then, doctors found lesions on her lungs, liver and spleen. An infection, perhaps. But tests for bacteria, fungi, other pathogens and even autoimmune disease came up negative.

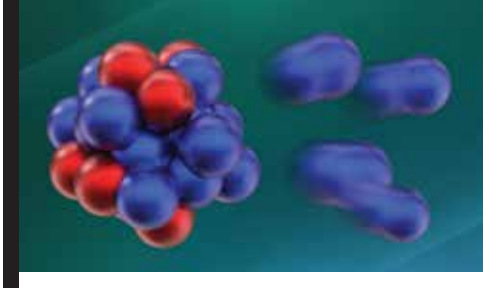
Three weeks later, the woman was in the hospital with a fever and cough. CT scans revealed a telling clue: Some of her lung lesions appeared to be migrating. A second clue came months later when the woman became forgetful and depressed.

FIRST

A newly made form of oxygen is surprisingly fragile

"Magic" numbers of physics might not be so magical after all. Using a particle accelerator, scientists have created an elusive variant of oxygen for the first time. The isotope, oxygen-28, was predicted to be extraordinarily stable due to its eight protons and 20 neutrons—"magic" numbers associated with stability in atomic nuclei. But observations of oxygen-28, reported in the Aug. 31 *Nature*, reveal that it is more ephemeral than enduring: It crumbles after about a zeptosecond.

Atomic nuclei are made up of set numbers of protons and varying numbers of neutrons. These types of subatomic particles occupy their own discrete energy levels called shells. Shells fill up when they hit certain numbers: two, eight, 20, 28, 50, 82 or 126. Nuclei with full outer shells of protons *and* neutrons are considered doubly magic—the nuclei are bound extra tight, making them extra stable. Oxygen-28, with eight protons and 20 neutrons, was therefore expected to be extra stable.



Oxygen-28 fell apart almost immediately after it was created, shedding four neutrons (illustrated blue) to become oxygen-24.

A team led by physicist Yosuke Kondo of the Tokyo Institute of Technology created the isotope by throwing fluorine-29 at liquid hydrogen to knock off a single proton. Almost immediately, the resulting oxygen-28 shed four neutrons to become oxygen-24.

Oxygen-28's instability hints something is amiss with theories about the force that binds protons and neutrons, says physicist Rituparna Kanungo of Saint Mary's University in Halifax, Canada. The finding will "probably trigger a lot of theoretical developments." —*Elise Cutts*

TOP TWO: CANBERRA HEALTH SERVICES; BOTTOM: ANDY SPROLES/OAK RIDGE NATIONAL LAB

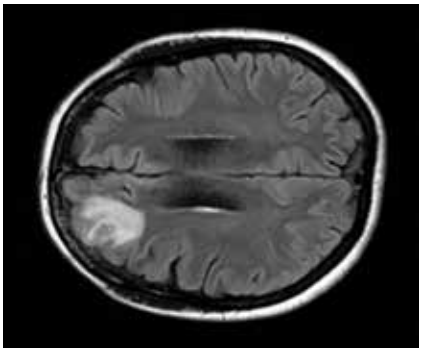
"She had a very astute [general practitioner] who thought, 'Something's not right here. I better do an MRI of the brain,'" says infectious disease physician Sanjaya Senanayake, of the Australian National University and the Canberra Hospital.

That brain scan turned up a ghostly glow in the woman's frontal lobe. It could have been cancer, an abscess or another affliction, Senanayake says. "No one thought it was going to be a worm."

During a biopsy, the woman's neurosurgeon spotted a suspicious stringlike structure and plucked it out with forceps. It was pinkish-red, about half the length of a pencil—and still alive.

"It was definitely one of those 'wow' moments," Senanayake says. But the doctors also felt relieved. It meant they had a diagnosis and treatment plan.

The worm, *Ophidascaris robertsi*, was a nematode whose main host is a snake, Senanayake and colleagues report in the September *Emerging Infectious Diseases*. The woman, from New South Wales, Australia, is the first known case of an infection in humans. *O. robertsi* is yet another parasite that has jumped from wild animals to people, Senanayake says. "We're starting to see more and more of these spillover infections."



An MRI scan of a woman's brain shows a lesion (light gray area) that contained a live worm.

The parasite in the woman's brain was far from its usual home. These worms typically shuttle between snakes and small mammals. Adult worms live inside carpet pythons (*Morelia spilota*), which shed worm eggs in their feces. Rats and other animals can ingest the eggs, which hatch larvae that burrow into the animals' flesh. Pythons then eat the infected animals, and the cycle continues.

Humans exist outside this loop, and it's unclear how the woman became infected. Doctors suspect edible plants that she foraged near a lake rife with carpet pythons may have been tainted with worm eggs. The eggs probably hatched inside the woman, and larvae wandered to her organs, causing damage that doctors saw on her CT scans. "If you handle vegetation or wildlife, just make sure you wash your hands," Senanayake says. "If you're cooking and consuming vegetation, make sure you cook it well."

The woman's symptoms improved after surgery and antiparasitic medications. She was "obviously not thrilled" about the worm, Senanayake says, but she was relieved to finally have a pathway to treatment. —*Meghan Rosen*

SOAPBOX

When discussing flora and fauna, don't forget about 'funga'

Fungi. They grow between toes, on bread and in the shower. But the organisms also produce food and medicine and act as ecosystem maids by decomposing dead matter—benefits that are sometimes overlooked (SN: *12/4/21, p. 20*). That's why the Fungi Foundation, an international nonprofit dedicated to fungi education and conservation, advocates for adding "funga" to the popular phrase "flora and fauna."

The mushrooming movement is also backed by the United Nations Convention on Biological Diversity, which in August called for the addition of "a third 'F'—funga—to address the planetary challenges of climate change and biodiversity loss." The term is already gaining popularity in over 20 countries, including Australia, Iceland and Brazil.

Historically, fungi have been left out of most conservation discussions and plans, says mycologist Giuliana Furci, founder of the Fungi Foundation. While flora refers to an area's plant diversity and fauna its animal diversity, fungi don't fit into either category. "Fungi didn't have a way in," Furci says.

Whether soil mold or mushrooms on a log, fungi face the same threats as other life-forms, including habitat loss and climate change. The International Union for the Conservation of Nature considers more than 100 fungal species as threatened or endangered. Fungi also form essential relationships with other organisms, including gut bacteria and plants. That means it is paramount that fungi are considered in conservation policies, Furci says. She and two other mycologists coined the term "funga" in 2018 in *IMA Fungus. Mycota*, derived from the ancient Greek word for mushroom, would have been more accurate, but *funga* seemed catchier, Furci says.

Mycologists call for adding the term "funga" to the phrase "flora and fauna." Their hope: Raise the conservation profile of mushrooms (example shown), molds, yeasts and more.

The phrase "flora, fauna and funga" has broad appeal, says Catherine Gehring, a mycologist at Northern Arizona University in Flagstaff who did not help coin the term "funga." Popularizing the updated phrase will be powerful for encouraging interest in fungi among policy makers and the public, she says. "It's great to see the movement is gaining traction." —*Jude Coleman*

FROM TOP: M.E. HOSSAIN *ET AL/EMERGING INFECTIOUS DISEASES* 2023; G. FURCI

HEALTH & MEDICINE

Pig embryos grow humanized kidneys

The feat brings scientists closer to making transplantable organs

BY AMANDA HEIDT

Scientists have successfully grown kidneys made of mostly human cells inside pig embryos — taking researchers yet another step down the long road toward generating viable human organs for transplant.

The results, reported in the Sept. 7 *Cell Stem Cell*, mark the first time a solid humanized organ with more human cells than animal cells has been grown inside another species.

"This is a considerable progress in human-animal chimerism," says Tao Tan, a cell biologist at the Kunming University of Science and Technology in China who helped create the first chimeric human-monkey embryo in 2021 but was not involved in the current study.

In the United States alone, more than 100,000 people currently sit on an organ transplant waiting list. A vast majority of those people need a kidney transplant. To meet this demand for lifesaving organ transplants, scientists have been pursuing new methods to grow organs and tissues in animals (SN: 2/18/17, *p.* 6).

Advances in the last few years have included growing humanized skeletal muscle and endothelial tissue in pigs. But significant hurdles remain, due in part to how challenging it is for human cells to thrive inside a foreign host. Human induced pluripotent stem cells, or iPSCs, which function as a starter kit for growing many kinds of human tissue, often die when introduced into animals because the species' cells have different physiological needs.

Stem cell biologist Liangxue Lai of the Guangzhou Institutes of Biomedicine and Health in China and colleagues spent more than five years refining their methods to enhance the human stem cells' survivability.

While the pig embryos were still just single cells, the team used the gene-editing tool CRISPR/Cas9 to edit out two genes necessary for kidney development.

Scientists introduced human stem cells into pig embryos (one shown) engineered to lack kidneys. The stem cells then differentiated and grew into new organs made mostly from human cells.

J. WANG *ET AL*/*CELL STEM CELL* 2023

That created a niche in which the human iPSCs, once injected into the space, could develop into kidney cells. The human stem cells were also tweaked to have especially active genes that dampen apoptosis, or cell death, to keep the cells alive long enough to gain a foothold and begin forming the kidney.

More than 1,800 embryos were transferred into surrogate sows and then harvested for study within the first 28 days. Five of the embryos had normal kidneys consistent with their level of development, and the organs contained about 50 percent to 60 percent human-derived cells. That's the highest percentage of human cells yet observed in any organ grown inside a pig, Tan says.

Given more time, there's no indication that the kidneys wouldn't have continued to grow and develop normally, possibly with the human cells increasingly edging out the pig cells, Lai and colleagues say.

The study is "an important and interesting step," says Massimo Mangiola, a transplant immunologist at New York University Langone Health who was not involved in the research. But it's still many years out from fully functional xenotransplants, Mangiola notes.

While the stem cells did differentiate into several cell types, including kidney tubular cells and developmental tissue, the human kidney has over 70 unique cell types that scientists will need to recapitulate. And until researchers can create an organ that is 100 percent human, it's likely that such transplants will prompt rejection.

In addition, a few iPSCs erroneously differentiated into neural cells in the brains and spinal cords of the embryos. Mangiola says that the cells appear to be random, unlike the kidney cells, making him think they're not likely to result in animals with human brains — which would create an ethical quandary.

To avoid such ethical issues, Lai's team says it will knock out genes that orchestrate the stem cells' differentiation into neurons as well as into eggs and sperm, which pass genetic information on to offspring. The team is also pursuing growing other human organ precursors in pigs as well, including the heart and pancreas.

"We feel that we have accomplished a milestone in the field, but this is only the first step, and many challenges remain," Lai says. "We are optimistic that with time and effort we may be able to overcome these challenges too." ■

GENETICS

The Y's genetic puzzle is finally solved

Scientists sequenced the male sex chromosome from tip to tip

BY TINA HESMAN SAEY

The human Y chromosome, responsible for determining male sex, finally has gotten an end-to-end examination.

Researchers sequenced the chromosome, which contains many genes involved in sperm production and fertility, from a male of European descent. The new telomere-to-telomere, or tip-to-tip, construction adds more than 30 million DNA bases to a previously assembled Y chromosome, the team reports in the Sept. 14 *Nature*. It is the final piece of the human pangenome, an effort to catalog all human DNA (SN: 6/3/23, p. 6).

The Y chromosome is the smallest of the 46 human chromosomes. "In the old time, people thought that it's just a junkyard for human genomic material, and it only serves one purpose … to determine male sex," says Yun-Fai Chris Lau, a human geneticist at the University of California, San Francisco who was not involved in the work. Like comedian Rodney Dangerfield, the Y chromosome gets no respect, he says.

But it's clear that the Y chromosome does more than determine male sex, Lau says. Some males lose the chromosome from some of their cells, putting them at risk for cancer, Alzheimer's disease and other illnesses (SN: 11/29/14, p. 13). Having a truly complete encyclopedia of Y chromosomes will allow researchers to better understand the role the chromosome plays in the body, he says.

Though small, the Y chromosome has intimidated many researchers because it has so many repetitive bits of DNA, says Adam Phillippy, a bioinformatics researcher at the U.S. National Human Genome Research Institute in Bethesda, Md., who led the work.

There are repeated DNA sequences made up of millions of building blocks, or bases, laid end to end—like seemingly endless rows of identical puzzle pieces. Some parts of the chromosome have the puzzle pieces inverted. And some stretches of DNA contain palindromes; the bases read the same in both directions. Then there are multiple copies of individual genes.

All that repetition makes it difficult to tell exactly where in the puzzle a particular piece goes, so scientists saved those repeating parts for last, Phillippy says. "When you're putting your puzzle back together again you always save the repetitive bits, like the grass or the trees or the sky, for the end."

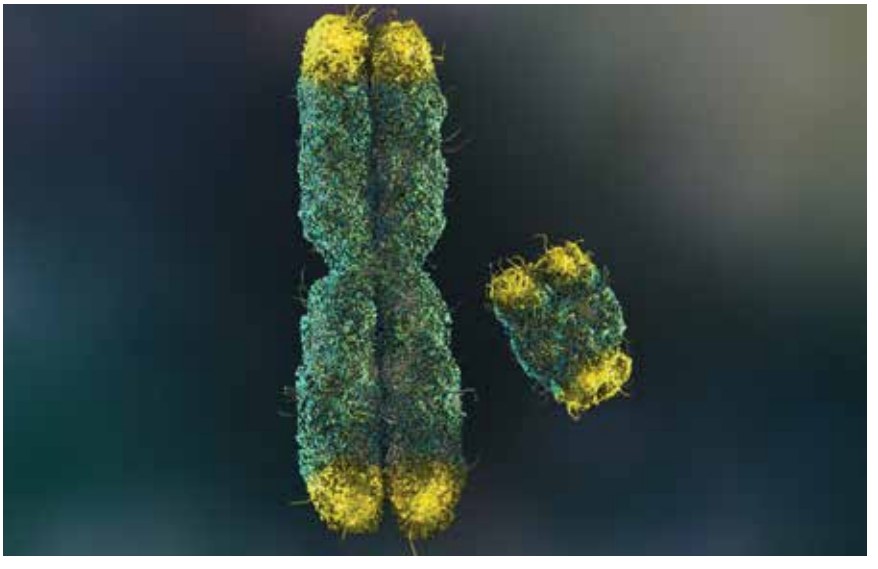
A separate study, also published in the Sept. 14 *Nature*, sequenced the entire Y chromosome from 43 people, including 21 of African descent. That study found that the male sex chromosome can vary in length from person to person by millions of bases, meaning that in some people, the chromosome has extra copies of some genes or other bits of DNA. For instance, males may have between 23 to 39 copies of TSPY genes, which are involved in sperm production, the researchers found.

