SN
SCIENCE NEWS MAGAZINE
SOCIETY FOR SCIENCE & THE PUBLIC
JUNE 10, 2017

Dating *Homo Naledi*

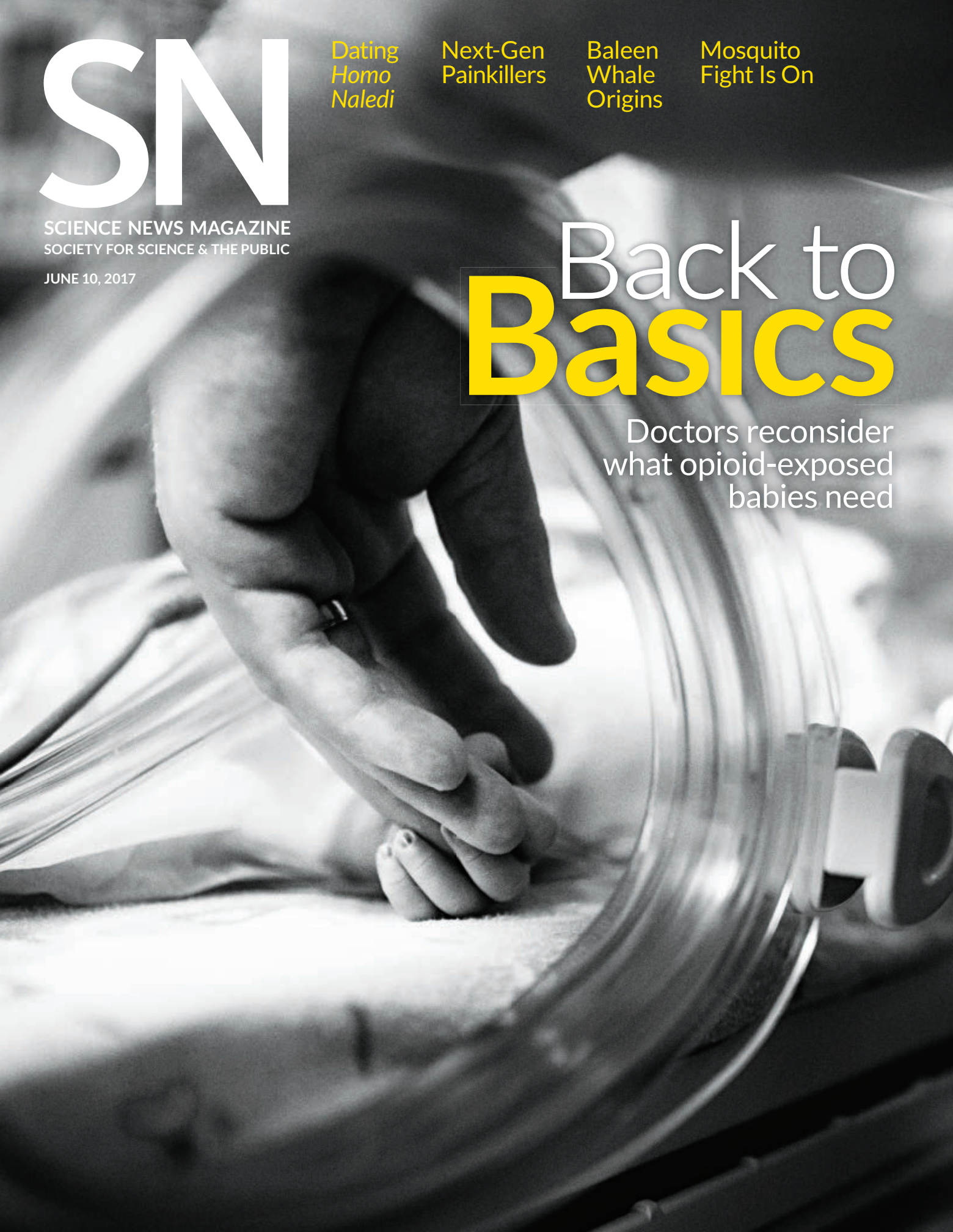
Next-Gen Painkillers

Baleen Whale Origins

Mosquito Fight Is On

Back to Basics

Doctors reconsider what opioid-exposed babies need



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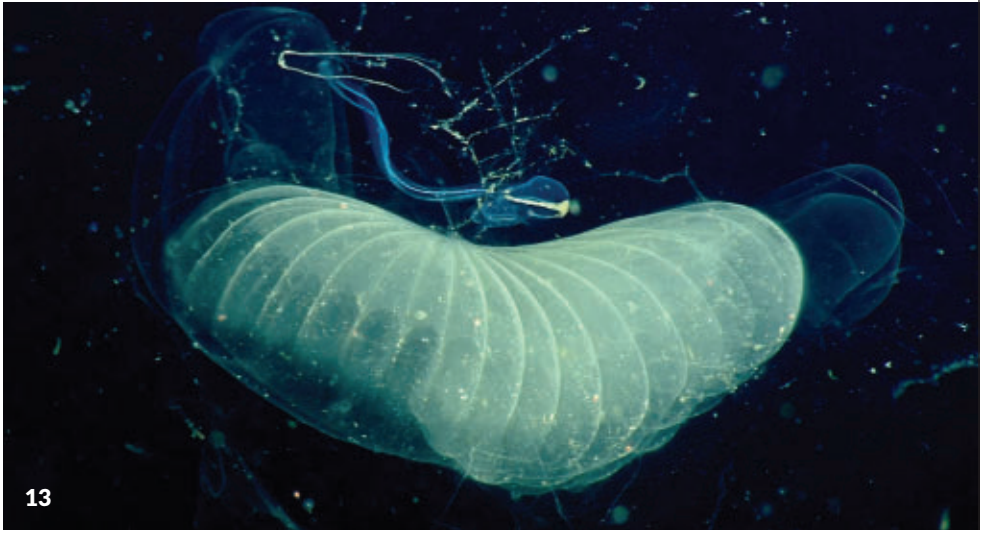
News



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Departments

SOCIETY UPDATE
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COVER For a faster recovery, babies exposed to opioids in the womb are moving out of the NICU and into parents' arms. *Felicia Chang/Offset*

Some topics call for science reporting from many angles

I'm warning you up front. There's heartbreak in this issue. In two stories, beginning on Page 16, *Science News* writers investigate new facets of the ongoing opioid epidemic in the United States. According to the Centers for Disease Control and Prevention, 91 Americans die on average each day from opioid overdoses, quadruple the deaths from opioid overdoses in 1999. Today, nearly half of those deaths involve prescription painkillers. "I don't think we've ever seen anything like this. Certainly not in modern times," Robert Anderson, chief of mortality statistics at the CDC's National Center for Health Statistics, told the Associated Press late last year.

In the first story, "Shaky start," Meghan Rosen writes about the youngest victims of the epidemic — babies born to a mother who uses opioids who then go through withdrawal themselves. In rural areas, nearly 8 in 1,000 babies suffer from neonatal abstinence syndrome, which can include trembling, excessive crying and intestinal troubles. Pediatrician Nicole Villapiano describes these babies as "miserable." Then on Page 22, Laurel Hamers investigates efforts to find new pain-killing drugs. Opioids bring scary side effects and the risk of addiction, but for some people, they are still the best option to alleviate excruciating pain.

The opioid epidemic is among those unfortunate (and not-so-rare) happenings that offer science journalists the opportunity to tackle a topic that matters greatly to people's lives. And it's one of those problems that demand attention from different angles. *Science News* has long been committed to finding the science stories (emphasis on plural) behind the problems facing our families, communities and world. In the 1940s and '50s, there was the polio epidemic. In the '80s, there was AIDS. This isn't the first time *Science News* has covered the opioid epidemic, either: Last July, for example, Susan Gaidos reported on research into vaccines to fend off opioid addiction (*SN: 7/9/16, p. 22*).

Diseases appear commonly on the list of "unfortunate opportunities" because their effects are literally visceral. But there are plenty of other topics that fall into this category: *Science News* has covered worries about nuclear war, the science behind terrorism, poverty, pollution and of course climate change, likely to get ever more visceral as time passes. By digging into research questions in specific subfields — the network science of terrorism or the psychology of poverty, for example — *Science News* can cover sides of stories that other outlets aren't telling.

These articles don't always make for uplifting copy. They can be more troubling to read than stories about mucus houses (Page 13), whale origins (Page 12) or oxygen on comets (Page 9). But reporting on scientific advances often does offer hope. Rosen's report on doctors reevaluating therapies for opioid-exposed babies notes that the simple strategy of time with mom and dad might improve treatment. And Hamers devotes much of her story to promising ways to tweak opioids to maintain their pain-killing power without all the negative effects.