Having complete Y chromosomes from multiple people helped clear up a mystery. The old reference Y chromosome had the TSPY2 gene located near one tip of the chromosome. But the telomere-to-telomere version showed it close to the centromere—the pinched-in part of the chromosome—and backward compared with the reference.

"We confirmed that it was correct in our assembly, so then we were just assuming that it was an error in the old assembly," Phillippy says. But the second study showed that both versions were right. TSPY2 has jumped around on the chromosome. Some people have it at one location, while others have it at another spot.

Having multiple copies of TSPY genes, and the varying location of TSPY2, may affect the genes' activity and effect on sperm production, Lau says. Some previous studies have hinted that varying numbers of copies may affect fertility, while other studies have found no relationship. The more precise information from the new studies may help settle the debate, or at least give researchers more clues about how the genes influence sperm production, he says.

The new research may also help scientists learn more about the evolution of the Y chromosome, Phillippy says. And eventually, studying its genes and their variants may lead to a better understanding of fertility and treatments for infertility, he says, but such medical applications are years away. ■



NATHAN DEVERY/ISTOCK/GETTY IMAGES PLUS

New efforts to sequence the human Y chromosome (illustrated right; X chromosome shown left) may shed light on its role in fertility and the risk of developing cancer and Alzheimer's disease.

ANIMALS

Leafy swabs pick up animal DNA

The new technique could help scientists monitor biodiversity

BY DARREN INCORVAIA

Just a few swabs from a handful of leaves can say a lot about what animals are roaming in the area.

Two dozen leaf swabs from plants in Uganda's Kibale National Park revealed a stunningly accurate genetic picture of the park's vertebrate diversity, scientists report in the Aug. 21 *Current Biology*. The swabs picked up environmental DNA, or eDNA, shed from 52 types of animals, 30 of which could be identified to the species level. The quick and easy technique is a potentially revolutionary way to monitor biodiversity.

"The fact that they could just swab a few leaves like that and get that many species is really kind of cool and remarkable," says biologist Julie Lockwood of Rutgers University in New Brunswick, N.J.

While people often picture DNA sitting safe and snug inside of cells, the truth is that particles of the genetic material are loose all over the environment. This eDNA often pools together in bodies of water or on surfaces like tree bark. Finding and analyzing eDNA can reveal what species are in an area—even those that are hard to spot.

Biologist Jan Gogarten wanted to compare his eDNA source—flies that consume DNA from feces and dead animals—with that of biologist Christina Lynggaard, who collects eDNA from the air (SN: 2/26/22, p. 4). The two scientists set out to compare their respective techniques in Kibale National Park. Setting up the air filters was time-consuming, so after collecting his flies, Gogarten decided to swab some nearby leaves while he waited for Lynggaard.

"It was not something that we had planned before," says Lynggaard, of the University of Copenhagen.

Swabbing, done across three areas of the park, took a total of 72 minutes, or about three minutes per swab on average. For comparison, Lynggaard ran air filters to collect eDNA for at least 30 minutes each in a previous study, not including time to set up and clean the apparatus.

Scientists swabbed leaves in Uganda's Kibale National Park and identified DNA from 52 types of animals in a new study. The method could revolutionize biodiversity monitoring, researchers say.

The researchers then brought the swabs back to Denmark for analysis. The eDNA turned up many charismatic birds and mammals that are known to live in the park, including the great blue turaco (*Corythaeola cristata*) and African bush elephant (*Loxodonta africana*), but there were a few surprises too.

Colin Chapman, a collaborator on the project and a biologist at Vancouver Island University in Nanaimo, Canada, "has been working in the forest for 30-something years," says Gogarten, of the University of Greifswald in Germany. "He had bird species on the list that he hadn't seen before," but that have been spotted in the park by other people. "There's a lot out there that we just don't see" that can be revealed with eDNA, Gogarten says.

The swabs are more convenient to travel with compared with air filters and other sampling devices. Lockwood, for example, samples eDNA from plant surfaces using paint rollers. With the swabs, she says, "you can just use established forensic techniques to save the swabs and get them out of the field and take them back to the lab."

Because biodiversity is declining in many areas around the world, sampling eDNA using techniques like leaf swabs could be "a revolutionary step forward in our ability to document those changes and respond to them," Lockwood says. "There's not one tool for gathering the eDNA and processing everything that works in every case. So the more tools we have, the better off we are."

Gogarten and Lynggaard hope that other researchers will take their swabbing technique and run with it. The method can even be used by nonscientists. "People interested in citizen science could ... help researchers fight this biodiversity loss that we're having worldwide," Lynggaard says. Gogarten suggests that schoolchildren could use swabs to sample leaves in their own backyards and produce a picture of their area's biodiversity. ■

ANDREAS SACHSE

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CLIMATE

Why hurricanes intensify so swiftly

Record-high ocean temperatures are amping up cyclones in hours

BY CAROLYN GRAMLING

On September 5, a loosely swirling system of thunderstorms formed in the central tropical Atlantic Ocean. By September 6, the system had become a Category 1 storm, with maximum winds of about 130 kilometers per hour.

Within 24 hours, fueled by record-warm waters of the North Atlantic Ocean, Hurricane Lee whipped itself into a Category 5 monster — doubling its wind speeds to 260 km/h.

As the oceans continue to stockpile heat from global warming, stories of such rapid intensification of tropical cyclones are becoming more commonplace, and not just in the Atlantic. While Hurricane Lee gained steam, tropical storm Jova in the eastern Pacific transformed into a Category 4 hurricane within 36 hours.

These storms formed less than two weeks after Hurricane Idalia, which rapidly intensified as it crossed the Gulf of Mexico. Idalia's wind speeds shot up from about 120 to 209 km/h in 24 hours. Soon after, the hurricane slammed into Florida.

These three hurricanes easily met the National Hurricane Center's definition of rapid intensification, in which a storm's maximum sustained winds jump by at least 56 km/h in less than a day. Such storms can leave people little time to prepare, making the hurricanes particularly dangerous to lives and property.

The key ingredients to boost a storm's power quickly are very warm ocean waters, a lot of moisture in the atmosphere and low vertical wind shear, says atmospheric scientist Philip Klotzbach of Colorado State University in Fort Collins.

Vertical wind shear is what happens when winds at different heights in the atmosphere are moving at different speeds and in different directions. Those winds can chip away at a storm as it tries to organize into a tight swirl by pulling heat and moisture away from the storm's center and sweeping away the upper structure of the storm.

This year saw the onset of an El Niño climatic phase, which tends to bring more vertical wind shear conditions to the North Atlantic. That means El Niño years tend to feature fewer Atlantic tropical storms (SN: 7/1/23, *p.* 9).

But so far in 2023, El Niño hasn't done much to minimize hurricane formation or dampen the storms' power. "The first half of the season has not seen the unfavorable upper-level wind conditions in the western Atlantic that are typically observed in an El Niño year," says meteorologist Ryan Truchelut of WeatherTiger, a weather consulting firm based in Tallahassee, Fla. That's true even in the Caribbean Sea, where El Niño's shearing power tends to be strongest, Truchelut says.

Generally, there's more of a temperature difference between the Atlantic and Pacific ocean basins during an El Niño year — the weather pattern heats up the eastern tropical Pacific while the Atlantic stays relatively cool. But 2023 has seen record-breaking ocean temperatures in the North Atlantic Ocean and in the Gulf of Mexico (SN: 7/15/23 & 7/29/23, *p.* 5). While the El Niño–warmed Pacific is about 1.5 degrees Celsius above normal, parts of the Atlantic are 1 to 3 degrees above normal. "Temperature contrasts drive jets," high-altitude air currents that can drive shear winds, Truchelut says. "The lack of this contrast is likely responsible for the missing shear."

Extremely warm waters in the Atlantic and the Gulf of Mexico set the stage for rapid intensification. All the storms needed was a window of time with favorable wind conditions, says John Kaplan, a hurricane modeler with the National Oceanic and Atmospheric Administration who is based in Miami. "What it really comes down to is whether the conditions for rapid intensification are favorable for even a short period of time," Kaplan says. "If there's a window — even if not a very long one — the system can take advantage of it. That was the case for both Lee and Idalia."

Though it certainly *feels* like most of the hurricanes in recent years are rapidly intensifying, is that a true trend? And is it linked to climate change?

Studies suggest that the observation isn't just anecdotal. The yearly number of tropical storms around the world that rapidly intensified close to shore (within 400 kilometers) increased by about three per decade over the last 40 years, researchers report August 24 in *Nature Communications*. In the 1980s, there were

Hurricane Lee, shown over the Atlantic Ocean on September 8, intensified from a Category 1 to a Category 5 storm in just 24 hours. Such storms are rapidly intensifying more often as Earth warms.

STAR/NESDIS/NOAA

fewer than five such storms per year. By 2020, there were about 15 per year.

Open-ocean storms showed no discernible trend. But that's perhaps not wholly reassuring, as it's the storms closer to shore that are most threatening to coastal populations. A 2021 study in *Science* found that tropical cyclones have been migrating closer to the coasts since 1982.

In 2019, another team focused on observational records of wind-speed changes over 24-hour increments. Those data suggest that episodes of rapid intensification in tropical storms tripled from 1982 to 2009, the researchers reported in *Nature Communications*. Using climate simulations, the team determined that the rapid intensification trend was strongly linked to human-caused climate change.

What's more, a large proportion of tropical cyclones are now undergoing rapid intensification at some point in their life cycle, members of that team reported in 2022 in *Nature Communications*.

Regional and local weather patterns "could dampen rapid intensification trends locally," Truchelut says. "But there is strong objective evidence that anthropogenic global warming is driving increased proportions of tropical cyclones to undergo rapid intensification worldwide."

Klotzbach and colleagues, meanwhile, found another fingerprint of climate change in the rapid intensification of cyclones. Increases in global sea surface temperatures correlate well with an increase in the potential intensity of tropical cyclones over the last 30 years, the team reported in 2022 in *Geophysical Research Letters*. That was especially true for the most monstrous storms — those whose wind speeds increased by a whopping 93 km/h or more in a single day.

By mid-September, Lee and Jova had neared the end of their runs. Lee made landfall in Nova Scotia as a post-tropical cyclone while Jova fizzled out at sea. Since hurricane season ends November 30, there's still time for all that warm water in the Atlantic to fuel the next big ones. Indeed, at publication time, the National Hurricane Center warned of yet another storm brewing in the Atlantic that had the potential to rapidly intensify. ■

ANIMALS

A pirate spider's hunting trick revealed

The arachnid cleverly exploits the way other spiders build webs

BY ELIZABETH ANNE BROWN

A Costa Rican pirate spider lives up to the family name: It tricks closely related orb weaver spiders into walking the plank, right to their doom.

The world's many pirate spiders exploit a very particular food source — other spiders. But while most pirate spiders invade the webs of other arachnids, one species dupes potential prey into building a web right into a trap, researchers report July 27 in *Animal Behaviour*.

In the rainforests of Costa Rica, the pirate spider *Gelanor siquirres* hunts other arachnids by tricking them into hitching silk lines to a trap.

Like any respectable pirate, pirate spiders have an extensive bag of tricks. Some species delicately strum the threads of other spiders' webs to convince the arachnids they've caught an insect and then strike when the web owner comes to collect its prey. Others mimic on a web the signature rhythms of a different spider's courtship dance, luring would-be suitors to their deaths.

On a trip several years ago to a biological reserve in Costa Rica, arachnologist Laura Segura-Hernández and colleagues were the first scientists to witness a hunt by a little-known pirate spider called *Gelanor siquirres*. To get a meal, the arachnid exploits the way other spiders make their webs, the team realized.

At nightfall in steamy lowland rainforests, orb weavers let loose floating lines — single strands of silk that blow in the breeze until the free end sticks on a surface such as a tree branch. The orb weaver then scurries across to secure the second anchor point, and this first moored line serves as the foundation for the web.

But in some cases, the orb weaver does not scuttle across this bridge to welcoming vegetation. Instead, it walks into a trap; *G. siquirres* has already cast its own silk lines to intercept the orb weaver's.

During their trip, the researchers pieced this together when they came upon a perplexing scene: An unusual configuration of multiple strands of silk converged on a single leaf. The team also noticed another spider's floating line caught on one of those strands. Then, as the floating line's owner — a juvenile orb weaver — scuttled across, a pirate spider emerged from behind its leaf hideout and crept down toward the intersection.

Probably feeling vibrations from the approaching pirate spider, the orb weaver attached a dragline (the arachnid's version of a bungee cord) and flung itself off its bridge line. The pirate spider pursued close behind from its own dragline.

It was a dramatic scene, says Segura-Hernández, of the University of Nebraska–Lincoln. "They're hanging there, fighting," she says, like two swashbuckling pirates exchanging blows while swinging from the rigging. The encounter ended with a surprisingly swift attack from the pirate that instantly immobilized its victim.

The hunting strategy is a total surprise, says biologist Gustavo Hormiga of George Washington University in Washington, D.C. Exploiting how other spiders build their webs is "pretty sophisticated," he says. "I don't know of anything like that in any [other] spider group."

The finding helps bring *G. siquirres* to life, says Hormiga, who helped name and describe *G. siquirres* in 2016. Until now, the species was known to science through only a museum specimen collected in 1994.

The finding also underscores the importance of scientists getting out into the field, Hormiga says. "For many of us, this is really what brought us into science." ■

G. BARRANTES, L. SEGURA-HERNÁNDEZ AND D. SOLANO-BRENES/*ANIMAL BEHAVIOUR* 2023

ARCHAEOLOGY

A complex mummy-making recipe

Jars holding the innards of an ancient Egyptian noblewoman from roughly 3,500 years ago contain hints of one of the most complex mummification balms yet discovered.

During mummification, the viscera would be removed from the body and placed in decorative jars along with a balm meant to preserve organs. To find out exactly how the noblewoman's innards were preserved, archaeological chemist Barbara Huber and colleagues ran chemical analyses on the residue in the jars (the top of one shown at left) that once held the lungs and liver.

The remains were preserved in a blend of substances that included oils, fats, beeswax, tree resins, tarlike bitumen and, in a possible first, the sap from larch trees, the researchers report August 31 in *Scientific Reports*.

"We were lucky because we identified one of the most complex mummification balms ever found," says Huber, of the Max Planck Institute of Geoanthropology in Jena, Germany. Some of the ingredients may have come from as far away as Southeast Asia. This suggests that Egyptians may have had certain far-reaching trade routes up to a millennium earlier than previously thought. — *Luis Melecio-Zambrano*

CHRISTIAN TEPPER/MUSEUM AUGUST KESTNER

HEALTH & MEDICINE

Protein linked to brain rejuvenation

Mouse studies hint at a way to treat age-related decline

BY SIMON MAKIN

A single molecule may play a central role in rejuvenating aging brains, albeit in multiple ways, new research suggests.

Studies in mice of three different techniques for combating the cognitive decline that accompanies aging found that they all increase levels of a protein called platelet factor four, or PF4. This in turn improved cognitive performance and biological signs of brain health, three research groups report August 16 in *Nature Aging*, *Nature* and *Nature Communications*.

"PF4 may be an effective factor, and this kind of work will help bring it toward a therapeutic agent" for age-related cognitive decline, says bioengineer Michael Conboy of the University of California, Berkeley, who wasn't involved in the work.

One of the research groups, led by neuroscientist Dena Dubal of the University of California, San Francisco, was studying klotho, a hormone linked to longevity. Injecting the hormone into mice boosts cognition, but since klotho is too large to cross the blood-brain barrier, it must act on the brain indirectly via a messenger.

To search for this intermediary, Dubal's team injected mice with klotho and measured changes in the levels of six proteins in the blood. PF4 increased the most, the team reports in *Nature Aging*.

Platelets are known for their role in wound healing and clotting, and they release proteins — including PF4 — called platelet factors into the blood. "My first reaction was, what do platelets have to do with cognitive enhancement? This is crazy," Dubal says. Follow-up work in mice found that PF4 enhanced neural connections in the hippocampus, a region crucial for memory.

Another UC San Francisco team, led by neuroscientist Saul Villeda, had previously shown that blood plasma from young mice rejuvenates the brains of elderly mice. A look at how young plasma differs from old revealed that young plasma contains much more PF4, the team reports in *Nature*. Injecting PF4 into old mice returned the immune system to a more youthful state, lowering levels of inflammatory proteins and reducing inflammation in the brain.

Separately, neuroscientist Tara Walker, of the University of Queensland in Brisbane, Australia, and colleagues found that exercise boosts PF4 in mice. Delivering PF4 directly to mice's brains spurs new nerve cell growth in the hippocampus, the team reports in *Nature Communications*.

The new studies all show that PF4, on its own, improves cognition. "More and more research is pointing toward a link between the immune system, cognitive decline and diseases like Alzheimer's," Villeda says.

The main limitation of these studies is that few findings in mice translate into safe and effective therapies in people. But in humans, as in mice, PF4 declines with age.

In July, Dubal and colleagues reported that klotho improves cognition in aging monkeys, whose brains are much more similar to ours. But whether that improvement involves PF4 is not known.

Researchers plan to start testing treatments based on PF4 in humans within the next few years, Villeda says. ■

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ANIMALS

Some songbirds excel at brainteasers

A study of over 20 species links vocal learning ability with smarts

BY DARREN INCORVAIA

By now, it's no secret that the phrase "bird brain" should be a compliment, not an insult. Some of our feathered friends are capable of complex cognitive tasks, including tool use (SN: 3/11/23, p. 12). Among the brainiest feats that birds are capable of is vocal learning, the ability to learn sounds and use them to communicate. In birds, this leads to beautiful calls and songs; in humans, it leads to language.

The best avian vocal learners, such as crows and parrots, also tend to be considered the most intelligent birds. So it's natural to think that the two traits could be linked. But studies with smart birds have found conflicting evidence. Although vocal learning may be linked with greater cognitive capacity in some species, the opposite relationship seems to hold true in others.

Now, a massive analysis of 214 birds from 23 songbird species shows that there is indeed a link between vocal learning and at least one advanced cognitive ability — problem-solving. The study, described in the Sept. 15 *Science*, is the first of its kind to analyze more than just one species.

To compare species, biologist Jean-Nicolas Audet and colleagues had to devise a way to assess all the birds' vocal learning and cognitive abilities.

For vocal learning, the team scoured the scientific literature to find how many songs and calls a particular species could learn, whether it could learn vocalizations throughout life or just for a set developmental period, and whether it could mimic other bird species. "Our novel way of measuring vocal complexity integrates those three features together," says Audet, of the Rockefeller University in New York City.

The researchers next developed cognitive tests that could be adapted for different species. A test built for a tiny house wren (*Troglodytes aedon*), for instance, might not work for a bulky mourning dove (*Zenaida macroura*). Audet and research assistant Mélanie Couture ultimately presented birds with seven cognitive tasks over six days.

Four of the tasks tested problem-solving ability. For example, one task involved pulling a cork lid off a flask to access food inside. The other three tasks assessed learning and self-control, other hallmarks of advanced cognition.

The team then analyzed whether the species with more complex vocal learning abilities, such as bigger song repertoires, mimicry and lifelong learning, performed better on intelligence tests than the species with limited abilities.

Problem-solving, but not learning or self-control, is strongly associated with more complex vocal learning in birds, the researchers found. "The more advanced vocal learning ability, the more advanced problem-solving skills," says coauthor Erich Jarvis, a biologist at Rockefeller University.

Take the tufted titmouse (*Baeolophus bicolor*), for example. This species learns about 63 vocalizations and can learn throughout its life. It completed the problem-solving tasks faster than the brown-headed cowbird (*Molothrus ater*), which learns only about nine vocalizations within a set developmental window.

The new finding is a "very convincing, positive result," says William Searcy, a biologist at the University of Miami who studies birdsong. Audet's team also found a link between complex vocal learning, better problem-solving ability and bigger brains relative to body size. That could partially explain the result, Searcy says. A bigger brain is likely necessary to excel at both vocal learning and problem-solving.

The researchers euthanized some of the birds and saved their brains to search for the genes underlying the linked traits. That future work could have implications for scientists' understanding of how human language evolved. "There is a chance that we will discover genes related to problem-solving and vocal learning that are possibly also used in humans for those same behaviors," Audet says. ■

The tufted titmouse (*Baeolophus bicolor*) can learn about 63 vocalizations and was the top problem-solver in a study of 23 bird species that links intelligence with vocal learning.

M. COUTURE

Watch a video of birds solving brainteasers at **bit.ly/SN_BirdBrain**

PLANETARY SCIENCE

Space rocks may light up Venus' sky

Meteors, rather than lightning, could trigger mysterious flashes

BY SID PERKINS

Occasional flashes light up Venus' shroud of clouds. Previous analyses have hinted that the bursts of light could be lightning in the hellish world's atmosphere. But most of the flashes may be nothing more than the brief yet brilliant blazes of meteors, a new study suggests.

Upcoming missions planned for Venus, have scientists eager to figure out the light's origin. If the flashes are lightning, the electrical phenomenon could pose risks to future probes in the Venusian atmosphere, says planetary scientist Claire Blaske of Stanford University. Small meteors that burn up in the atmosphere, however, wouldn't pose much of a danger.

Previous landers on Venus have detected electromagnetic static similar to the type caused by lightning during thunderstorms on Earth, Blaske says. And orbiters and Earth-based telescopes have discerned brief, bright flashes in the atmosphere. But the static and optical flashes have never been detected simultaneously, Blaske says.

Given how little is known about the dynamics of its atmosphere, "it's not clear there is the potential for lightning on Venus," says Paul Byrne, a planetary scientist at Washington University in St. Louis who was not involved in the study.

While at Arizona State University in Tempe, Blaske and colleagues wondered whether meteors could be masquerading as lightning on Venus. Two previous surveys counted the flashes of light: one by a telescope on Arizona's Mount Bigelow and one by instruments aboard Japan's Akatsuki orbiter (SN: 1/9/16, p. 14).

The team's analysis of that data suggests Venus experiences between 10,000 and 100,000 of these flashes each year, the researchers report in the September *Journal of Geophysical Research: Planets*.

That may seem like too many flashes to be caused solely by meteors. After all, Venus is a smaller cosmic target and encounters fewer meteors than Earth. But meteors there will be substantially brighter and more noticeable because they are traveling faster on average: The space rocks enter Venus' atmosphere at about 25 kilometers per second compared with about 20 km/s for those entering Earth's. In part, that's because Venus is traveling around the sun faster than Earth is.

Accounting for those factors, the team concluded that meteors could be numerous enough to account for nearly all the flashes expected to occur in Venus' skies.

The analysis "does a nice job of establishing a plausible explanation," Byrne says. Measuring the flashes and electromagnetic static at the same time could help resolve the mystery. But such observations may not rule out a form of flashless lightning that could pose a risk to probes. ■

HEALTH & MEDICINE

A lullaby helps calm newborns' pain

Music could be a beneficial addition to pain-relief tactics

BY AIMEE CUNNINGHAM

The soothing tones of a classical lullaby may help to relieve the pain newborns can feel from routine medical procedures.

In a randomized clinical trial, newborns received a sugar solution, a standard method to lessen pain, before a heel prick. About half of the infants also heard a lullaby before, during and after the procedure. The lullaby group scored lower on a pain scale than the group that got only sugar, researchers report August 29 in *Pediatric Research*.

"Since they gave sucrose, it's hard to say yes, music by itself would help," says Mallory Perry-Eaddy, a pediatric intensive care unit nurse and a nurse scientist at the University of Connecticut in Storrs. But combining music with other pain-relieving methods "could be really useful."

Until recently, the medical community did not think newborns experienced pain. But over the last several decades, studies have revealed that infants do perceive pain and may be more sensitive to painful stimuli than adults are. Enduring repeated pain-inducing procedures without pain relief can have lasting neurological consequences for infants, including a heightened perception of pain.

"It's very important that we do try to stay on top of [pain] prior to procedures," Perry-Eaddy says, rather than just trying to alleviate pain afterwards.

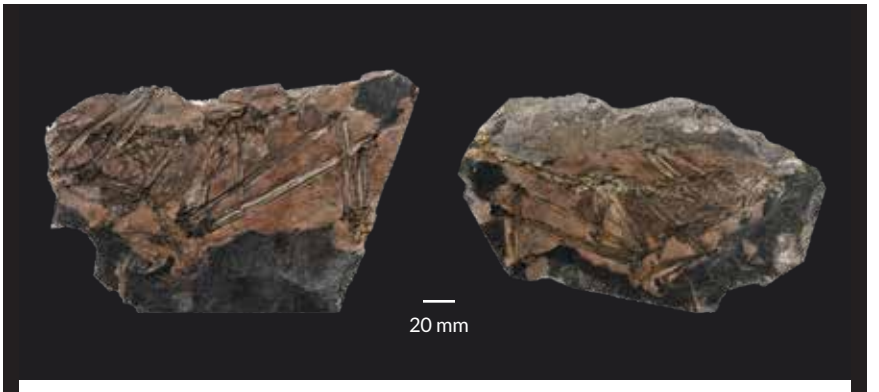
Heel pricks and shots are among the routine procedures newborns have that can cause pain. Generally, for minor procedures, doctors and nurses turn to pain-reducing methods that don't involve medication, says Saminathan Anbalagan, a neonatologist at Lincoln Medical and Mental Health Center in the Bronx, N.Y. These methods include skin-to-skin contact between a parent and an infant, breastfeeding and a sugar solution.

Anbalagan and colleagues studied music as another potential option that could be easily implemented and cost-effective. The team randomly sorted 100 infants born at Lincoln into a lullaby and a no-music group. For the lullaby group, the piece "Deep Sleep" from *Bedtime Mozart: Classical Lullabies for Babies* began playing 20 minutes before a heel prick and continued for five minutes after. The researchers assessed pain with a neonatal infant pain scale that considers newborns' facial expressions, whether they cry, their breathing patterns and other signs. The pain scale ranges from 0 to 7.

During the heel prick, the no-music group had an average pain score of just under 7. But serenading the infants reduced the score to below 5. After that peak, the overall score steadily dropped for both groups in the next five minutes, with the lullaby group still scoring lower.

More research is needed to better understand neonatal pain and determine the most effective ways to relieve it, including the optimal combination of methods, Anbalagan says. But "proven and safe therapies are currently underused for routine minor, yet painful procedures," according to the American Academy of Pediatrics. Anbalagan and colleagues sought to bring awareness to newborn pain with their study.

"While the misconception [about newborns and pain] has faded, it continues to be a common way of thinking in some health care settings," Anbalagan says. "Why some hospitals don't have protocols for pain relief from minor procedures in neonates remains puzzling." ■