If nothing else, there's promise in the knowledge that people are seeking solutions. There are a lot of scientists out there who see the problems of the world and are concerned, curious and creative enough to find ways to help.
— Elizabeth Quill, Acting Editor in Chief

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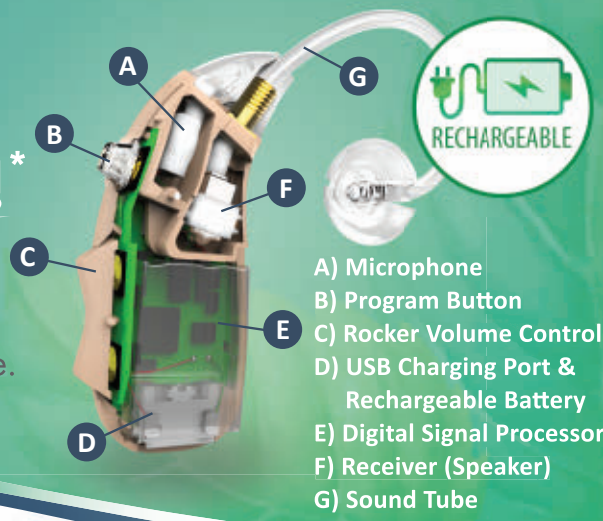

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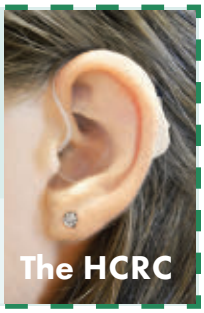

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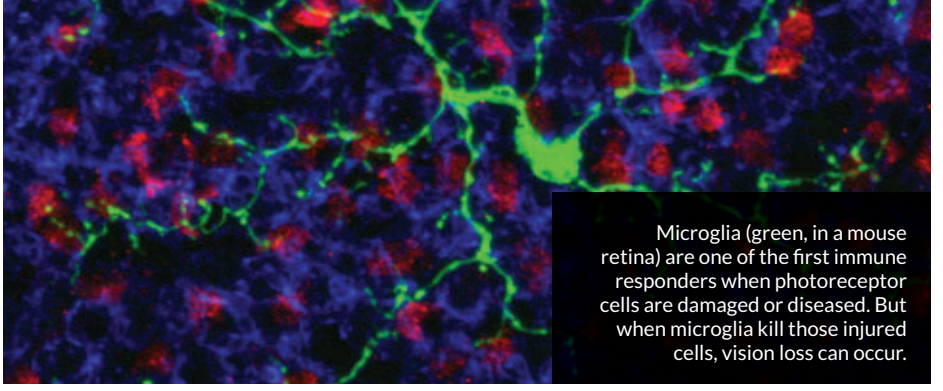
Excerpt from the June 10, 1967 issue of *Science News*

50 YEARS AGO

Bacteria ganging up on drugs

With the discovery of sulfa drugs and antibiotics came man's confidence in his ability to control infectious diseases. But now, that confidence is being shaken by once defenseless germs that have learned to outwit man and thrive in the face of his wonder drugs.... One way to cut down on drug resistance transfer is to stop prescribing antibiotics almost indiscriminately, but that is not an altogether workable solution.

UPDATE: In 1945, Alexander Fleming, the discoverer of penicillin, warned that bacteria could become resistant to the wondrous antibiotic. Yet our love affair with antibiotics is still going strong — with consequences. In 2014, U.S. doctors prescribed close to 266 million outpatient courses of antibiotics — at least 30 percent of which were probably unnecessary. In the United States, more than 2 million illnesses per year and at least 23,000 deaths are caused by antibiotic-resistant infections. In 2016, *E. coli* in the United States showed new resistance to the last-resort antibiotic, colistin (*SN Online: 5/27/16*).



Microglia (green, in a mouse retina) are one of the first immune responders when photoreceptor cells are damaged or diseased. But when microglia kill those injured cells, vision loss can occur.

THE SCIENCE LIFE

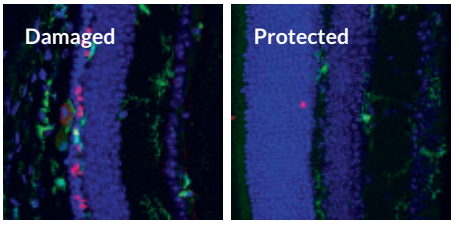
An eye-opening role for a cancer drug

When the eyes of her mice looked normal, Xu Wang was certain she had done something wrong. She was blasting the mice with blinding light to study how a specific gene affected the animals' response to eye injury. All the mice were given the drug tamoxifen. Half were engineered to respond to the drug by disabling the gene — a step that would protect their eyes. The control mice, with all genes intact, should have lost sight as photoreceptors — the light-sensitive cells in the retina — died.

Instead, the retinas of the control mice looked just fine. "I was kind of despondent because it didn't agree with our hypothesis," Wang says. She and her mentor, Wai Wong, both ophthalmologists at the National Eye Institute in Bethesda, Md., could have started over with another kind of mouse. But they decided to do the test again. And again.

The spared vision was no mistake. Many experiments later, Wang, Wong and colleagues have shown that tamoxifen, a drug used to treat breast cancer, can help preserve photoreceptors — and sight — in mice with eye injuries.

After exposure to blinding light, injured photoreceptors send distress signals to summon microglia, immune cells that are the first line of defense in the brain and spinal cord. Microglia support photoreceptors by keeping the connections between them intact. But a photoreceptor "SOS" brings microglia swarming in to destroy damaged photoreceptors, resulting in vision loss. The same happens in progressive genetic vision disorders such as retinitis pigmentosa. The microglia's murderous tendencies are meant to protect, but, Wong notes, their enthusiastic efforts can be overkill.



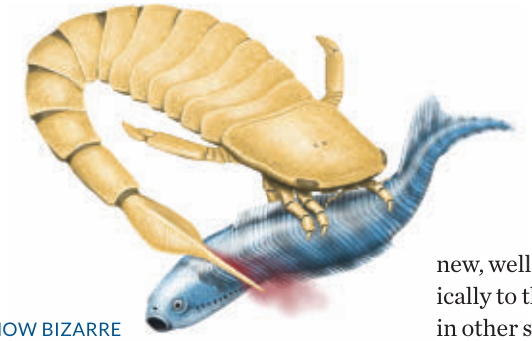
Exposure to blinding light killed photoreceptor cells in the retinas of mice (left, dying cells colored pink). Animals given tamoxifen before the light (right), had almost no cell death.

When mice ate chow containing tamoxifen (about six to eight times the dose usually given to humans), the microglia didn't overreact and the photoreceptors were spared, the researchers found. Tamoxifen offered the same protection in mice with a form of retinitis pigmentosa. "The killing power of microglia can be reduced by tamoxifen and this resulted in protection," Wong says. The group reported its findings in the March 22 *Journal of Neuroscience*.

The researchers are looking into whether lower doses of the drug can be protective, too. And there are plenty of other questions, such as how exactly tamoxifen protects against microglial malfeasance. Other scientists have shown that tamoxifen and similar drugs might also reduce nerve cell damage in the spinal cord and brain. The drug is widely used to treat women with certain types of breast cancer. But the eyes present their own challenges. In rare cases, tamoxifen has been tied to vision loss in women taking the drug. The scientists didn't see any sign of that in their mice, but Wong is quick to note that mice are not people.

Wang recalls her early days with patients facing blindness. "I felt so helpless," she says. "I thought, 'I want to find a way to solve their problems.'" She has new optimism. "It opens a new window," she says. "An old drug can be used in a new way."
— *Bethany Brookshire*

FROM TOP: MINHUA WANG/WONG LAB; YIKUI ZHANG, X. WANG, W. WONG



Ancient sea scorpions (one illustrated) may have used serrated, swordlike tails for swimming or as weaponry.

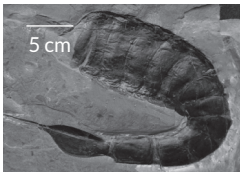
HOW BIZARRE

Sea scorpion was a swinging slasher

Ancient sea scorpions were hacks.

Some of the marine creatures had a thin, serrated spine on the tip of their tail — and that tail was surprisingly flexible, based on a 430-million-year-old fossil found in Scotland. *Slimonia acuminata* may have had the range of motion to strike large predators and prey, researchers report online April 18 in *American Naturalist*.

Scientists had thought that the ancient animals largely used their tails for swimming, primarily flapping them up and down like today's lobsters and shrimp do and, to a limited degree, side to side like a rudder. But the tail on the new, well-preserved fossil curls dramatically to the side — a flexibility not seen in other sea scorpion specimens.

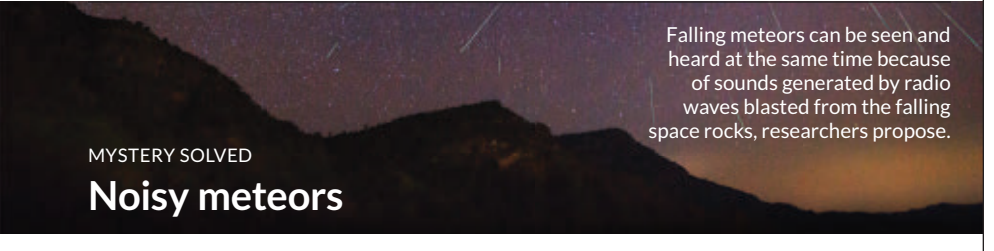


This *Slimonia acuminata* specimen shows all tail segments as well as a serrated tip.