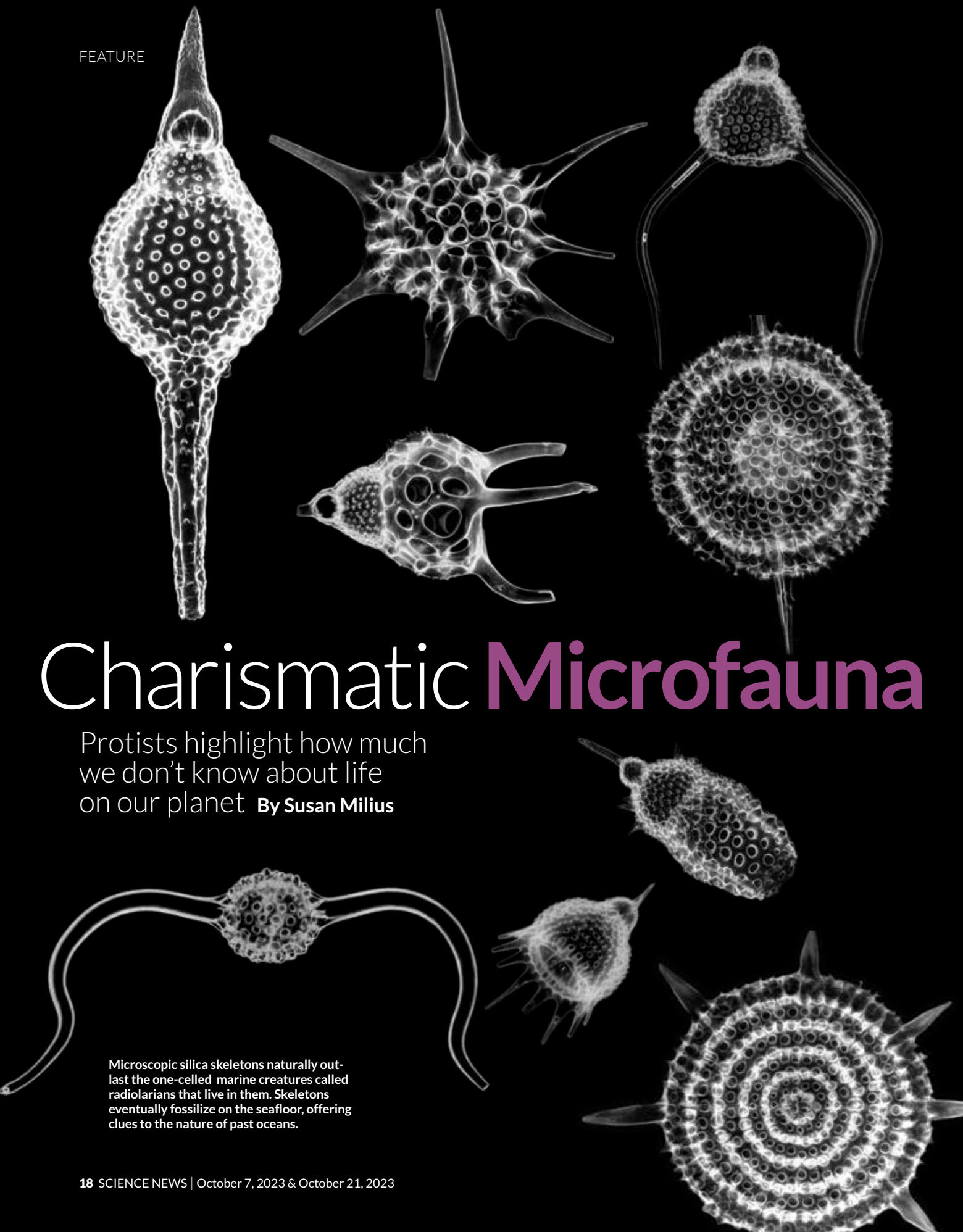


M. WANG

PALEONTOLOGY

Leggy dino kicks off a bird evolution rethink

Early birdlike dinosaurs are thought to have lived lofty lives up in the trees. But a newly discovered creature had surprisingly long legs that may have made for a life on the run. *Fujianvenator prodigiosus*, described in the Sept. 14 *Nature*, lived about 150 million years ago and is one of the earliest known avialans — a group that split from the rest of dinosaurs and eventually became birds. But the fossilized creature (two views shown above) displays a trait not found among any other known avialan or even *Archaeopteryx*, one of the earliest known birds. The pheasant-sized dinosaur's lower leg bones are twice as long as its thigh bones. "It looks quite similar to *Archaeopteryx* … except the legs," says paleontologist Min Wang of the Chinese Academy of Sciences in Beijing. "*Fujianvenator* has really, really long legs." Until now, early avialans were thought to be short-limbed, which would have made moving among trees a breeze. *F. prodigiosus*, found with fossils of aquatic and semiaquatic species in southeastern China, probably lived in swamplike environs and could have waded through water like a primitive crane, Wang says. The finding paints a more complex picture of the first avialans, he says. — *Nikk Ogasa*



Charismatic Microfauna

Protists highlight how much we don't know about life on our planet

By Susan Milius

Microscopic silica skeletons naturally outlast the one-celled marine creatures called radiolarians that live in them. Skeletons eventually fossilize on the seafloor, offering clues to the nature of past oceans.

Gumdrop with an earring.

That's what pops to mind when I look at Sebastian Hess' photos of a kind of plump, violent, single-celled creature he collected from a pond rich in sphagnum moss in southern Germany. The shape-shifting amoebozoan cell, prowling for algal cells to attack, curls its long strand of a flagellum into an earringlike loop. Holding the loop steady, the cell somehow glides. Yet the loop doesn't flick, lash or wave. "They look basically like tiny flying saucers," Hess says.

He first collected the creatures, with no species name and a baffling form of locomotion, in 2010 and wondered for years how the locomotion worked. Hess has been seeking and tending such single-celled wonders since he was a teenager with a windowsill microzoo. As a grown-up, now at Technical University of Darmstadt in Germany, he specializes in the microscopic group his zoo featured: the protists.

This big, varied group of single cells are among the closest microbial cousins to multicellular life, and they wrap their genetic material inside a cell nucleus just as animals, plants and fungi do. Schoolroom trees of life for much of the 20th century and sometimes afterward often relegated the protist kingdom to some lower branch beneath the glorious crown of mostly multicellular kingdoms. Biologists think a little differently now, and bigger than mere kingdoms.

Today's more modern schemes feature at least two vast hoops of microbial creatures, called the domains of Bacteria and Archaea. A third hoop, the Eukaryota, sweeps together the protists and the formerly proud treetop kingdoms: the animals, plants and fungi. Another sweep may be imminent, as the whole domain of eukaryotes, including the protists and the people who classify them, appear to be a branch of Archaea.

As for the flying saucers, Hess and colleagues worked off and on for almost 10 years to understand how such a cell moves so strangely. It's a form of locomotion never found before in a living being, Hess says. This toroidal, or "doughnut," swimming inspired Hess and colleagues in 2019 to put the newfound species in its own new genus — *Idionectes*, roughly meaning "peculiar swimmer."

More in a bit on how to swim like a doughnut, but the species, *Idionectes vortex*, makes a fine example of how high-tech biology plus old-fashioned boots-in-mud exploration are creating a rush of discovery for a charismatic group of tiny lives on Earth. These single-celled organisms are far from boring little dots. Plus, they're adding some unexpected twigs and branches to the evolutionary tree of life.

Non-animal planet

To pick just a few examples of 2023's new protists, a species named in June has the one-celled equivalent of a rotating head. In this roughly globe-shaped cell discovered in a South American termite's gut, the top spins steadily around without ripping or self-strangling. Discoverers picked a demon-themed name, *Daimonympha friedkini*, inspired by the spinning head of the demonically possessed child in director William Friedkin's 1973 film *The Exorcist*.

Some other new species belong to the odd-looking but ecologically important coccolithophores. This branch as a whole may do as much as 10 percent of the oceans' photosynthesis, turning sunlight into stuff other creatures eat. Each coccolithophore cell covers itself in what look like tiny hubcaps. Among the distinctive features of the newly named *Calciopappus curvus* is a pair of thumblike stubs on some of those hubcaps.

Researchers in China named a notably small species in the *Euplotes* genus, *E. mazeii*. *Euplotes* cells grow several sets of skinny projections called cirri that look like stick-drawing legs. Even with no brain or nervous system, the various kinds of *Euplotes* can move their legs with enough coordination to walk on an underwater surface. Engineers seeking inspiration for microscale robots have been analyzing such gaits.

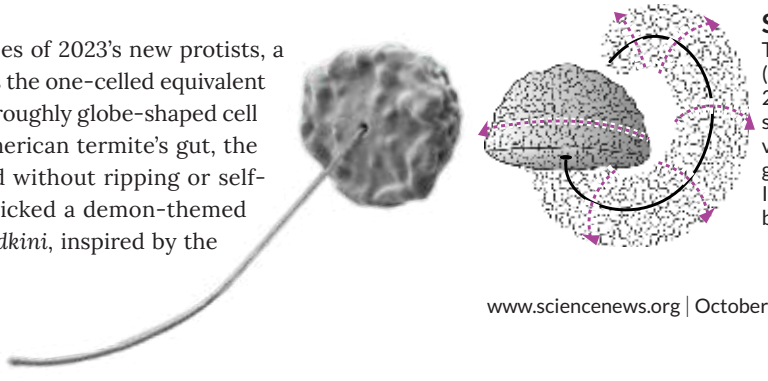
Even long-known protists have allure as a form of microwildlife. Like big cats and polar bears, many of these charismatic microfauna deserve their own nature documentaries. Hess has helped film one of his longtime favorite protists, a kind of *Lacrymaria*. This mildly pretty teardrop-shaped cell chases prey by shooting out a cartoonishly long swan neck that can stretch more than seven times the organism's original body length. The neck, with a headlike bump at the end, swerves this way and that lithe as a snake, until a sudden pounce finally snags dinner.

"Stunning" is Hess' word for protists. "They really behave like entire organisms. But they are just cells."

Or consider five new species of tiny, voracious cells nicknamed nibblerids. Only about 3 micrometers across in their sickle-shaped hungry form, these protists bite (sort of) their typically larger victims by closing down on them with a special body groove armored with hardened toothlike bits called denticles.

The nibblerids and their closest known relatives, called nebulids, represent such a distinct and ancient lineage that they deserve their own big branch on the eukaryote family tree, evolutionary biologist Patrick Keeling of the University of British Columbia in Vancouver and colleagues reported last year. Keeling speaks passionately about the importance of predators as more than nature-watching fun. "If you took all the lions and cheetahs and killed them all," he says, "the whole ecosystem would go wacky." That's likely the case with protists, too.

Today's protists are sorted into supergroups, which are branches bigger than the classic eukaryote kingdoms and give a broad and deep view of evolution. The Amorphea supergroup,



Spin and swim
The protist *Idionectes vortex* (left) was discovered in 2010, but only recently did scientists show that it moves via toroidal swimming. Its flagellum loops like a doughnut. It and the dome-shaped part both rotate (purple arrows).

OPPOSITE PAGE: PICTUREPEST/FLICKR (CC BY 2.0); THIS PAGE: S. HESS *ET AL*/*NATURE MICROBIOLOGY* 2019

for example, spans all animals and fungi plus some one-celled relatives including many amoebas. The new supergroup named for the nibblerids and nebulids, Provora, alludes to "devouring voracious protists," Keeling and his colleagues wrote.

Idionectes too, for all its serene UFO-like travel, is a fierce predator. When it finds algae to feed on, the gliding spaceship becomes an attack amoeba. It dissolves a hole through the algal cell wall but doesn't feed tiger-style, flesh-ripping from outside the kill. Instead, *Idionectes* slides through the hole in the wall, decanting itself into the doomed prey cell. Then this hunter devours its prey from the inside.

Watching protists could be terrifying, if they were bigger. Or if humans were smaller.

Same place, different world

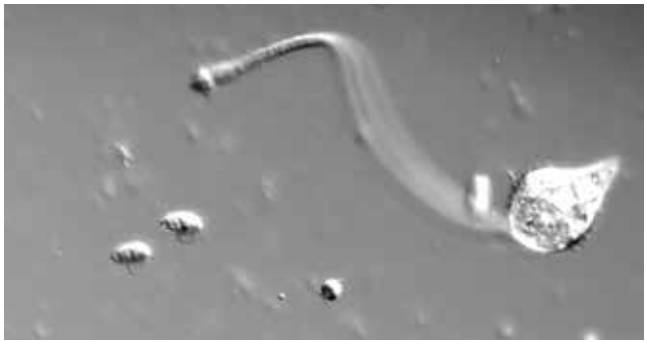
"We spend so much time trying to imagine alien worlds," says Keeling. "There's one right under our noses, more weird than anything we can think of."

He's not being theatrical. Consider the way specks of protist bodies experience water, for example. It's radically different from the way giant lumbering humans and other macroscopic swimmers do. Lone cells are so tiny, the properties of plain water push them down evolutionary paths barely recognizable to us.

Dive into a swimming pool and, "if you're not kicking, you still go forwards for quite a while until you stop, right?" Keeling says. A single cell, though, is so small that even the viscosity of water means the tiny swimmer barely glides at all (SN: 7/4/09, *p.* 22). If it stops swimming, it just … stops. "It's more like you're in corn syrup," Keeling says.

Besides slowing locomotion to a creep, the Syrup World no longer allows for certain swimming strokes. A scallop normally jets around by opening its shell slowly and closing it fast. But if magically miniaturized, the scallop would be stuck in place, flapping, physicists have predicted. It would make progress by shutting its shell but unmake that progress opening it again.

On the upside, though, motions that are useless for full-size people or scallops could propel a tiny swimmer. In 1952, physicist Geoffrey Ingram Taylor theorized that a microbial swimmer shaped like a doughnut could move itself with a sort of inward rotation. (The idea gets credited to a charming talk in 1976 by U.S. Nobel laureate and physicist Edward Mills Purcell, but Taylor came before Purcell.)



This teardrop-shaped single cell, a kind of *Lacrymaria*, hunts by shooting out a long necklike projection (pointing to the left above). The neck can follow fleeing prey until the enlarged end gets a grip.

That rotation is basically how the loop *Idionectes* cell turned out to swim, Hess and colleagues announced nearly 70 years after Taylor's suggestion. The cell's long, stringy flagellum curls into the scrawniest, skinniest thing ever likely to be described as a doughnut. It's far more hole than dough, but it still approximates Taylor's notion.

In a diagram developed by Taylor, the sides of a doughnut rise through the hole, over the rim and wrap around the other side for another slide into the middle. At first, Hess could tell that his gumdrop cell clearly spun, but looking at the flagellum's skimpy doughnut-shape with plain microscopy, "you cannot see any movement," he says. But when he and colleagues made underwater blizzards of latex microparticles in syrupy fluid (a technique that gave the researchers a breakthrough eight years into their efforts), Hess saw telltale particle movements showing the flagellum was rotating.

Age of discovery

Vittorio Boscaro, in Keeling's lab at the University of British Columbia, has another rotation mystery. "We have no idea why they're doing this," he says. We're on a video call, and he's sharing his screen to show the new protist species with a rotating head, *D. friedkini*. In the ghostly grays of light microscopy video, a chunky cell swims as its top, like a large knobby polar ice cap, steadily rotates. It's mesmerizing.

The 2023 paper announcing the discovery of *D. friedkini* calls rotating wheel structures "famously rare" in biology. Bacteria can freely spin their flagella without twisting themselves into pieces, but cells with more built-in structures rarely manage.

Still, this wasn't the first spin-top among complex cells. Analyzing genetic material, researchers worked out a probable family tree of near and far relatives. Oddly, this beast doesn't seem that closely related to another species with a rotating head informally called rubberneckia, which researchers have sporadically written about since 1974. To study protists is to live in weirdness.

That the new species came from a termite gut was no big deal, Boscaro gently tells me, because protistologists have been gutting termites in search of new species of rotating protists (rubberneckia and *D. friedkini* both belong to a group called Parabasalia) for more than a century.

Protists are everywhere. Kiran More, then an undergraduate at Dalhousie University in Halifax, Canada, picked up a bunch when he added a little bit of species prospecting to a family trip in 2016.

As summer waned before More's senior year, his family went driving through the eastern countryside of Nova Scotia. They stopped at a village on Cape Breton Island to admire a replica of the beloved 1920s schooner pictured on the Canadian dime, and More scooped up some shore sand. It took only a matter of minutes; he had packed a set of sampling tubes just in case. "I just carried it from hotel room to hotel room and stuck it in the minifridge, when there was a minifridge," he says.

S.M. COYLE *ET AL/CURRENT BIOLOGY* 2019

When he returned to school, the sludge became part of his undergraduate project looking for unknown species of marine amoebas called vampyrellids (SN: 11/28/15, p. 13). The name may conjure nightmares, but even two of More's ferocious finds look less jaw-and-claw and more bed-and-breakfast. They resemble a fried egg.