That bendiness suggests a purpose beyond propulsion, say study authors W. Scott Persons, a paleontologist, and John Acorn, an entomologist, both at the University of Alberta in Canada. The tail could have twisted around horizontally to strike a victim or dispatch a foe with the pointy end, and the saw-edged weapon would have encountered little water resistance.

Sea scorpions may have even pinned down prey with their front limbs while delivering lethal blows with their tails.

Because *S. acuminata* appears quite early in sea scorpion evolution, slicing and dicing may have been the norm early on for the ancient critters, the researchers write. — *Helen Thompson*



Falling meteors can be seen and heard at the same time because of sounds generated by radio waves blasted from the falling space rocks, researchers propose.

MYSTERY SOLVED

Noisy meteors

For centuries, skywatchers have reported seeing and simultaneously hearing meteors whizzing overhead, which doesn't make sense given that light travels roughly 800,000 times as fast as sound. Now scientists say they have a potential explanation for the paradox.

The sound waves aren't coming from the meteor itself, atmospheric scientists Michael Kelley of Cornell University and Colin Price of Tel Aviv University propose April 16 in *Geophysical Research Letters*. As the leading edge of the falling space rock vaporizes, it becomes electrically charged. The charged head produces an electric field, which yields an electric current that blasts radio waves toward the ground. As a type of electromagnetic radiation, radio waves travel at the speed of light and can interact with metal objects near the ground, generating a whistling sound that people can hear. Just 0.1 percent of the radio wave energy needs to be converted into sound for the noise to be audible as the meteor zips by, the researchers estimate. This same process could explain mysterious noises heard during the aurora borealis, or northern lights (*SN: 8/9/14, p. 32*). Like meteors, auroras have been known to emit radio wave bursts. — *Thomas Sumner*

SAY WHAT?

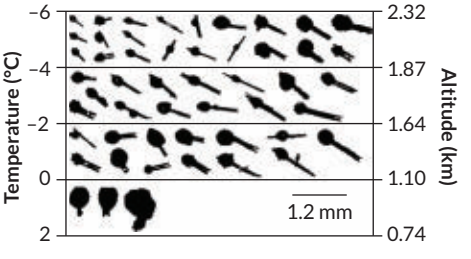
Ice-lolly

\AIS LOL-ee\ n.

Tiny ice particle made of a needle-shaped ice crystal and a drizzle-sized water droplet

Right now, somewhere in the world, it could be raining lollies. A 2009 research flight through clouds above the British Isles gathered ice particles with an unusually sweet look. Each millimeter-sized particle consisted of a stick-shaped piece of ice with a single water droplet frozen on the end, giving it the appearance of a lollipop. Atmospheric scientist Stavros Keppas of the University of Manchester in England and colleagues report the discovery of the atmospheric confections in a paper to be published in *Geophysical Research Letters*.

The ice-lollies, as Keppas dubs them, started as pristine, six-sided ice crystals formed in the tops of clouds. A stream of relatively warm air cut through the clouds, creating a zone of water droplets on the verge of freezing, the scientists found during the research flight. As the crystals fell through the warmer layer, droplets grabbed on, froze in place and then exploded, forming ice needles. When other droplets froze onto those needles, ice-lollies formed. Like real lollipops in a kindergarten class, the little lollies may not last long, probably melting or deforming before hitting the ground. On their way down, they may drain moisture from clouds, Keppas says. — *Thomas Sumner*



Sky candy A newly discovered type of ice particle is made of a "stick" with a frozen water droplet attached, making it a lollipop doppelgänger. Observed variations of the shape at different altitudes, and thus temperatures, are shown.

FROM TOP: NATHAN ROGERS; W.S. PERSONS AND J. ACORN/*AMERICAN NATURALIST* 2017; SRIPFOTO/ISTOCKPHOTO; S. KEPPAS *ET AL*/*GEOPHYS. RES. LETTERS* 2017

HUMANS & SOCIETY

Homo naledi's age surprises scientists

Ancient-looking hominid dates to time of humankind's origins

BY BRUCE BOWER

Fossils of a humanlike species with some puzzlingly ancient skeletal quirks are surprisingly young, its discoverers say. It now appears that this hominid, called *Homo naledi*, inhabited southern Africa close to 300,000 years ago, around the dawn of *Homo sapiens*.

H. naledi achieved worldwide acclaim in 2015 as a possibly pivotal player in the evolution of the human genus, *Homo*. Retrieved from an underground chamber in South Africa, fossils of this species were thought to be anywhere from 900,000 to at least 1.8 million years old (*SN: 8/6/16, p. 12*). A younger age for the species resolves one mystery about these cave fossils. It doesn't, however, answer questions about how long ago *H. naledi* first appeared and when it died out.

What is now known is that *H. naledi* bodies somehow ended up in Dinaledi Chamber, part of South Africa's Rising Star cave system, between 236,000 and 335,000 years ago, an international team of researchers reports May 9 in one of three papers in *eLife*. Paleoanthropologist Lee Berger of the University of the Witwatersrand in Johannesburg headed the team. Geoscientist Paul Dirks of James Cook University in Townsville, Australia, directed the dating effort.

In the first paper, two methods of measuring the concentration of natural uranium and other radioactive elements, and damage caused by those elements over time, provided key age estimates for three *H. naledi* teeth. A thin sheet of rock deposited by flowing water just above the fossils was also dated.

In a second new paper, Berger's group — led by paleoanthropologist John Hawks of the University of Wisconsin–Madison — describes 131 newly discovered *H. naledi* fossils from a second cave in the Rising Star system, dubbed Lesedi Chamber. The finds come from at least three individuals and include an adult male's partial skeleton comparable in completeness to the 3.2-million-year-old Lucy's famous remains from East Africa. Both of these specimens consist of about 40 percent of the skeleton. The researchers named the Lesedi partial skeleton "Neo," which means *gift* in Sesotho, a language spoken in South Africa.

Berger and colleagues say the Lesedi discoveries support their controversial suggestion that *H. naledi* deliberately put bodies of the dead in Rising Star's underground chambers (*SN: 5/14/16, p. 12*). The researchers say there are no signs that either predatory animals or streams carried *H. naledi* corpses into the caves.

Individuals from both chambers display the same distinctive pattern of skeletal features, signs that they all belong to *H. naledi*, not to *Homo erectus* or any other previously identified *Homo* species, the investigators contend. These features include relatively small, orange-sized brains and curved fingers like those of *Homo* species that lived around 2 million years ago, as well as wrists, hands, legs, feet and body sizes comparable to those of Neandertals and humans.

A cache of newly discovered *Homo naledi* fossils includes this skull. New dating suggests that the species is much younger than thought.

WITS UNIV., J. HAWKS

Though the Dinaledi finds are unexpectedly young, *H. naledi*'s ancient-looking characteristics suggest that it originated near the root of the *Homo* genus, 2 million years ago or more, Berger and colleagues propose in the third new paper. That would make the South African species a possible ancestor or close relative of *H. erectus*, which dates to around that time.

Another possibility, Berger's team says, is that *H. naledi* originated a few hundred thousand years ago and is most closely related to early *H. sapiens* or other *Homo* species that may have inhabited southern Africa at that time. A relatively late origin for *H. naledi* would suggest it evolved from larger-brained ancestors, the researchers say. That would be unusual: Scientists have long held that the brain became only larger as *Homo* species evolved.

But that proposed scenario has some parallels to Indonesia's *Homo floresiensis*. Better known as hobbits, these hominids, whose remains date to between about 100,000 and 60,000 years ago (*SN: 4/30/16, p. 7*), had chimp-sized brains, short statures and, like *H. naledi*, some skull features resembling early *Homo* species. Hobbits either evolved smaller brains or retained small brains after splitting from a much older *Homo* species in Africa.

Unlike *H. naledi*, hobbits lived on an island where a lack of competition with other *Homo* species may have assisted their survival. It's unclear how *H. naledi* survived in Africa alongside larger-brained *Homo* species, perhaps even *H. sapiens*. Occasional interbreeding in southern Africa — similar to what occurred later among *H. sapiens*, Neandertals and Denisovans in Eurasia (*SN: 10/15/16, p. 22*) — may have benefited *H. naledi*, Berger's team suspects.

H. naledi DNA would help clarify the species's evolutionary status. But attempts to extract DNA from Dinaledi

236,000–335,000

years old

New age estimate for *Homo naledi* fossils

fossils have so far failed. Researchers have yet to test Lesedi fossils for DNA or to try to generate age estimates for the new finds.

"My intuition is that *Homo naledi* points to a diversity of African *Homo* species that once lived south of the equator" in Africa, Hawks says. It's unlikely *Homo* evolution proceeded in a straight line, from one species to the next, in a specific part of subequatorial Africa, he proposes.

Paleoanthropologists familiar with the new reports interpret the findings differently.

An "astonishingly young" age for *H. naledi*, given its ancient-looking features, suggests that the species was the sole survivor of an array of much older, closely related species, proposes Chris Stringer of the Natural History Museum in London. *H. naledi* probably made some of the many stone tools found at southern African sites dating to around 300,000 years ago that have not yielded hominid fossils, he adds.