Though vampyrellid body plans vary, in this case, the egg's "white" is the structure that breaks through the outer covering of prey to harvest the nutritious insides. Watching a small algal cell caught by the vampyrellid reveals the predator pressing against the algal cell until the victim stops moving, draining the dying cell's innards in five to 10 minutes.

More's single sample of collected sand ended up providing at least seven visibly different kinds of vampyrellid amoebas. *Placopus melkoniani* and *P. pusillus*, fried-egg vampyrellids now named as new species, hunt by rolling forward. Their outer membranes move "like a conveyor belt," More says, or the treads on a tank. "You can see all their cell contents inside also rotating as the outer membrane rotates, which is almost beautiful," he says.

In 2021, that same vacation sample delivered a third new species. More, by then a graduate student in systematics and evolution at the University of Alberta in Edmonton, Canada, and colleagues named that new species *Sericomyxa perlucida*, meaning "transparent silken slime." It looks like a road-killed badminton shuttlecock but with exquisitely delicate tufts. And it was not just a new species in a new genus but also represented a whole new family.

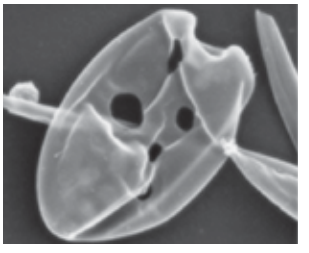
Any ornithologist or mammalogist would have been thrilled with the results. But in the giddy frontier of protist discovery, "I was disappointed," More says. "I was so determined that I was going to find an environmental lineage where no one had seen anything before."

When Swedish botanist Carl Linnaeus, the 18th century founder of Western science's biological naming system, studied single-celled organisms, he was limited to looking. He named relatively few single-celled organisms and put most in a genus he eventually called *Chaos*. Today's biologists have many more high-tech tools at their disposal, but the evolution of life on Earth still looks chaotic. One cell of a type of protist called a cryptomonad has seven separate sets of genes, according to research reported this year. Three of the extra sets come from little organs descended from long-ago free-living cells, two from symbiotic bacteria that had apparently become essential and another from a virus hitchhiking in one of the bacteria.

Little is big

"We're an aberration," says Maureen O'Malley, a philosopher of microbiology at the University of Sydney, as one multicellular earthling talking to another. In the modern view of life, single-celled microbes — protists among them — dominate the planet. Big multicellular life-forms now look like the rare, outlier freaks. A 2018 comparison estimates that Earth's protists account for twice the gigatons of carbon as all the animals put together. Add in other microbes, and together they hold 40 times the biomass.

Earth was entirely a microbe's world for some 2.5 billion years or more, the majority of life's history, O'Malley points out. We big



A recently discovered protist named *Placopus melkoniani* looks like a fried egg (above). It and another new member of its genus, *P. pusillus*, create holes in algal cells (left) and eat the innards. The species are members of the ominous-sounding vampyrellids.

multicellulars evolved on the backs of microbe innovations. Just a few examples: The oxygenated atmosphere came from cyanobacteria photosynthesizing 2.7 billion years ago. Even today an estimated half of the oxygen we breathe comes from microbial sources, not from plants. And plants' ability to generate oxygen came from engulfing the microbial technology we know as chloroplasts.

Termites "eat" wood thanks to the protists packed into their guts. Tomato plants grow better with more of the predatory protists in the soil around their roots. Bobtail squid get the glow in their light organs from engulfed bacteria. Tsetse flies can't sustain milk-feeding for their bizarre live-birthed young without specialized live-in bacteria to provide B vitamins. The list goes on and on for influential microbes. They shaped the world and keep us alive in it.

O'Malley sums up microbes as "the dominant life-forms not only in today's world, but also in all past eras of the living Earth." For bird watchers, wildflower lovers and nature enthusiasts of all stripes, truly seeing these invisibly small creatures for the first time can be like realizing dark matter exists. And not only that it exists, but that it makes up so much more of the universe than the supposed ordinary stuff.

New discoveries of protists and other microbial species and their ways of living are creating a very different view and appreciation for life in all its forms. With a few quirky exceptions — including us — to be an earthling is to be microscopic. ■

Explore more

- Fabien Burki *et al.* "The new tree of eukaryotes." *Trends in Ecology & Evolution.* January 2020.

K. MORE *ET AL./J. OF EUKARYOTIC MICROBIOLOGY* 2018

In 2018, Will Ungerer, shown with doctor Jerry Mendell at Nationwide Children's Hospital in Columbus, Ohio, received experimental gene therapy for Duchenne muscular dystrophy, a disease that breaks down muscle.

S. UNGERER

Delivery Dilemmas

Gene therapy for rare diseases still faces big scientific hurdles

By Tina Hesman Saey

Will Ungerer isn't a typical fourth-grader.

The 10-year-old from Midlothian, Va., plays tag with his friends and swims in the ocean. "I think his peers would describe him as someone who is kind, sweet and funny, and supersmart," says his mother, Sheila Ungerer. He won a countywide citizenship award and was named classroom student of the year.

But "he's not a really fast runner," his peers might say. "He doesn't really run." Will was born with Duchenne muscular dystrophy, a genetic disease that causes muscles throughout the body to break down over time. That includes not only skeletal muscles, but also the heart and diaphragm, which controls breathing. Eventually those important muscles stop working properly, leading to death. The disease is caused by mutations in the gene responsible for dystrophin, a protein that acts as a shock absorber to prevent damage as muscles contract. It affects

an estimated 4.8 out of 100,000 people worldwide, mainly boys and young men. About 10,000 people in the United States have Duchenne muscular dystrophy.

Will celebrated his birthday last year at a laser tag park, his mother says, but other kids his age with Duchenne's "don't ride the bus. They don't carry their tray in the lunchroom."

The difference is that Will received an experimental gene therapy when he was 5 years old. Just before Christmas in 2018, doctors at Nationwide Children's Hospital in Columbus, Ohio, gave Will an infusion of viruses. Those viruses delivered instructions to his muscles for making a short form of the dystrophin protein. Scientists at Sarepta Therapeutics in Cambridge, Mass., the company that makes the gene therapy, developed this version, called microdystrophin, to act as a replacement, hopefully protecting muscles from harm.

Though the therapy did not show statistically meaningful improvements compared with a placebo in one randomized controlled trial and results of an ongoing clinical trial to determine efficacy aren't yet published, Will and the 83 other boys in Sarepta's clinical trials now make the microdystrophin protein. Based in part on that evidence, the U.S. Food and Drug Administration approved the therapy earlier this year for use in 4- and 5-year-olds, and the first child to get the therapy after approval was infused on August 2.

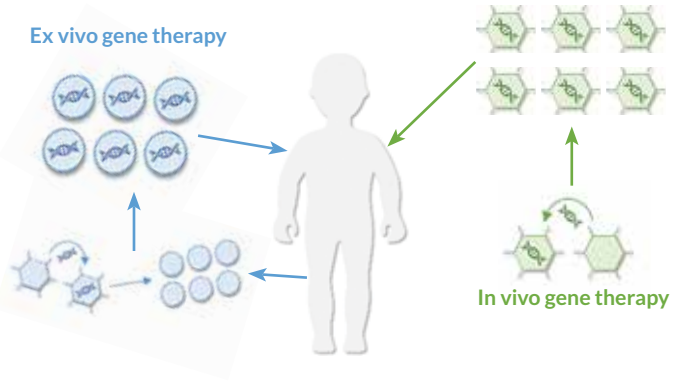
For Sheila Ungerer, there's no question that the gene therapy is working for Will. He now does everyday things he couldn't before, such as climb stairs easily and brush his teeth and get dressed on his own. He can ride a bike and swims up to 500 meters at swim team practice.

A few months after the infusion, Sheila overheard Will talking to his younger brother Adam. "I was just outside the door, and he said, 'Adam, remember when my legs used to hurt all the time? They don't hurt anymore,'" she recalls. "That was his experience of life with inflamed muscles in his legs that were being damaged constantly. And then for that to subside is just an immeasurable impact on his life."

The FDA has approved seven other gene therapies for rare genetic diseases, all since 2017. Each puts a healthy copy of a gene into cells to compensate for a missing or mutated one. Some potential treatments for rare diseases that use gene editing, a type of gene therapy that makes targeted changes at the DNA level, may soon win approval too.

Around the world, more than 2,000 gene therapies are in development, according to the American Society of Gene and Cell Therapy. That figure includes cells that have been genetically engineered to fight diseases, such as immune cells called CAR-T cells programmed to kill cancer or keep lupus from attacking the body (SN: 2/26/22, p. 15; SN: 10/8/22 & 10/22/22, p. 6). But unlike these therapies for cancer and autoimmune diseases — which could treat potentially millions of people, making them financially attractive to drug companies — each gene therapy for a rare disease may help thousands of patients or fewer.

Since gene therapy was first proposed to treat such genetic diseases in the 1970s, it has had thrilling highs — including the first successful gene therapy, in 1990, in a 4-year-old born with severe combined immunodeficiency, or SCID — and deeply troubling lows. Clinical trial participants have ended up with cancer and other serious health complications and have even died. The biggest problem appears to be the viruses used to ferry replacement genes where they need to go. Viruses are the obvious choice for delivery: They can carry the replacement gene in their own DNA or RNA and have built-in mechanisms for getting into cells. But viruses can't always get the genes to the right cells, can slip their cargo into the wrong spot in the DNA and can trigger the immune system to set off deadly inflammation.



In or out Many early gene therapies remove stem cells (circles) from a patient's body, modify them with the help of viruses (hexagons) and then return the modified cells. This ex vivo approach often requires chemotherapy and only works for some diseases. In vivo therapies modify cells in the body, but getting the therapies to the right cells can be a problem.

Challenges and setbacks, including the death of a teenager named Jesse Gelsinger in 1999, nearly derailed gene therapy. But researchers, companies and patient advocacy groups persevered. Today, researchers are finding new ways to tackle their delivery dilemmas. Some are developing better viruses or nonviral ferries, while others are using new tools to repair or replace damaged genes in place. One technique, tested so far only in mice, relies on technology similar to what has been used in COVID-19 vaccines.

Some researchers say the outlook has never been brighter for gene therapy for a wide variety of inherited diseases. Others are frustrated by the slow progress.

Insert gene here

When scientists discovered the gene that is mutated in cystic fibrosis in 1989, gene therapy was just about to be demonstrated in clinical trials in people. "We were all saying, 'There's going to be gene therapy next year,'" says Garry Cutting, a geneticist at Johns Hopkins University who studies the disease.

But that prediction didn't pan out. There have been at least 36 gene therapy trials involving more than 600 people with cystic fibrosis, none with lasting success, researchers reported in 2022 in *Frontiers in Pharmacology*.

"And what's the problem? The problem has always been delivery," Cutting says. "How do you get it in the right place?"

G. CONSIGLIERI ET AL/HEMATOLOGY/ONCOLOGY CLINICS 2022

For cystic fibrosis, which affects more than 160,000 people worldwide, the right place is the lungs, where mutations in a gene called *CFTR* result in the buildup of sticky mucus that makes it hard to breathe. Numerous clinical trials have attempted to slip a healthy copy of the gene into stem cells that replenish the airway lining. But it's not easy for viruses to get through the sticky mucus, past patrolling immune cells, through layers of unrelated cells and into the stem cells. "It's a harsh environment. It's a tough problem," Cutting says.

Because of similar struggles, many of the first gene therapies to win approval instead harvest a patient's blood-forming stem cells, grow and genetically modify the cells in the lab and then return the modified cells to the patient, usually in the form of a bone marrow transplant. That is also the approach that CAR-T cell therapies for cancer use.

Editing cells outside the body, or ex vivo, has worked for rare diseases that affect the blood or immune system. Yet it comes with limitations, since scientists haven't worked out ways to extract stem cells from tissues other than blood and bone marrow and replace them later. It also comes with its own dangers. It typically requires chemotherapy to kill existing bone marrow so the modified cells can take hold and replicate. And the viruses ferrying the replacement genes into the cells in the lab can still be problematic.

Early gene therapies used retroviruses, which often insert their DNA cargo near active genes. Some children who got gene therapy in 1999 and 2000 for inherited diseases that disable the immune system developed leukemia when the inserted gene ramped up activity of nearby cancer-causing genes (SN: 1/18/03, p. 43; SN: 8/10/13, p. 19).

Most gene therapies today instead rely on viruses engineered to deliver their cargo to safer locations and to cause less of an immune response. But still, the track record is far from spotless.

In September 2022, for example, the gene therapy company bluebird bio, based in Somerville, Mass., received FDA approval for an ex vivo lentivirus-delivered gene therapy for children with a rare, fatal neurodegenerative disease known as cerebral adrenoleukodystrophy. About 1 in 4,000 to about 1 in 50,000 babies born will have adrenoleukodystrophy, and 35 percent to 40 percent of boys with the disease develop the severe form, which typically leads to death within five to 10 years if treatment doesn't work. The approval came despite three cases of a type of cancer called myelodysplastic syndrome among clinical trial participants. The company determined that the lentivirus was indeed at fault and the therapy, called Skysona, comes with a warning about the cancer risk and recommendation for yearly cancer screening for 15 years.

Researchers have had successes with gene therapies that work in the body for some forms of blindness (SN: 6/19/21, p. 6) and with a degenerative nervous system disorder called spinal muscular atrophy. Will Ungerer's gene therapy also relies on an in vivo approach. In all three cases, the replacement genes are delivered by adeno-associated viruses, or AAVs. These viruses usually drop their cargo in the nucleus where it hangs out separately from the rest of a person's DNA.

But the payload size of AAVs is limited, they may not infect all cells equally, and they can trigger dangerous and deadly immune responses. Patients who have gotten gene therapies delivered by AAVs have also developed liver damage or failure and microscopic blood clots that can lead to organ damage.

On top of all those risks, once the immune system of a patient receiving in vivo gene therapy makes antibodies and defenses against a delivery virus, redosing becomes difficult or impossible.

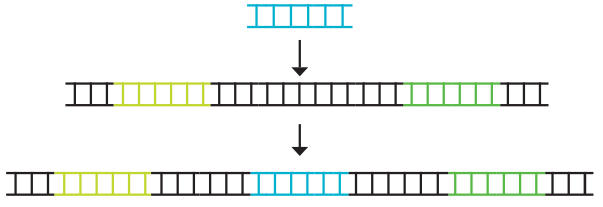
On March 22, 2018, Conner Curran of Ridgefield, Conn., then 7 years old, became the first person to get an experimental in vivo gene therapy developed by Pfizer for Duchenne muscular dystrophy. "Before gene therapy, he really struggled to go up the stairs," says Conner's father, Chris Curran. "Two months after gene therapy, he's running up the stairs."

Chris and his wife, Jessica, founders of the nonprofit Kindness Over Muscular Dystrophy, an organization that raises money for muscular dystrophy research, marveled at the improvements in Conner's strength and agility. That's just not something that happens for children with Duchenne muscular dystrophy, Chris says. "It's a progressive muscle-wasting disease.... You don't ever get better. You just get worse and worse and worse, and we actually saw him getting better."

Though the improvement continued for three to four years, Chris and Jessica have observed a slow decline over the last year. "We knew going into this that it wasn't necessarily a cure," Chris says. He is hopeful that the gene therapy may still buy Conner and other boys time by strengthening their heart and diaphragm muscles, but Conner may need another dose of gene therapy to keep his skeletal muscles from deteriorating.

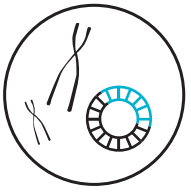
Unfortunately, now age 13, Conner has high levels of antibodies

Getting the DNA in All gene therapies for rare diseases that are approved today put a healthy copy of a gene into cells, but the therapies differ in how they get the gene in.



In a common approach used today, a virus delivers the gene of interest (blue) into the DNA. The gene usually does not end up in its typical location in the genome.

Some viruses instead drop the gene of interest in the nucleus. There, it can still be active, but it remains separate from the rest of a person's DNA.



C. CHANG

Antonio Vento, shown bottom right with his parents on a recent birthday, has a rare genetic disease that causes blisters and wounds on his skin. Scarring had obscured his vision until a gene therapy he'd been using for his skin was reformulated as eye drops. Vento, shown getting an eye exam at left, has recovered a lot of his vision after surgery and gene therapy, and the scarring hasn't returned (comparison at top right).

against the AAVs that delivered Pfizer's version of micro-dystrophin to his muscles. He will be one of six children who previously got gene therapy to enter a clinical trial aimed at lowering their antibody levels against the AAVs.

CRISPR therapy

Even when a virus gets its cargo to the right cells — the right zip code — that doesn't mean it'll find the right address. Even today's viruses don't usually deliver the gene to its normal location in the DNA, says Matthew Porteus, a physician-scientist at Stanford School of Medicine. The delivery locations aren't completely haphazard, but they're not entirely predictable either. It's a bit like ordering a pair of pants for store pickup at Old Navy. The pants will get to *an* Old Navy, but until they arrive, you won't know exactly which one.

For some genes, it's fine to place them elsewhere in the genome or let them hang out outside of chromosomes, Porteus says. Other genes have to be turned on at just the right time or active in precise amounts. That's hard to do when the genes aren't in their native habitat. Getting a gene to its normal location was no easy feat when Porteus started working on gene therapy in 1997, he says.

Then CRISPR gene editing came along. CRISPR is something like a molecular, GPS-guided pair of scissors — usually a protein called Cas9 — that seeks out and cuts DNA at precise locations. Since it debuted in 2012, researchers have been using the tool to cut, repair or insert genes in exactly the desired place in experiments with human cells grown in lab dishes and with animals (SN: 11/7/20, *p.* 13).

Some companies have begun using CRISPR-based gene therapies in clinical trials with people. Several are taking blood-forming stem cells from patients, editing the cells in a lab, then giving the cells back to patients in a bone marrow transplant. And again, transplanting edited cells back into a patient first requires chemotherapy to kill existing bone marrow to make way for the engineered cells. But viruses aren't always necessary to deliver the CRISPR scissors and GPS locator to the cells to be edited.

Vertex Pharmaceuticals, based in Boston, is collaborating with CRISPR Therapeutics, headquartered in Zug, Switzerland, to use CRISPR/Cas9 to break the DNA in a way that turns on fetal hemoglobin in people with either beta-thalassemia or sickle-cell disease (SN: 8/31/19, *p.* 6). Both conditions mess with oxygen-carrying hemoglobin in red blood cells. About 60,000 people worldwide are born with symptomatic cases of beta-thalassemia each year, and sickle-cell disease is estimated to affect about 100,000 people in the United States alone, with Black and Hispanic people most likely to get the disease.

Victoria Gray, the first person to get the therapy for sickle-cell disease, in 2019, recounted her experience March 6 in London at the Third International Summit on Human Genome Editing. When her red blood cells collapsed into sickles and clogged blood vessels because of faulty hemoglobin, Gray faced sudden, unpredictable bouts of intense pain, she said. "The pain I would feel in my body was like being struck by lightning and hit by a freight train all at once." She was often hospitalized to get blood transfusions and opioid painkillers that didn't always help. One particularly bad episode struck in October 2010. Gray, a 37-year-old mother of four from Mississippi, said she didn't leave the hospital until the following January. Even afterward, she couldn't feed herself or walk on her own.

But on July 2, 2019, Gray got three vials of her own bone marrow cells edited to make fetal hemoglobin. The worst part was the recovery from chemotherapy, she said. "It took about seven to eight months for me to physically feel and mentally accept

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that I was better," she told the crowd of scientists, ethicists and other experts. Thanks to her "super cells," she now has a full-time job, attends her children's football games and cheerleading events and can enjoy family outings. "The life that I once felt like I was only existing in, I'm now thriving in."

The preliminary results of the clinical trials, announced in June, showed that 24 of 27 people with beta-thalassemia who previously required blood transfusions hadn't needed a transfusion for at least a year after getting the therapy. Of 17 sickle-cell disease patients analyzed, 16 had made it at least a year without a pain crisis. All 17 avoided hospitalization for at least a year.

This approach and another sickle-cell therapy from Editas Medicine in Cambridge, Mass., break one gene to compensate for another. Porteus, of Stanford, is instead interested in using CRISPR to get a healthy replacement gene in. Such a strategy might work well for diseases where any one of thousands of mutations in a gene can be to blame, Porteus says. For cystic fibrosis, for example, 719 different mutations in the *CFTR* gene have been shown to cause the disease.

The team is working on techniques to increase the chances that the cuts the CRISPR scissors make will be repaired by inserting a healthy copy of the gene into the breach. This copy-and-paste method, known as homology-directed repair, rarely works, but Porteus and colleagues are making improvements. In one study, cells taken from patients with sickle-cell disease were edited and then transplanted into mice. Up to 20 percent of the defective genes had been replaced, his team reported in 2021 in *Science Translational Medicine*.

Other researchers are pursuing what's called CRISPR base editing to alter just the typo that causes a genetic disease. This tool can fix single DNA-letter mutations, chemically changing one DNA base, the information-carrying portion of the DNA molecule (SN: 11/25/17, p. 7).

Cells edited outside the body can be examined before they go back in, to ensure safety. But researchers are also trying to push CRISPR editing into the body. Those strategies, though, come with concerns over misplaced cuts that can cause stray mutations, plus some still may require potentially risky viral delivery.

In October 2022, 27-year-old Terry Hogan died after getting an AAV-delivered CRISPR gene therapy for Duchenne muscular dystrophy in a trial sponsored by the nonprofit organization Cure Rare Diseases. Hogan's death was the result of an immune reaction to high doses of the AAV9 virus needed to carry the gene therapy to his muscles. That immune reaction set off a cytokine storm that damaged his lungs and led to his death, researchers reported May 30 in a preprint posted to medRxiv.org.

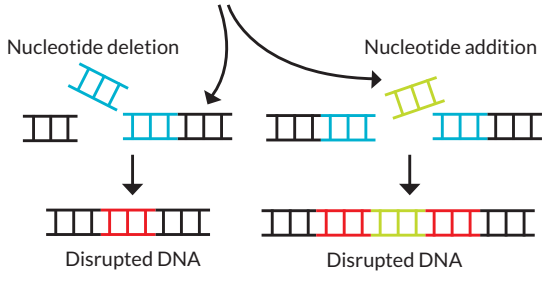
Inside jobs

Cutting, the geneticist at Johns Hopkins, has high hopes for nonviral delivery vehicles for in vivo therapies. These molecular FedEx trucks are usually composed of lipids, proteins and chemicals that form bubbles that protect the genetic cargo and transport it to where it needs to go. If you got a Pfizer or Moderna COVID-19 vaccine, you've already had such nanoparticles — in this case carrying messenger RNA — injected into your body. Messenger RNA, or mRNA, is an RNA copy of DNA's instructions for building a protein.

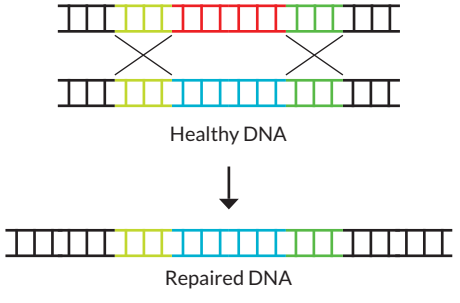
Researchers have deployed nanoparticles to edit blood-forming stem cells in mice without removing the cells. The nanoparticles were studded with antibodies that targeted them to blood-forming stem cells in the bone marrow, says Hamideh Parhiz, a pharmacologist and biotechnologist at the University of Pennsylvania Perelman School of Medicine. The researchers also edited human cells carrying the sickle-cell mutation in the lab. In that case, the mRNA carried instructions for making a CRISPR base editor, which converted the sickle-cell mutation to a base that doesn't cause sickling. Up to 88 percent of cells were edited, and under conditions that usually cause sickling, the crescent shapes were almost absent, Parhiz and colleagues reported July 28 in *Science*.

"In proof of principle, this paper is basically talking about the medicine of [the] future," says Stefano Rivella, coauthor of the paper and a molecular biologist at Children's Hospital of Philadelphia. He predicts such in vivo editing — because it dispenses with harvesting stem cells and chemotherapy — will be much cheaper than current gene therapies, which can cost millions of dollars. Rivella imagines vials of mRNA-loaded nanoparticles shipped to Africa or other places where there are many people with sickle-cell disease.

CRISPR potential Some gene therapies that may be approved soon use tools like CRISPR/Cas9 to disrupt or edit DNA directly.



One approach removes or adds a segment of DNA to disrupt a gene (red) that in turn counteracts a misfunctioning gene.



In homology-directed repair, CRISPR triggers cellular machinery to swap a healthy copy of a gene (blue) for a dysfunctional one (red). X's represent genetic recombination.

C. CHANG

Defining success

But that's not where we are today. Consider, for example, 14-year-old Antonio Vento. He was born with dystrophic epidermolysis bullosa, which is caused by a mutation in a gene that produces a collagen protein that helps layers of skin stay together. Antonio and others with the condition develop blisters and wounds when even slight friction tears the outer layer of their skin or mucus membranes away from the middle layer. Scarring in the mouth and esophagus can make swallowing difficult.

Extensive scarring also obscured Antonio's vision. He had two surgeries in 2016 and 2017 on his left eye to remove the scars, but they came back two to three months later. The procedures kept failing, so "we decided not to do any additional surgeries," ophthalmologist Alfonso Sabater of the Bascom Palmer Eye Institute at the University of Miami Health System and the Miller School of Medicine said July 24 during a news conference. There appeared to be little hope for saving Antonio's vision.

But in 2020, as part of a clinical trial, Antonio had been using a gene therapy gel developed by Krystal Biotech in Pittsburgh to keep his skin from blistering. The therapy, which is applied to the skin, uses herpes simplex virus to deliver the collagen *COL7A1* gene to skin cells. It received FDA approval in May.

Desperate for a solution for his patient, Sabater worked with Krystal Biotech to reformulate the gene therapy as eye drops that might work for Antonio. The eye drops went through two years of testing for safety and efficacy. After that long haul, last year, the FDA granted permission for Antonio to get the eye drops on a compassionate use basis.

He's the only person in the world getting the drops, which he started using weekly after surgeries to remove existing scarring. "It's hard to say that this treatment is effective for these type of patients just with one case," Sabater said. "But so far, the results look promising. And we're very excited about the future, because definitely this treatment may open new possibilities."

Antonio has recovered nearly all of his vision in one eye and about 60 percent in the other, and the scars haven't returned. But since the effects are temporary, it's likely that he will need regular doses for years.

Antonio's situation highlights one of the big challenges of gene therapy. For now, it's a boutique treatment, Porteus says, and that is expensive. The rarity of the diseases makes it hard for drug companies to recoup what they've invested, and thus makes them reluctant to invest to begin with.

Having the technology is not enough, notes Maria Grazia Roncarolo, the cofounder, president and head of research and development for Tr1X, a biotech company in La Jolla, Calif.

In the 1980s, Roncarolo helped pioneer a gene therapy for "bubble babies," children with SCID caused by mutations in the gene encoding adenosine deaminase, also called ADA-SCID. While at the San Raffaele Telethon Institute for Gene Therapy in Milan, Roncarolo and colleagues reported curing two children in 2002. The pharmaceutical giant GSK licensed the therapy, called Strimvelis, and got approval from the European Medicines Agency in 2016 to use the treatment for children who don't have a suitable bone marrow donor. "This was a beautiful story. And when the product was approved in 2016, we celebrated [with] champagne," Roncarolo says.

S. UNGERER

Since receiving gene therapy, Will Ungerer, shown in a recent picture, can do everyday things, including climb stairs easily and get dressed on his own. He's also on a swim team.

Despite this approval though, patients can get the therapy only by going to Italy for compassionate use treatment. "GSK decided to disinvest in rare genetic diseases because they thought that was a market which was not big enough and profitable enough," Roncarolo says. Orchard Therapeutics, based in London, which inherited the therapy, announced in 2020 that it was reducing its investment in ADA-SCID to focus on less rare diseases. The Telethon Institute now holds rights to the therapy and is trying to commercialize it, she says. "You can imagine the frustration for me and all the people that contributed to bring this product to the market."

Similarly, the European Medicines Agency approved an AAV-based gene therapy for beta-thalassemia from bluebird bio in March 2019, but the company pulled the product from the European market in 2021. European health care systems were trying to negotiate lower prices for the therapy than the company thought it was worth.

Showing that a therapy is safe and effective is just one part. "The real challenge for these products," Roncarolo says, "is to make sure — especially for rare genetic diseases — that they find a home in a company that has the motivation and resources to commercialize them."

The stories of Antonio Vento, Will Ungerer, Victoria Gray and others show that patients are benefiting from gene therapy today. There are plenty of signs of progress over the last decades. But even if the biggest scientific hurdles fall, there remain many hurdles to fixing broken genes. ■

Explore more

- Hongshu Sui *et al*. "Gene therapy for cystic fibrosis: Challenges and prospects." *Frontiers in Pharmacology*. October 11, 2022.