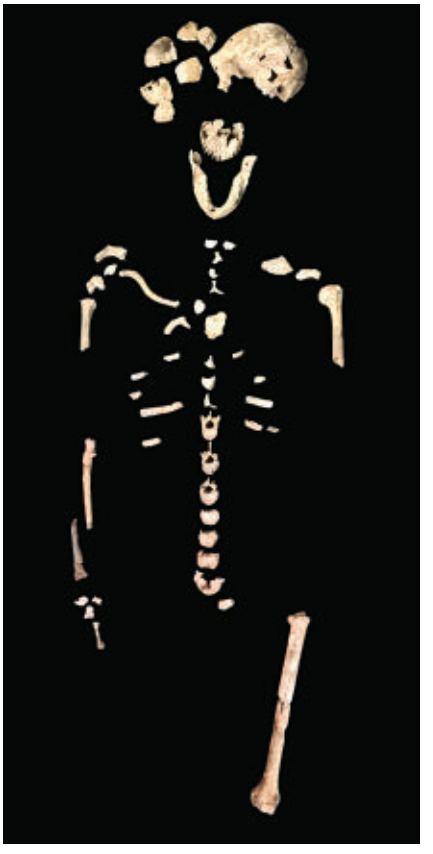
Despite Berger and colleagues' claims, Stringer doubts a creature with a brain size close to that of a gorilla disposed of its dead deep within a pitch-black, difficult-to-navigate cave system, especially since the controlled use of fire for torches was probably also needed.

Berger's team plans to excavate near openings to the Rising Star cave system where stone tools and signs of fire use may turn up.

However complex *H. naledi*'s behavior may have been, ancient aspects of its anatomy rule it out as an ancestor of *H. sapiens*, says Donald Johanson of Arizona State University in Tempe. Johanson, codiscoverer of Lucy, argues that *H. sapiens* originated in East Africa. Researchers generally place that evolutionary turning point, wherever it occurred, at between 200,000 and 300,000 years ago.

"The Rising Star Cave hominids, much like the hobbits, evolved in isolation and have no relevance to the origins of humankind," Johanson says.

Still, says paleoanthropologist Fred Smith of Illinois State University in Normal, even a largely isolated *H. naledi* population may have occasionally interbred with other *Homo* species in southern Africa. Later *Homo* evolution, he adds, "is far more complex than has generally been thought." ■



A partial *Homo naledi* skeleton unearthed in South Africa's Rising Star cave system is about 40 percent complete. Nicknamed Neo, the skeleton belonged to an adult male.

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BODY & BRAIN

'Exercise pill' boosts mice's endurance

Potential drug tricks body into burning fat like a trained athlete

BY LAURA BEIL

An experimental drug touted as "exercise in a pill" has dramatically increased endurance in couch potato mice, even after a lifetime of inactivity. The drug appears to work by adjusting the body's metabolism, allowing muscles to favor burning fat over sugar, researchers report in the May 2 *Cell Metabolism*.

Sedentary mice prodded into exercising ran for an average of about 160 minutes on an exercise wheel before reaching exhaustion. But mice given the drug for eight weeks could run for 270 minutes on average. These mice burned fat like conditioned athletes, even though they had spent their whole lives taking it easy, molecular biologist Michael Downes and colleagues found.

Normally, running, cycling or other prolonged exercise eventually depletes available glucose in the blood, leaving the brain short of energy. The brain then sends an emergency stop signal. Athletes call this "hitting the wall." Training and conditioning shift the body to burning fat for energy, leaving an ample supply of glucose for the brain and other organs.

Researchers developed the drug, called GW501516, to activate a protein that regulates genes triggered during exercise. "We believe it's tricked the body into thinking it's done some training," says Downes, of the Salk Institute for Biological Studies in La Jolla, Calif.

GW501516 has been under study for over a decade. Previous research found that it improved endurance, but only when combined with regular exercise (*SN: 7/3/10, p. 18*). The goal is not to boost athletic performance but to help those who can't exercise or lack stamina: people who are sick, disabled, elderly, obese or diabetic, Downes says.

"We know a lot about exercise, but we still don't know how we obtain all the benefits," says molecular and cellular biologist Rick Vega of Sanford Burnham Prebys Medical Discovery Institute in Orlando, Fla. He praises the work as adding valuable information to the understanding of exercise and the drug in development.

"The next step is really to show this has value in a medical application" in humans, he says. ■

BODY & BRAIN

A newborn's pain registers in the brain

Monitor picks up spikes in nerve cell activity after a jab or a stick

BY LAURA SANDERS

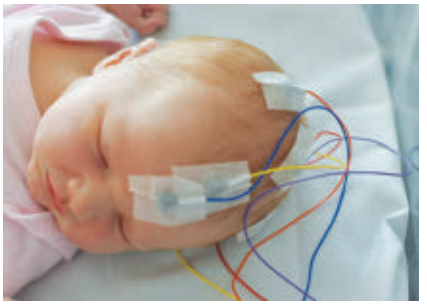
An electrode on top of a newborn's scalp, near the soft spot, can measure when the baby feels pain. The method, described in the May 3 *Science Translational Medicine*, isn't foolproof, but it brings scientists closer to being able to tell when infants are in distress.

Pain assessment in babies is both difficult and extremely important for the same reason: Babies don't talk. That makes it hard to tell when they are in pain, and it also means that their pain can be overlooked, says Carlo Bellieni, a pediatric pain researcher at University Hospital Siena in Italy.

Doctors rely on a combination of clues such as crying, wiggling and facial grimacing to guess whether a baby is hurting. But these clues can mislead. "Similar behaviors occur when infants are not in pain, for example if they are hungry or want a cuddle," says study coauthor Rebeccah Slater of the University of Oxford. By relying on brain activity, the new method offers a more objective measurement.

Slater and colleagues measured brain activity in 18 newborns between 2 and 5 days old. Electroencephalography, or EEG, recordings from electrodes on the scalp picked up collective nerve cell activity as babies received a heel lance to draw blood or a low-intensity bop on the foot, a touch that's a bit like being gently poked with a blunt pencil. An electrode perched on the top of the head was particularly useful. Called the Cz electrode, it detected a telltale neural spike between 400 and 700 milliseconds after the painful event. This response wasn't seen when these same babies received a sham heel lance or an innocuous touch on the heel.

The Cz electrode detected similar brain responses to painful procedures in tests of 14 other newborns. Loud sounds, flashing lights and nonpainful touches didn't elicit the same response in those newborns. This brain signature changed when pain-relieving gel was used in another group of babies who were on average 25 days old. After treatment with a topical anesthetic, babies' brain responses to foot thumps were smaller than when the taps were delivered to unmedicated feet.



When a newborn is in pain, the brain can show an uptick in activity detected by scalp electrodes, researchers say. Such activity could one day provide an objective measurement of pain.

On average, babies born prematurely between 34 and 36 weeks of gestation showed similar neural responses to pain. It's unclear whether this presumed pain signature would be present in babies born earlier or in older infants, Slater says.

In its current form, the method isn't reliable enough to be a definitive readout of pain in individual babies because not all babies' brains responded to pain similarly. Ten of 28 babies who had heel lances didn't show this neural signature.

And the brain signature didn't always track with other pain indicators. Of the 17 babies who indicated pain by changing facial expressions during a presumably painful event, 13 also showed the brain signature and four did not. Of the 11 babies who did not change expressions, five showed the signature and six did not. Slater says that an approach that relies on multiple pain indicators might be useful.

Even if improved, this method might not be clinically useful, Bellieni says. A method that measures quick, severe pain can't be used to change a painful situation in real time. "When you get the results, the procedure is already over," he says. Still, he suspects that such a measurement will be a valuable research tool. ■

BODY & BRAIN

New 'rules' for finding antibiotics

Tests give clues to fighting gram-negative bacteria

BY AIMEE CUNNINGHAM

Like entry to an exclusive nightclub, getting inside a gram-negative bacterial cell is no easy feat for chemical compounds. But now a secret handshake has been revealed: A new study lays out several rules to successfully cross the cells' fortified exteriors, which could lead to the development of sorely needed antibiotics.

"It's a breakthrough," says Kim Lewis, a microbiologist at Northeastern University in Boston who was not involved with the work. The traditional way to learn how compounds get across the bacterial barrier is to study the barrier, he says. The researchers "decided to attack the problem from the other end: What are the properties of the molecules that may allow them to penetrate across the barrier?"

The work describing these properties is reported in the May 18 *Nature*.

E. coli and other gram-negative bacteria — so described because of how they look when exposed to a violet dye called a gram stain — have two cellular membranes. The outer membrane is impermeable to most antibiotics, says chemical biologist Paul Hergenrother of the University of Illinois at Urbana-Champaign. "Even if a drug might be really good at killing that gram-negative pathogen, it may not be able to get in the bacteria."

Many antibiotics that have been effective against gram-negative bacteria are becoming unreliable, as the bugs have developed resistance. To encourage drug development, in February the World Health Organization released a list of pathogens that are resistant to multiple drugs. All of the bacteria in the "critical" priority group are gram-negative.

Gram-negative cells' outer membrane is dotted with proteins called porins. These channel structures allow the cells

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to take up nutrients. Antibiotics that get inside gram-negative bacteria typically pass through porins, Hergenrother says.

To uncover the dos and don'ts of porin passage, Hergenrother's group synthesized 100 compounds that share characteristics with antimicrobials found in nature, such as those from plants. The researchers took each compound, incubated it with *E. coli* bacteria in a tube for 10 minutes and then measured how much got inside the cells.

One feature stood out among the dozen compounds that significantly accumulated inside the bacterial cells: They all contained an amine group, a chemical group with the element nitrogen.

Next, the team collected a larger set of compounds that have amine groups and again measured whether the compounds accumulated inside *E. coli* cells. The researchers used a computer program to predict what other attributes would be necessary to get through porins. This analysis revealed that a compound should be rigid (rather than flexible) and flat (as opposed to spherical). It's much easier to put a ruler through a narrow opening than a basketball, notes Hergenrother.

To test the new rules, the researchers turned to an antimicrobial known as deoxynybomycin. This compound is effective only against gram-positive bacteria, which have just one cellular membrane. Deoxynybomycin is flat and rigid, so it already has "the right geometrical parameters," Hergenrother says. That makes it a good compound "to try to add an amine to, in a place that doesn't disrupt how it interacts with the biological target."

The team synthesized a derivative of deoxynybomycin with an amine group and tested the compound against 21 different strains of gram-negative pathogens that are resistant to many antibiotics. The altered deoxynybomycin successfully killed all but one of the types of pathogens tested.

It's possible other antibiotics that specifically target gram-positive bacteria could be converted into drugs that kill gram-negative bugs too by following the new rules, Hergenrother says. And keeping these guidelines in mind when assembling compound collections could make screening for drug candidates more successful.

The research could also "revive the failed effort to rationally design antibiotics," Lewis says. Knowing the rules, it may be possible to build a compound that both hits its bacterial target and has the features needed to penetrate the target's barrier. ■

ATOM & COSMOS

Comet's oxygen may be homegrown

Newfound chemical reaction could produce the gas on 67P

BY ASHLEY YEAGER

Oxygen on comets might not date all the way back to the birth of the solar system.

Instead, interactions between water, particles streaming from the sun and grains of sand or rust on the comet's surface could generate the gas. Those interactions could explain the surprising abundance of molecular oxygen detected in the fuzzy envelope of gas around comet 67P/Churyumov-Gerasimenko in 2015 (*SN: 11/28/15, p. 6*), researchers report May 8 in *Nature Communications*. Such reactions might also reveal how O_2 forms in other regions of space.

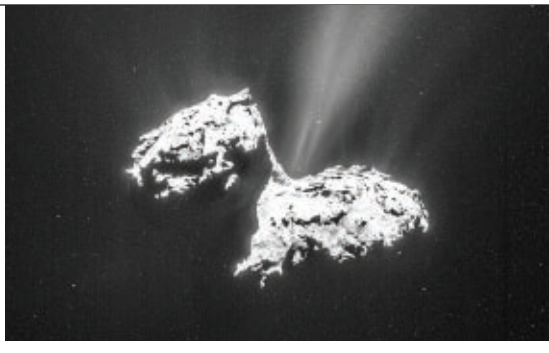
"Molecular oxygen is very hard to find out there in the universe," says Caltech chemical engineer Konstantinos Giapis. When the Rosetta spacecraft detected oxygen around 67P, astronomers argued it was primordial, trapped in water ice as the comet formed about 4.6 billion years ago. Giapis and Caltech colleague Yunxi Yao wanted to see if an alternative way to create O_2 existed. Drawing on their work with fast-moving charged particles and materials such as silicon, they performed experiments that showed that charged water particles could slam into rust or sand grains and generate O_2.

Something similar could happen on comet 67P, Giapis and Yao suggest. As the sun evaporates water from the comet's surface, ultraviolet light could strip an electron from the water, giving it a positive charge. Then, fast-moving particles in the solar wind could shoot the ionized water back toward the comet's surface, where it could collide with rust or sand particles. Atoms of oxygen from the water could pair with atoms of oxygen from the rust or sand, creating O_2.

The idea is plausible, says astrophysicist Paul Goldsmith of NASA's Jet Propulsion Laboratory in Pasadena, Calif. He helped discover O_2 in the Orion Nebula and says the reaction might happen in places where young stars are forming and in other regions of space.

Rosetta mission scientist Kathrin Altwegg of the University of Bern in Switzerland is skeptical the new work explains comet 67P's O_2. As the comet gets closer to the sun, a protective bubble develops around 67P, Rosetta data show; that bubble would prevent solar wind or other ionized particles from reaching the comet's surface, Altwegg says. Data show that the ratio of oxygen to un-ionized water also stays constant over time. It should be variable if this chemical reaction were generating oxygen, she says.

Goldsmith suggests researchers keep an open mind and design missions to test whether this newly detected reaction does, in fact, generate oxygen in space. ■



Molecular oxygen detected around comet 67P may not be primordial. Instead, the gas may be created by interactions of water, the solar wind and sand on 67P's surface, researchers suggest.

NAVCAM/ROSETTA/ESA (CC BY-SA IGO 3.0)

LIFE & EVOLUTION

To fight skeeters, disrupt their sex lives

Florida tests one of two opposing bacteria-based control tactics

BY SUSAN MILIUS

Near Key West, Fla., mosquito-control officers are trying something new. They're releasing more mosquitoes.

In a 12-week test running through early July, 40,000 male mosquitoes are being released each week with the eventual goal of preventing the spread of mosquito-borne diseases such as Zika and dengue.

Instead of trying to kill the mosquitoes directly, a losing battle in Florida, a Kentucky company called MosquitoMate has infected *Aedes aegypti* mosquitoes with a strain of *Wolbachia* bacteria that makes the males disastrous dads. When these males mate with uninfected wild females, their offspring die before hatching.

> Flooding a neighborhood with bad dads should shrink the local population of *Aedes aegypti* mosquitoes.

The Florida trial is a recent example of worldwide tests of two conceptually opposite approaches to using mosquitoes infected with *Wolbachia* for disease control. The better-known tack is to render mosquitoes less able to carry disease but leave them free to do what mosquitoes do. The approach being tried in Florida would instead try to stomp down their numbers.

The first salvo in this new battle began on the afternoon of April 18, when staff of the Florida Keys Mosquito Control District worked their way along some streets on Stock Island. At 20 predetermined spots, workers opened fat cardboard tubes packed with male mosquitoes shipped overnight in a cooler from Kentucky — 20,000 mosquitoes in all. Blowing gently at one end of the tubes encouraged males to lift into the air and whine off in search of females.

Wolbachia bacteria make these males biologically incompatible with uninfected females. Over time, flooding a neighborhood with bad dads should shrink the local population of *Ae. aegypti* mosquitoes.

That species "is very difficult to control," says Andrea Leal, executive director of the control district. *Ae. aegypti* is the domestic cockroach of mosquitoes, sticking inside, under or near human homes, where heavy pesticide use is restricted. Larvae can grow in just bottle-capfuls of rainwater. Saucers under potted plants or puddles in a crumpled tarp can become a public health menace.

Ae. aegypti can spread yellow fever and chikungunya viruses, as well as Zika, which broke out in Miami last year. The mosquito can also carry dengue, a painful disease that has made appearances in Key West over the last eight years, including one case in 2016.

Infecting mosquitoes with certain strains of *Wolbachia* can sabotage the spread of such viruses, though biologists are still exploring how. One proposed scenario: *Wolbachia* competes with viruses for precious resources inside cells, such as cholesterol.

Forms of *Wolbachia* are found naturally in various ants, butterflies and many other arthropods. But no form of the bacteria had taken to *Ae. aegypti*, so researchers have gone to years of effort working out how to coax bacterial strains from other insects into the troublesome mosquito.

Scientists were able to infect mosquitoes with the bacteria without genetically modifying either species, a plus because a recent proposal to release genetically modified mosquitoes as pest control in nearby Key Haven stirred fierce protests (*SN Online: 8/5/16*).

The bacterial infection technique that finally worked was simple in concept, though not to execute, says entomologist Stephen Dobson of the University of Kentucky in Lexington. Researchers used a vanishingly slender glass needle to poke the bacteria into mosquito eggs.

Entomologist Catherine Pruszynski frees male mosquitoes from their shipping tube at the start of a 12-week test for the Florida Keys Mosquito Control District.

BETH RANSON/FLORIDA KEYS MOSQUITO CONTROL DISTRICT

That method developed the lineages of mosquitoes now being released twice a week on Stock Island. One advantage of the test's population-crashing approach, says Dobson, also MosquitoMate's CEO, is that workers puffing a thousand insects out of a shipping tube near someone's yard are releasing only males, which don't bite. "People might accept that more," Dobson says. To replace the mosquito population with a safer one — the better-known strategy — requires releasing females, too, which Dobson points out, "bite people and drink their blood."