8 GMOs tell a brief history of GENETIC MODIFICATION

It has been a boon for agriculture, medicine and more

By Darren Incorvaia

Half a century ago, the first genetically modified organism ushered in a new era of biological innovation. To mark this anniversary, here are eight milestone GMOs. Many have had, or are poised to have, a dramatic impact on our lives.

1. *Escherichia coli*

In November 1973, geneticist Stanley Cohen and colleagues reported that they had built a plasmid, a ring of DNA, that carried a gene from another organism into an *E. coli* cell—the birth of genetic engineering. The team later showed that such modified cells could produce the protein associated with a foreign gene (*SN: 6/1/74, p. 348*). *E. coli* has since been modified to mass-produce therapeutic drugs, break down plastics and more. "The most important GMO is the microbes that are used to make insulin," says geneticist Matthew Cobb of the University of Manchester in England. In 1978, facing problems with insulin derived from pigs and cows, scientists engineered *E. coli* to make human insulin for treating diabetes (*SN: 9/16/78, p. 195*). The lifesaving drug hit the market in 1982.

2. Transgenic mice

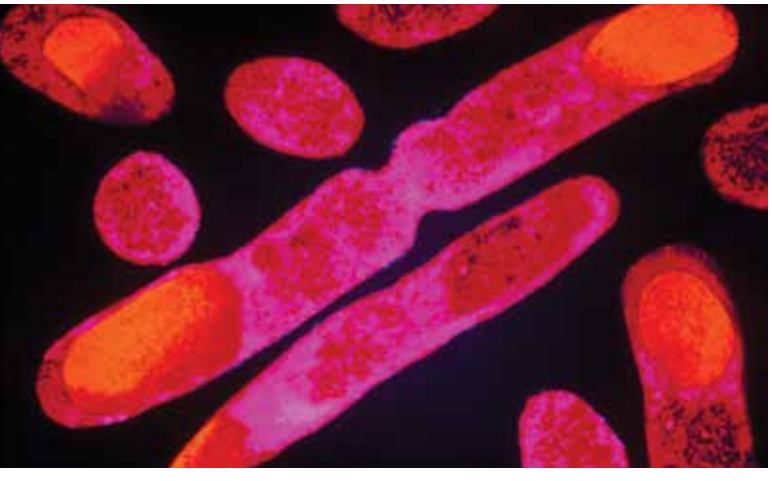
Mouse models are a go-to for scientists who want to study human disease in a controlled way in the lab. In 1974, biologists Rudolf Jaenisch and Beatrice Mintz laid the groundwork for these models by injecting DNA from simian virus into mouse embryos, which were later born with viral DNA in their genomes. In papers published in 1980 and 1981, a team led by biologists Jon Gordon and Frank Ruddle incorporated viral DNA into mouse genomes so that it was passed on to subsequent generations (*SN: 9/13/80, p. 163*). The star rodents were called "transgenic" mice. Since then, transgenic and knockout mice, where a single gene is broken or removed, have been developed to mimic and study human diseases from Alzheimer's to alcoholism to depression and cancer.

3. Bt tobacco and more

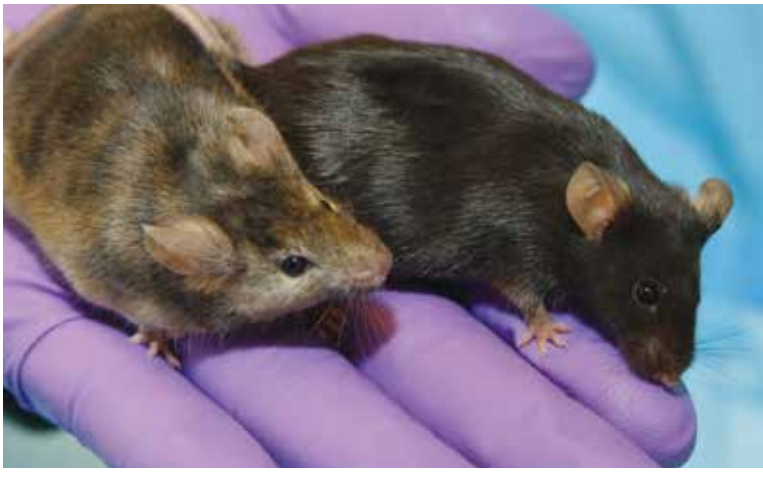
In 1987, geneticist Mark Vaeck and colleagues reported that they had genetically engineered tobacco to produce Bt toxins. These toxins, made by the bacterium *Bacillus thuringiensis*, affect only certain insects, including several common agricultural pests. Pesticides derived from the toxins take time and money to spray, but the new tobacco plant had built-in protection. Estimates suggest that more than 1 billion hectares of Bt crops—corn, cotton, soybeans and more—have been grown since, with no known safety issues for consumers. These crops have improved yields while reducing the need for pesticides. They "are grown on massive scales, in many countries around the world," says Emma Kovak, a food and agriculture analyst at the Breakthrough Institute, an environmental think tank in Berkeley, Calif. "They've had a massive impact."

FROM LEFT: VOLKER STEGER/SCIENCE SOURCE; MAGGIE BARTLETT, NHGRI

These *E. coli* are engineered to produce human insulin.



The mouse on the left is missing a gene affecting hair growth.



Flavr Savr tomatoes (right) last longer than their ordinary counterparts.

A GM salmon (left) is bigger than a non-GM salmon of the same age.

FROM LEFT: MARTYN F. CHILLMAID/SCIENCE SOURCE; AQUABOUNTY

4. Flavr Savr tomato

The impact of the Flavr Savr tomato, introduced in 1994, is largely symbolic. Its genome was modified to block the production of an enzyme responsible for fruit softening, thus keeping the fruit firm longer (SN: 5/28/94, *p.* 342). High production and distribution costs ultimately doomed the Flavr Savr, but it was the first genetically engineered crop to be approved by the U.S. Food and Drug Administration and to be commercially sold. GM crops have boomed since the Flavr Savr flopped. In 2019, more than 190 million hectares were planted with GM crops. Such crops include potatoes, squash, sugar beets, papayas and corn.

Some people also trace a rise in GMO opposition back to the Flavr Savr tomato, Kovak says. The tomato went through intense safety tests, but people opposed to GMO foods more generally, then and now, point to potential health and environmental risks.

5. Biofortified rice

More than 2 billion people worldwide face micronutrient deficiencies. Traditional breeding and genetic engineering can amp up those nutrients, and rice has been an obvious target. "More than half of the world's population, including many of those living in poverty, rely on rice for most of their daily calories," says B.P. Mallikarjuna Swamy, a rice biofortification researcher at the International Rice Research Institute in Los Baños, Philippines.

Golden rice, developed in the late 1990s by a team led by biologists Ingo Potrykus and Peter Beyer, contains genes from a daffodil and a soil bacterium that enable it to produce a precursor to vitamin A. Food safety regulators have approved it in the United States, Australia, Canada and New Zealand, and it was recently approved for commercial use in the Philippines. Despite its promise, though, golden rice has not yet seen widespread adoption due to regulatory hurdles and GMO opposition.

6. AquAdvantage salmon

The FDA approved AquAdvantage salmon for human consumption in 2015 — making the salmon the first GMO animal to be OK'd as human food in the United States (SN: 2/6/16, *p.* 22). Canada followed in 2016. With a growth hormone gene from Chinook salmon, AquAdvantage salmon reach full size in half the time of traditional farm-raised Atlantic salmon. Fast-growing farmed salmon could have widespread appeal, but there are concerns that if the engineered salmon escape, they could push out wild salmon. For now, AquAdvantage salmon are only trickling into the U.S. supply chain.

7. American chestnut

Some researchers are turning to GMOs for conservation. The American chestnut, which once dominated the eastern seaboard, offers an early example of what such efforts might look like. These "redwoods of the East" were severely reduced by the mid-1900s by a parasitic fungus introduced from imported trees. Historical efforts to develop a blight-resistant chestnut using traditional breeding haven't panned out, but the Darling chestnut might be the answer. This genetically engineered tree is more resistant to the fungal blight disease thanks to a wheat gene that breaks down the harmful chemical the pathogen produces. The tree has been under review by regulatory agencies since January 2020. After approval, the American Chestnut Research and Restoration Project at the State University of New York College of Environmental Science and Forestry in Syracuse plans to start distributing it to restoration programs and the public.

8. Mosquitoes

Genetically modifying animals that spread disease, including mosquitoes, could save a lot of lives; malaria alone kills hundreds of thousands of people each year. "We're already using genetically modified mosquitoes for disease control," says biologist Vanessa Macias of the University of North Texas in Denton. Tests in 2021 in Florida, for example, released male *Aedes aegypti* mosquitoes genetically engineered so female offspring die before adulthood. The goal? Reduce the population of insects that spread the Zika and dengue viruses. Modified mosquitoes have also been released in Brazil, the Cayman Islands, Panama and India.

Other research teams are adding genes that make mosquitoes resistant to a pathogen, says Macias, thereby preventing disease spread. And advances in gene editing mean it's now possible to use what are known as gene drives to spread genetic modifications through entire populations (SN: 12/12/15, *p.* 16). Yet open questions remain, including whether it is ethical or wise to transform entire animal populations (SN: 6/4/22, *p.* 20). "We're talking about unknown unknowns," Macias says. ■

Darren Incorvaia is a freelance writer based in the San Francisco Bay Area of California.

CONVERSATIONS WITH MAYA

FATIMA CODY STANFORD
Obesity medicine physician-scientist, educator and policy maker at Massachusetts General Hospital and Harvard Medical School

Maya Ajmera, President & CEO of the Society for Science and Executive Publisher of Science News, chatted with Fatima Cody Stanford, an obesity medicine physician-scientist, educator and policy maker at Massachusetts General Hospital and Harvard Medical School. As an expert in obesity medicine, she works at the intersection of medicine, public health, policy and disparities. She is also an alumna of the 1995 International Science and Engineering Fair (ISEF), a competition owned and produced by Society for Science.

How did ISEF influence you?

ISEF was pivotal in shaping who I am as a physician-scientist. When you start as early as I did and are taken seriously as a young person through your participation in a program like ISEF, you build up confidence. That gives young people a mental framework of how to proceed in science. You feel like you can do this.

Where did you grow up?

I was born and raised in Atlanta, and I am a product of the Atlanta public school system. I went to Benjamin E. Mays High School, which had a math and science academy that I attended. As part of the program, I spent whole summers doing science projects. I worked in the Rollins Research Center at Emory University with a scientist named Dale Edmondson, and I received funding from the National Institutes of Health for the work. I didn't understand how outstanding that was at the time.

The experience of working in a productive lab at that age helped me gain independence. The Ph.D.s and postdocs there didn't have much time to spend with a high schooler, so I learned how to navigate the space independently.

You are one of the first fellowship-trained obesity medicine physicians worldwide and one of the most highly cited obesity medicine physician-scientists, with more than 190 peer-reviewed publications. What drew you to this field?

I thought I would be an orthopedic surgeon. But the universe had different ideas. When I got my master's in public health from Emory in the late '90s, much of my work was in obesity. I came to learn that I didn't understand obesity. I told my patients to eat less and exercise more, but nothing would change. I thought, "There must be something more to this story."

That said, my path to obesity research was circuitous. After receiving my MPH, I attended the Georgia School of Medicine and did my residency in internal medicine at the University of South Carolina. I was trying to figure out what I wanted to do with my life.

I remember being on call in the pediatric ICU in the middle of the night. I had just intubated a child, meaning I wasn't going to sleep. I sat at the nurses station and Googled obesity and medicine, and a fellowship at Harvard University popped up. I got excited and called my husband—even though it was about 2:30 a.m.

A few years later, I was a fourth-year resident at the University of Massachusetts Chan Medical School and had an "aha" moment. I realized that we have tools to treat patients with obesity. I wasn't thinking about the biology because no one ever taught me the biology. I questioned: "Why are we not studying this?" I asked why we weren't analyzing patient data and working with other institutions. And that was really what launched me into researching the clinical implications of obesity.

In your writing and lectures, you have clarified the distinction between the words "obesity," which is a disease, and "obese," which is often deployed as a stigmatizing label. Can you talk about the importance of overcoming stigma for your patients?

I think stigma is more pervasive in obesity than in any other area of medicine. Obesity is a disease you wear, and with this visibility comes judgment. It's heartbreaking to hear the stories of what my patients go through in their daily lives.

Even more hurtful is that we, as physicians and health care providers, also have significant biases toward patients. This bias starts so early in life that by the time someone is in medical school, they have set, distinct beliefs. It's highly problematic and pervasive. It affects our compassion—or lack thereof—for patients because we make judgments without taking the time to understand that the patient is human and that this is a treatable disease.

What is your obesity research specifically about?

I'll say it's multifactorial. Some of my work looks at the impact of metabolic and bariatric surgery on cardiometabolic outcomes in children and adults. Some of my research looks at pharmacotherapy and some of it looks at issues surrounding BMI. My research speaks to my diverse interests. I love clinical work, but health policy is essential. Obesity is too big an issue to compartmentalize into one area. It would be best to look at the policy implications through the public health lens.

What factors do you consider in the treatment of obesity?

One of the first things I do about treatment is look at a patient's insurer because that will dictate what therapies are available. Instead of treating the patient with the best tool, I must use their insurance to guide our actions. For example, if you are a Medicare patient and want to meet with a dietitian because you have obesity and wish to refine your diet, the visit would not be covered. But if you have diabetes, the visit would be covered. We disagree with that as a strategy. It's problematic that we must wait for patients to get diabetes or a cardiac-equivalent disease to get coverage for treatments that prevent these things.

Fatima Cody Stanford worked at Emory Rollins Research Center as a high school student in 1994.

As a woman in STEM, you have achieved so much at such a young age. You are considered a trailblazer. What sort of challenges have you faced?

I wrote a piece for the *Lancet* a few years ago that speaks to the fact that I must do 10 times more than my peers to be recognized. My current CV is 198 pages, which seems bewildering to people, but I always feel like it's not enough. People will tell me that I need to do more of this, or that I'm not quite ready for that. Regardless of my climb, someone will challenge my value or worth.

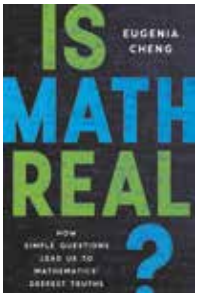
I think a lot of that is because I am a Black woman in STEM who's very outspoken and willing to raise my voice. People want to identify you as domineering or too aggressive in situations where the behavior would be appropriate for someone else.