That vampire-release route has advantages, argues Scott O'Neill of Monash University in Melbourne, Australia. He leads an international nonprofit collaboration called Eliminate Dengue (*SN: 7/14/12, p. 22*), which works in developing countries with vast areas at risk of disease but minuscule budgets. Instead of suppressing mosquitoes and risking a comeback, his approach relies on the bacteria to spread and maintain themselves.

Wolbachia can sweep into a population extraordinarily fast. But for it to do so, infected females also have to be released. *Wolbachia*-carrying males have no problem siring baby mosquitoes if the mom also carries bacteria, and the young then carry the bacteria, too.

With mosquitoes doing the work, "we can sort of march across the landscape," O'Neill says. One of the project's first release sites, in Australia, still hums with *Wolbachia*-carriers six years later with no need for additional treatment. "We have a very lousy business model," he says, not sounding very sorry.

Eliminate Dengue is marching over swaths of five countries. In Rio de Janeiro,

the project is treating about 190 square kilometers over the course of two to three years and aims to protect 2.5 million city dwellers for years to come.

The biggest roadblock to bacteria-based mosquito control hasn't appeared yet, and researchers don't know if it will. If viruses such as Zika or dengue evolve a way to thrive in *Wolbachia*-infected cells, the benefit could dwindle away.

O'Neill hasn't seen signs of resistance, but he has a plan if he does: Eliminate Dengue could release mosquitoes with a new combination of *Wolbachia* strains to spread through a population and replace ones that are losing effectiveness. The project has already developed mosquitoes infected with just such a combination of bacterial strains, he says.

This possibility of developing resistance, much as some pests develop resistance to pesticides or antibiotics, is reduced with the MosquitoMate approach, Dobson says. The suppression approach shouldn't leave survivors in which viral evolution could take place.

Florida will be a high-profile test for the approach — but it won't be the first. Dobson and colleagues have tested two other species of *Wolbachia*-carrying mosquito: *Ae. polynesiensis* on Pacific islands to combat lymphatic filariasis and its elephantine swellings, plus, in the United States, the aggressively biting tiger mosquito, *Ae. albopictus*, which can spread viruses.

MosquitoMate has applied to the Environmental Protection Agency for approval to sell booby-trapped tiger mosquitoes as a biopesticide in the United States. The third of Dobson's saboteur insects, *Ae. aegypti* was first deployed last year in Clovis, Calif.

Now the group hopes to create at least a 7-to-1 ratio of bacteria-carrying Kentucky males to native Floridian male rivals. That's the initial result that Leal, of the mosquito control district, is focusing on.

Residents of Stock Island would love to see a big drop in the mosquito's numbers, too, but Leal says that's the next stage. For now, getting enough of the dud dads out there mating with female mosquitoes will be a big accomplishment. ■

ATOM & COSMOS

Exoplanet's skies hint at origin story

HAT-P 26b formed close to its star, chemical data suggest

BY ASHLEY YEAGER

A watery world about 430 light-years from Earth may have had a relatively calm origin.

HAT-P 26b, a Neptune-mass planet, has surprisingly low levels of heavy elements in its atmosphere, hinting that the planet formed close to its star, scientists report in the May 12 *Science*. That's different from how the solar system's ice giants, Neptune and Uranus, formed. The finding may offer insights into the ways planets originate throughout the galaxy.

"With the observations of exoplanets' atmospheres, we are looking outward to look in," says study coauthor Hannah Wakeford, an astronomer at NASA's Goddard Space Flight Center in Greenbelt, Md.

Scientists mostly use computer simulations to study how planetary systems form. These simulations are based in part on how planets coalesced in the solar system, but it's unclear how common these types of planetary origins are.

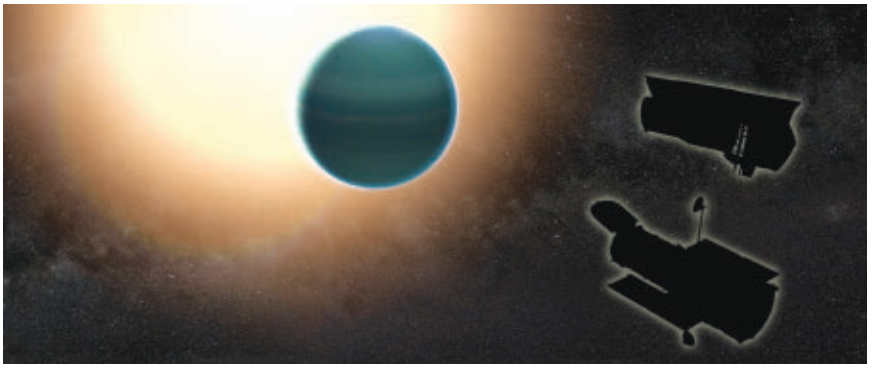
The abundance of heavy elements in a planet's atmosphere can offer formation clues. In the solar system, more massive planets have a lower abundance of elements heavier than hydrogen and helium. Neptune's abundance of heavy elements is about 100 times that of the sun. Jupiter, 18 times as massive as Neptune, has about five times the solar abundance. Neptune's abundance is probably higher because it formed farther outward, toward the edge of the disk of dust and gas that circled the young sun. There, icy rocks accumulated, bombarding Neptune and enriching its atmosphere as the rocks disintegrated.

Previous studies of three exoplanets in separate planetary systems have shown a similar relationship between a planet's mass and heavy element abundance.

To study HAT-P 26b, researchers used the Hubble and Spitzer space telescopes to watch the planet pass in front of its star, blocking some of the star's light. A fraction of that starlight is filtered by the planet's atmosphere, which absorbs some wavelengths of light, giving clues to its composition. The team found a prominent sign of water in visible and infrared wavelengths. From that signature, the team inferred that the planet's atmospheric heavy element abundance is only four to five times as high as the sun's.

Such a low abundance suggests that HAT-P 26b formed nearer to its star than Neptune did to the sun. That proximity could have protected the planet from bombardments. HAT-P 26b, whose orbit is about four Earth days, also drew in gas directly from the disk in which the star and planets formed, the researchers say.

Astrophysicist Adam Burrows of Princeton University says the data don't conclusively show that HAT-P 26b developed differently than Neptune or Uranus. Data from additional wavelengths of light would be needed to definitively describe the exoplanet's history. ■



GSFC/NASA

New observations of exoplanet HAT-P 26b (illustrated here) from the Spitzer and Hubble space telescopes indicate that planets in the Milky Way can form in many different ways.

MATTER & ENERGY

Singularities may reveal themselves

These spacetime oddities don't stay hidden in some universes

BY EMILY CONOVER

Certain stealthy spacetime curiosities might be less hidden than thought, potentially exposing themselves to observers in some curved universes.

These oddities, known as singularities, are points in space where the standard laws of physics break down. Found at the centers of black holes, singularities are generally expected to be hidden from view, shielding the universe from their problematic properties. Now, in the May 5 *Physical Review Letters*, scientists report that a singularity could be revealed in a hypothetical, saddle-shaped universe.

Previously, scientists found that singularities might not be concealed in hypothetical universes with more than three spatial dimensions. The new result marks the first time the possibility of such a "naked" singularity has been demonstrated in a three-dimensional universe. "That's extremely important," says physicist Gary Horowitz of the University of California, Santa Barbara. Horowitz, who was not involved with the new study, has conducted research that implied that a naked singularity could probably appear in such saddle-shaped universes.

In Einstein's theory of gravity, the general theory of relativity, spacetime itself can be curved (*SN: 10/17/15, p. 16*). Massive objects such as stars bend the fabric of space, causing planets to orbit around them. A singularity occurs when the warping is so extreme that the equations of general relativity become nonsensical — as occurs in the center of a black hole. But black holes' singularities are hidden by an event horizon, which encompasses a region around the singularity from which light can't escape. The cosmic censorship conjecture, put forth in 1969 by mathematician and physicist Roger Penrose, proposes that all singularities will be similarly cloaked.

Another feature of general relativity is that hypothetical universes can take on various shapes. The known universe is nearly flat on large scales, meaning that the rules of standard textbook geometry apply and light travels in a straight line. But in universes that are curved, those rules go out the window. To demonstrate the violation of cosmic censorship, the researchers started with a curved geometry known as anti-de Sitter space, which is warped such that a light beam sent out into space will eventually return to the spot it came from. The researchers deformed the boundaries of this curved spacetime and observed a region in which the curvature increased over time to arbitrarily large values, producing a naked singularity.

"I was very surprised," says study coauthor Jorge Santos, a University of Cambridge physicist. "I always thought that gravity would somehow find a way" to maintain cosmic censorship.

LIFE & EVOLUTION

Fossil whale hints at baleen makeover

Ancient relative of humpbacks mixed primitive, new features

BY LAUREL HAMERS

A 36-million-year-old fossil skeleton is revealing a critical moment in the history of baleen whales: what happened when the ancestors of these modern-day filter feeders first began to distinguish themselves from their toothy, predatory predecessors. The fossil is the oldest known mysticete, a group that includes baleen whales, such as humpbacks, researchers report in the May 22 *Current Biology*.