Here is one example of a challenge I faced. In medical school, I ran for president of my class. After being elected president, I learned that at one point in the school's history, the Medical College of Georgia's Anatomy and Physiology Department purchased an enslaved person, Grandison Harris, to rob Black grave sites so that anatomy classes could study the bodies. I brought the issue back to my fellow class officers and recommended acknowledging Harris and his contributions. Many fellow officers disagreed and thought I was bringing up dirty laundry.

When I used my executive privilege as president to acknowledge him, I had things thrown at me in class. An anonymous newsletter was published about my Black features. It went out to the faculty, students and staff. When I think that these people are now practicing physicians around the country, I wonder how they treat their patients. They are people that I would never want my family or friends ever to see.

There are many challenges facing our world today. What's keeping you up at night?

Obesity is something that I think about a lot. It's such a significant disease. There's so much I must think about and so many areas I must approach. I also think a lot about the inequities in our society: The recent U.S. Supreme Court decision to eliminate affirmative action in colleges and universities is something I wrote and published about in the *Proceedings of the National Academy of Sciences* in April. The decision is erecting more barriers to those from underrepresented backgrounds or those with lower socioeconomic status. It is quite worrisome to me. I think about all the hoops I've had to jump through and recognize that those coming after me may have an even more difficult time—precisely the opposite of what I'm trying to accomplish.



Is Math Real?
Eugenia Cheng
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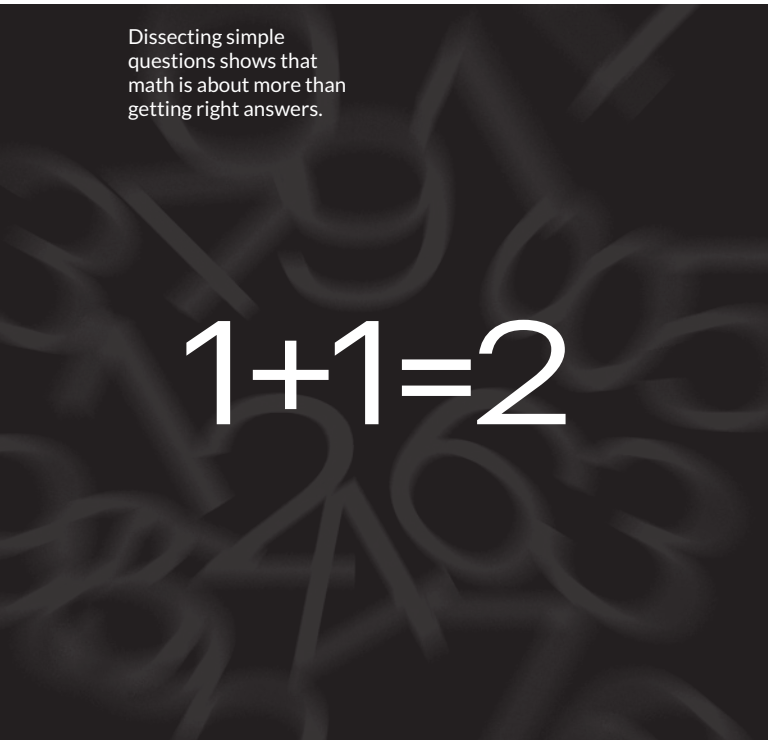
A deep mathematical journey starts with simple questions

Every mathematician has a story that goes something like this. You're at a party, and someone asks what you do for a living. "I'm a mathematician," you say. "You must be a genius!" they reply. Or perhaps you end up being an impromptu therapist to someone who needs to vent about traumatic experiences they had in math class decades ago. Mathematics is treated with both reverence and fear: People often see math as an objective, apolitical tool that can buttress or refute arguments, but they also feel intimidated and anxious when they think they might have to use it.

Mathematician Eugenia Cheng has spent much of her career working to alleviate those anxieties. As scientist in residence at the School of the Art Institute of Chicago, she teaches mathematics to artists, many of whom have never seen themselves as "math people." She has also written several books, for both adults and children, that seek to cultivate mathematical curiosity and illustrate some of the ways mathematical thinking can enrich our lives. Her latest, *Is Math Real?: How Simple Questions Lead Us to Mathematics' Deepest Truths*, demonstrates the ways that seemingly naïve questions can unlock fascinating journeys to understanding math for math's sake, rather than purely in service of real-world applications.

Math has a reputation for supplying concise, black-or-white answers to questions. Getting straightforward math questions right or wrong is often presented as the litmus test of whether someone has mathematical ability. But that view of math is simplistic, Cheng explains. Rather than a tool for obtaining objective right answers, math is a method for asking questions and exploring the possibilities those questions raise.



Dissecting simple questions shows that math is about more than getting right answers.

Students are naturally curious about numbers and patterns, but math classes often teach them that math facts should be accepted without question. For instance, a student might learn that a prime number is defined as a whole number — a positive number without a fractional or decimal part — that is only divisible by itself and 1. The number 1, however, is not considered a prime number. If a student asks why not, they will likely be told it just isn't; deal with it.

But in fact, there is a good reason to exclude 1 from the prime numbers. As Cheng describes, the prime numbers are the multiplicative building blocks of the whole numbers; every whole number greater than 1 can be broken down as a product of prime numbers. Because multiplying by 1 doesn't do anything to a number, 1 isn't needed to build the other whole numbers, at least when multiplication is considered. (For addition, it's a whole different story.) Excluding 1 from the primes allows us to break every whole number greater than 1 down into a product of primes in only one way — 12 is the product of two copies of 2 and one copy of 3, for example, and cannot be broken down into any different set of primes. If 1 were a prime number, those products would no longer be unique. You could toss any number of 1s into the mix and still get the same product.

Mathematicians have found the uniqueness of these products useful for exploring properties of numbers, so they came to the consensus not to include 1 in the primes about a century ago. Considering the reasons mathematicians define primes precisely the way they do is more interesting than simply accepting the definition so you can get an A on a math test.

The prime number example is just one of many simple questions that Cheng poses in the book to motivate deep dives into the logical foundations of Western mathematics: Why does $1+1=2$? Why does $-(-1)=1$? Why does $2+4=4+2$? And, yes, is math real? Cheng's answers to those questions touch not only on our understanding of mathematics itself, but also on her personal experiences with math education as both student and teacher. She also examines how mathematical thinking intersects with life within and outside of the classroom, from the subtle imperialism of the commonly used Mercator map projection, which inflates the perceived size of countries that were colonialist powers, to the parallels between open-mindedness to new mathematical ideas and open-mindedness to the experiences of marginalized groups in society.

Is Math Real? will help readers understand the questions that drive mathematicians and encourage people to see the value of math in their own lives. — *Evelyn Lamb*

T. TIBBITTS

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AUGUST 26, 2023

Dream on

Lucid dreamers — people who are aware they're dreaming while it's happening — are helping scientists probe the sleeping mind in real time, ***Maria Temming*** *reported in "Dispatches from the dreamscape"* (SN: 8/26/23, p. 16).

Several readers shared their experiences lucid dreaming.

"I have been able to control a dream just about as successfully as a captain can control an oil tanker. I can steer the dream but not completely control it," reader **Peter Adams** wrote. "I remember [my lucid dreams], and three have become the basis of science fiction stories I am writing.... I even dreamed a musical composition that I wrote down when I woke up. The music sounds rather good."

Reader **John** wrote: "I have been a lucid dreamer all my life. I am now 71, and I remember most of my dreams. I learned years ago that I could control and even change the direction that a dream was going.... I control them like a movie director.... I once dreamed that I was water-skiing, even down to the surface tension of the water I was on. And the next day, I tried skiing for the first time and got right up the first try and felt that same sensation."

Supplemental information?

Chemical analyses of 57 sports supplements revealed that only 11 percent contain an accurate amount of key ingredients advertised. Some of the supplements even contain compounds prohibited by the U.S. Food and Drug Administration, ***Meghan Rosen*** *reported in "Supplements lack key ingredients"* (SN: 8/26/23, p. 10).

Some readers asked why the story did not list the supplements studied.

Rosen also wondered which supplements were coming up short. But that information is not publicly available. "The researchers made an agreement with the lab they collaborated with to not make the names of the products they tested public," **Rosen** says. "In the meantime, consumers' best bet may be to look to third-party organizations that evaluate dietary supplements' quality."

Correction

In "The thymus isn't so expendable after all" (SN: 8/26/23, p. 7), *Science News* wrote that over 12 percent of people who underwent a thymectomy developed an autoimmune disorder within five years after surgery, compared with about 8 percent of those who kept their thymus — a 1.5 times greater risk. It would have been more accurate to write that thymectomy patients have 1.5 *times* the risk of patients who kept their thymus.

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These 90% Silver Dollars were minted from 1878 to 1904, then again in 1921. They came to be known by the name of their designer, George T. Morgan, and they were also nicknamed "cartwheels" because of their large weight and size.

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A little snake's big gulp may put all other snakes to shame

Hulking hunters like Burmese pythons are famous for scarfing up deer, alligators and other enormous prey. But one unassuming little African snake may take the title for most outsize meals. The nonvenomous, nearly toothless *Dasypeltis gansi* can open its mouth wider than any other snake of its size, biologist Bruce Jayne reports August 8 in the *Journal of Zoology*.

D. gansi, sometimes called the Gans' egg-eater, can swallow bird eggs whole (top right). It then cracks the egg with its spine and ingests the contents before spitting out the shells. At the University of Cincinnati, Jayne inspected 15 egg-eaters ranging from roughly 20 to 90 centimeters long. After euthanizing the animals, he slid increasingly wide 3-D printed cylinders into their gaping maws to determine the biggest thing they could swallow.

The biggest egg-eater that Jayne examined (middle) had a roughly 1-centimeter-wide head but could swallow a cylinder about 5 centimeters across. Previous data show that a petite Burmese python (*Python molurus bivittatus*) of the same length could gobble up prey 4.4 centimeters wide. The western diamondback rattlesnake (*Crotalus atrox*) rivaled the python's gift for gulp, but no other snake species came close.

Egg-eaters can open so wide because the soft tissue between the tips of their left and right lower jaws is so stretchy. "In Burmese pythons, about 40 percent of that gape area is a result of the stretch of the skin between the lower jaws, but these guys edge out the pythons," Jayne says, with about half of the egg-eater's gape due to soft tissue stretch.

Compared with what other snakes eat, such as rodents, most eggs are short. But they come in varying widths. That may be why *D. gansi* evolved its stretch, Jayne says. "If you get your mouth wider, then you can consume these larger eggs."

So far, maximum mouth size has been measured for only 13 of more than 3,500 known species of snakes. "Because the amount of stretch in the skin varies so radically in different species," Jayne says, "it's much more difficult to measure gape than simply take some calipers on a preserved museum specimen and measure bones."

Jayne plans to keep investigating mouth sizes for a wider variety of snakes, such as those that dine on fish. Those data could reveal whether egg-eaters truly have the biggest gulp for their gullet.
—Maria Temming

The biggest Gans' egg-eater biologist Bruce Jayne inspected (above) was about 94 centimeters long and could wrap its mouth around a cylinder 5 centimeters wide. The smallest egg-eater (left) was about 21 centimeters long and could fit a 1.4-centimeter-wide cylinder in its mouth.

TOP: B.C. JAYNE; BOTTOM TWO: B.C. JAYNE/*JOURNAL OF ZOOLOGY* 2023

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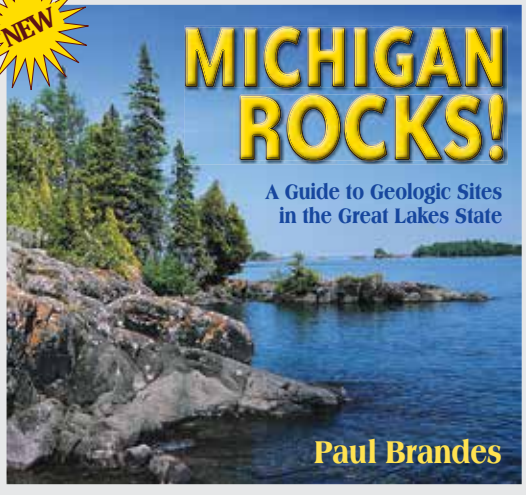

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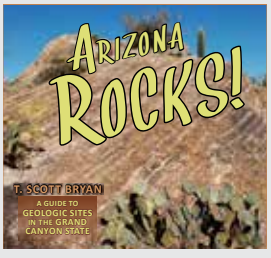

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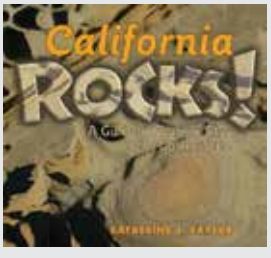

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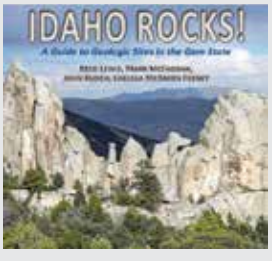

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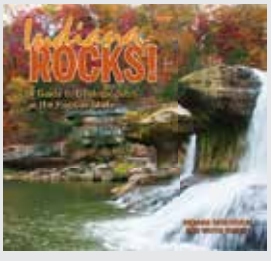

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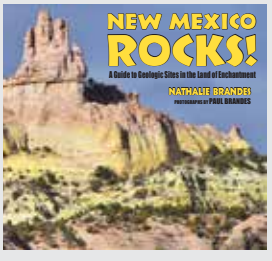

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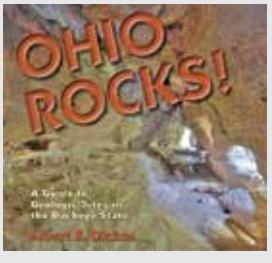

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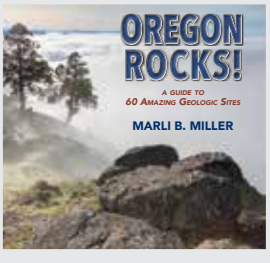

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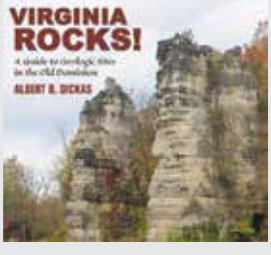

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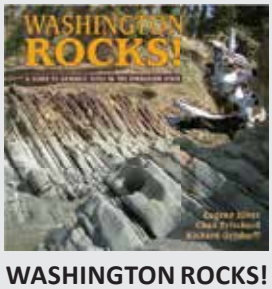

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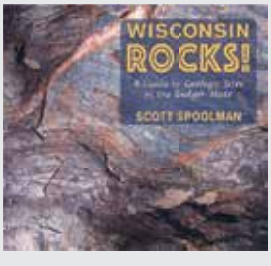

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