Mystacodon selenensis, an ancient whale found in Peru, was an early relative of baleen whales. Its skull had a flattened snout and teeth, which baleen whales later lost.

O. LAMBERT *ET AL*/*CURRENT BIOLOGY* 2017

Scientists had made predictions about what the first mysticetes might have looked like, but hadn't had much fossil evidence to back up those ideas, says Nicholas Pyenson, a paleobiologist at the Smithsonian National Museum of Natural History in Washington, D.C. "Here, we have something we've been waiting for: a really old baleen whale ancestor."

The earliest whales were predators — a legacy carried on by today's orcas, dolphins and other toothed whales. But at some point, the ancestors of modern mysticetes replaced teeth with baleen, fibrous plates that filter out small bits of food from seawater like a giant sieve. Such a huge lifestyle change didn't happen overnight, though. And the new find, dubbed *Mystacodon selenensis*, shows the start of that transition, its discoverers say.

Mystacodon was unearthed in the arid Pisco Basin of southern Peru. Like other early mysticetes, this one still had teeth. The creature was probably close to 4 meters long, far smaller than today's leviathan humpbacks, estimates study coauthor Olivier Lambert, a paleontologist at the Royal Belgian Institute of Natural Sciences in Brussels.

The whale holds onto some features of primitive whales, Lambert says. It still had a bit of a protruding hip bone, suggesting the presence of tiny hind legs left over from when whales' ancestors were four-legged, terrestrial creatures. "At this transition, scientists thought that this hind limb would be more or less gone," Lambert says. But the new find suggests that completely losing those limbs took a little longer than previously believed. And the process probably happened independently in toothed whales, instead of one time in the common ancestor of baleen and toothed whales.

But *Mystacodon* also shows some more modern features. Its snout was flattened,

Scientists had previously shown that cosmic censorship could be violated if conditions were precisely arranged to conspire to produce a naked singularity. But the researchers' new result is more general. "There's nothing finely tuned or unnatural about their starting point," says Ruth Gregory, a physicist at Durham University in England. That, she says, is "really interesting."

But, Horowitz notes, there is a caveat: Because the violation occurs in a curved universe, not a flat one, the result "is not yet a completely convincing counterexample to the original idea."

Despite the reliance on a curved universe, the result does have broader implications. That's because gravity in anti-de Sitter space is thought to have connections to other theories. The physics of gravity in anti-de Sitter space seems to parallel that of some types of particle physics theories, set in fewer dimensions. So censorship violation in this realm could have consequences for seemingly unrelated ideas. ■

just like in modern mysticetes. In the earliest whales, the joints in the front flippers — essentially elbows — could still be flexed, a relic of when those flippers were legs. Modern whales can't move those joints, and neither could *Mystacodon*.

"This is the first indication of a locked elbow, the final step of the transition of the forelimbs into flippers," Lambert says.

Wear patterns on *Mystacodon*'s teeth suggest that the whale was a suction feeder — vacuuming up its prey instead of chomping it. That could have been a step toward the filter-feeding strategies of today's baleen whales, Lambert says. (Other early mysticetes show similar wear, also suggesting suction-feeding.)

But the link between suction-feeding and filter-feeding isn't well-established, Pyenson says. Mysticetes didn't become true filter feeders until millions of years later, he says. And scientists still don't know what series of changes in the ocean and in mysticetes' bodies led to the transformation. "I don't think suction-feeding alone is the primary step." ■

A larvacean's pale inner house (rounded flank in foreground) and big, sticky outer envelope could be important in ocean carbon cycles.

LIFE & EVOLUTION

'Mucus houses' catch sea carbon fast

Laser tool measures filtering power of larvaceans' snot bubbles

BY SUSAN MILIUS

Never underestimate the value of a disposable mucus house.

Filmy envelopes of mucus, called "houses," get discarded daily by giant larvaceans, the largest of the sea creatures that exude them. The old houses, often more than a meter across, sink toward the ocean bottom carrying with them plankton and other biological tidbits snagged in their goo.

Now, scientists have finally caught the biggest of these houses in action, filtering particles out of seawater for the larvacean, a type of zooplankton, to eat. The observations could begin to clarify a missing piece of life's role in sequestering ocean carbon, researchers say May 3 in *Science Advances*.

Larvaceans' bodies are diaphanous commas afloat in the oceans: a blob of a head attached to a tail that swishes water through its house. From millimeter-scale dots in surface waters to relative giants in the depths, larvaceans have jellyfish-clear bodies but the inner support rod (a notochord) of animals closer to vertebrates.

The giants among larvaceans, with bodies in the size range of candy bars, don't form their houses when brought into the lab. So researchers at Monterey Bay Aquarium Research Institute in Moss Landing, Calif., relied on a standard engineering strategy. They tracked particle movement to measure flow rates by reengineering equipment to watch giant houses at work deep in the ocean.

Getting the hardware right was challenging, and so was deploying it remotely from a research ship at the surface of Monterey Bay. "This is a 1-millimeter-thick laser sheet bisecting an animal that's about 2 centimeters wide that is 400 meters below the surface vessel," says study coauthor Kakani Katija.

The setup measured water flowing through larvacean species. The top rate for *Bathochordaeus mcnutti*, more than 20 milliliters per second, broke the record (previously held by salps) for fastest filtration rates from zooplankton. If the bay's maximum population of giant larvaceans pumped water that fast, they would clean all the particles out of their home depth in about 13 days.

Larvacean feeding rates matter because the creatures send organic material, including carbon, to the deep ocean, explains biological oceanographer Stephanie Wilson of Bangor University in Wales. Larvaceans discard houses that become clogged with the filtered particles. The animals also send carbon to the seafloor in football-shaped excrement.

If carbon-containing fallout from the upper ocean falls fast enough, it bypasses other creatures and reaches depths where nothing much happens to it for a long time, says Sari Giering of the National Oceanography Centre in Southampton, England. "The faster a particle sinks, the more likely its carbon will be stored in the ocean for centuries."

Giering points out that researchers already suspected giant larvaceans could be important in sequestering carbon. But the fragile houses have been hard to study in action until now. ■

EARTH & ENVIRONMENT

Human noises invade wilderness

Sound pollution ratchets up volume in U.S. protected areas

BY LAUREL HAMERS

Even in the wilderness, humans are making a ruckus.

In 63 percent of America's protected places — including parks, monuments and designated wilderness areas — sounds made by human activity are doubling the volume of background noise. And in 21 percent of protected places, this racket can make things 10 times noisier.

Enough clatter from cars, planes and suburban sprawl is seeping into wild places to diminish animals' ability to hear mating calls and approaching predators, researchers based in Colorado report in the May 5 *Science*. Some places are so quiet to begin with that even the smallest amount of human noise can dominate, the team found.

"The world is changing, and protected areas are getting louder — the last strongholds of diversity," says ecologist Jesse Barber of Boise State University in Idaho. Studies like this one that show the impact of human-related noise across the entire United States instead of in a single park are important, he says, because "this is the scale at which conservation occurs."

Researchers measured the reach of human noise by tapping into a National Park Service dataset containing long-term audio recordings from 492 U.S. sites. At each, the scientists linked the sound volume in decibels (averaged over weeks of recording and adjusted to prioritize the frequencies that human ears are most sensitive to) to the presence or absence of dozens of possible features. Such factors included whether the terrain was mountainous or flat, if there was a river nearby, and how close the site was to a highway or a farm.

Machine learning algorithms then predicted the volume in areas without audio monitors, based on the features of that place — and figured out how much of the noise in any given location came from human versus natural sources.

The answer: quite a lot. In 12 percent of designated wilderness areas, human-made noises increase the median sound level three decibels above the predicted natural noise levels. That means the area over which a bird's squawk would register in human ears would be cut in half.

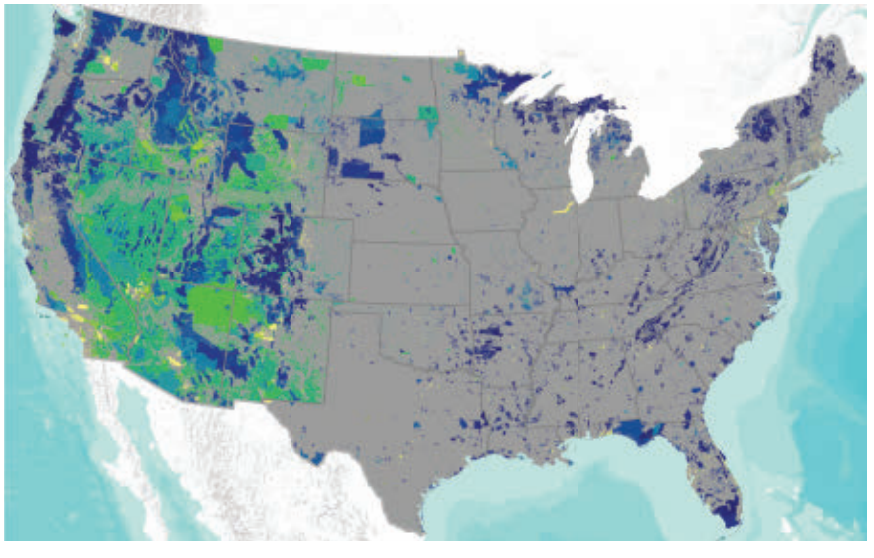
The more stringent the protections on the land, the lower the noise pollution, says study coauthor Rachel Buxton, an ecologist at Colorado State University in Fort Collins. Some categories of protection allow mining and grazing in limited amounts, which can boost noise levels. Areas labeled as "wilderness" ban such activity entirely. Overall, protected areas were 35 percent less noisy than nearby spots that weren't protected in any way.

Land managed by the federal government also tended to be less impacted by human noise than land under local control. That might come as a surprise to anyone who's faced a traffic jam while trying to find a parking spot in Yosemite or other popular national parks on a summer weekend. But unlike other U.S. land management agencies, the National Park Service "considers natural sounds to be a natural resource," Buxton says.

Many national parks have instituted restrictions on airplanes flying overhead, for instance, and implemented public transit to decrease park traffic. So while the area around the visitor center might feel like an amusement park, chirping birds and gurgling streams can dominate the soundscape deeper in the park.

Still, even a little extra noise can take a toll on an ecosystem. A humming highway can drown out birds' mating calls or prevent predators from hearing rustling prey (*SN: 2/21/15, p. 22*). And species don't need ears to be affected. Plants often depend on birds to spread their seeds, or on bees to get pollinated. If noise changes those animals' behavior, then the plants also face consequences.

"Noise is not strictly an urban phenomenon," says Clint Francis, an ecologist at California Polytechnic State University in San Luis Obispo. But there's hope for wild areas. "Solutions to noise are often readily available," he says. Quieter car engines and different types of road surfaces can help reduce traffic noise, for example. ■



R.T. BUXTON *ET AL*/*SCIENCE* 2017

Rural racket Noise made by humans boosts the natural sound level in U.S. parks and wilderness areas, new research shows. Human noises that raise background levels by 1.25, 3.01, 6.02 and 10 decibels correspond to 25, 50, 75 and 90 percent reductions in the area over which an acoustic signal like a birdcall can be detected by humans.

GENES & CELLS

Breast cancer cells spread in already armed mobs

COLD SPRING HARBOR, N.Y. — When breast cancer spreads, it moves in gangs of ready-to-rumble cells, a small genetic study suggests. Most of the mutations that drive spreading tumors were present in the original tumor, geneticist Elaine Mardis reported May 9 at the Biology of Genomes meeting.

For many cancers, it is the spread, or metastasis, of tumors that kills people. Because cancer that comes back and spreads after initial treatment is often deadlier than the original tumor, scientists had thought most mutations in recurrent tumors happened after they spread.

Mardis, of Nationwide Children's Hospital in Columbus, Ohio, and colleagues collected recurrent breast tumors from 16 women who died after their cancer had spread. Comparing the metastasized tumors with the originals, the team learned that multiple, slightly genetically different cells from the original site had broken away to establish the new tumors.

Scientists thought cancer spread when single cells slipped away. But recent work in mice showed cancer cells can migrate in groups (*SN: 1/10/15, p. 9*). The new study doesn't offer direct evidence of this group migration in humans. But genetic similarities between metastasized and original tumors suggest that cells moved together.

Only two women had cancer-driving mutations in their metastatic tumors not seen in the original. All metastasized tumors had mutated *TP53* genes. Such mutations could signal that a breast cancer is prone to spread, Mardis said. — *Tina Hesman Saey*

ATOM & COSMOS

Antiproton count may be sign of dark matter annihilation

Whiffs of dark matter may be blowing in on a cosmic ray breeze. Antiprotons streaming down on Earth from space may be hinting at the existence of the invisible substance, two research teams say.

Particles known as cosmic rays constantly whiz through space. These particles include protons and their antimatter partners, antiprotons. While antiprotons are produced in run-of-the-mill processes like particle collisions, additional ones could theoretically be birthed when dark matter particles annihilate one another.

In two papers in the May 12 *Physical Review Letters*, the teams — one from China and Taiwan, the other from Germany — analyzed antiprotons detected by the Alpha Magnetic Spectrometer located on the International Space Station. When dark matter's contribution was included in predictions of the numbers of antiprotons expected, the calculations better matched the data, hinting that some antiprotons might come from dark matter annihilation.

The results agree with another potential glimmer of dark matter: a glut of gamma rays in the Milky Way's center. "That could just be a coincidence," says Dan Hooper, a theoretical astrophysicist at Fermilab in Batavia, Ill. But "it does look pretty encouraging to me for that reason." Other physicists, however, have questioned the gamma rays' link to dark matter (*SN: 5/27/17, p. 15*). — *Emily Conover*

MATH & TECHNOLOGY

New exoskeleton stops tumbles

A wearable robot could prevent future falls among those prone to stumbles.

The exoskeleton packs motors on a user's hips and can sense blips in balance. In a small trial, the robot performed well in sensing and averting slips, researchers report May 11 in *Scientific Reports*.

Exoskeletons have the potential to help stroke victims and people with spinal cord injuries walk again (*SN: 11/16/13, p. 22*). But this new model focuses on a more ordinary problem: falling.

Most exoskeletons guide a wearer's movements, forcing the person to walk in a particular way. But the new device reacts only when needed. A computer algorithm measures changes in a wearer's hip joint angles to detect the altered posture that goes along with slipping. The robot uses its motors to push the hips back into position to prevent a fall.

At a rehab facility in Florence, eight elderly people and two amputees tried out the device while walking on a treadmill. The robot picked up on slips within 0.35 seconds of a change of balance.

A new wearable robotic device helps people who are at risk of falling find their balance.

HILLARY SANCTUARY/EPFL

Still, the device has some hurdles ahead. The exoskeleton is bulky. So Silvestro Micera, an engineer at École Polytechnique Fédérale de Lausanne in Switzerland, and his team are working on a sleeker model that would be less imposing for elderly users. — *Helen Thompson*

LIFE & EVOLUTION

'Baby Louie' dino gets official name

A dinosaur embryo known as "Baby Louie" has a new name. The dinosaur belongs to a newly identified species called *Beibeilong sinensis*, researchers report May 9 in *Nature Communications*.

In the 1980s and '90s, farmers found thousands of fossilized dino eggs in China's Henan Province and sold them. One chunk of rock held not only eggs but also an embryo, dubbed Baby Louie.

Paleontologists knew the dino was some kind of oviraptorosaur, a two-legged, birdlike dinosaur. But its species was a mystery. So in 2015, Junchang Lü of the Chinese Academy of Geological Sciences in Beijing and colleagues returned to the excavation site. They analyzed fossils there and examined the roughly 90-million-year-old Baby Louie.

Based on the structure of Baby Louie's facial bones and other traits, the team declared the dino a new species. Baby Louie was found with several eggs that looked like its egg. These eggs appear to have been abundant, which may mean birdlike dinos like Baby Louie were common in the Late Cretaceous. — *Ashley Yeager*

Watch a wearable robot prevent falls at **bit.ly/SN_exoskeleton**

This baby girl, born last November, was given methadone to treat her withdrawal from her mother's opioid pain medication.

SHAKY START

For babies exposed to opioids in the womb, parents may be the best medicine

By Meghan Rosen

The first thing you'll notice is the noise. Monitors beep steadily, relentlessly, ready to sound a car-alarm blare if a baby is in trouble.

The air has an astringent odor — not clean exactly, but reminiscent of an operating room (there's one next door). Ceiling lights shine fluorescent white. Half are off, but glare from the monitors throws out extra light. It's midday on a Friday, but it'll be just as bright at midnight.

Here on the fourth floor of Yale New Haven Children's Hospital, 10 tiny beds hold 10 tiny infants, each with Band-Aid–like patches stuck to their bodies to continuously monitor health. Between beds, nurses squeeze through narrow aisles crammed with folding chairs and plastic incubators. This space, one of five in the hospital's neonatal intensive care unit, has the people and equipment needed to keep sick babies alive — heart rate monitors, oxygen tanks, IV poles to deliver medications.

Until recently, Yale's NICU and hundreds like it across the country were considered the place to be for newborns withdrawing from opioid drugs. But now, as the number of drug-dependent babies surges, doctors here and elsewhere are searching for better options.

"We're really focused on trying to get these kids out of the NICU," says Yale pediatrician Matthew Grossman. "We're looking at moms and the dads as the first line of treatment."

The nationwide rate of babies withdrawing from opioids has soared — up nearly 400 percent from 2000 to 2012. The booming numbers are the bleak by-product of the United States' ongoing battle with the drugs: Sales of prescription opioid pain relievers alone quadrupled from 1999 to 2010, and overdose deaths tripled from 2000 to 2014.

When pregnant women use opioids, the drugs pass from bloodstream to baby. After exposure in the womb to Vicodin, methadone or heroin, for example, babies can become dependent. At birth, when the drug flow stops, babies can go through agonizing withdrawal — body shakes, intestinal

Beyond today's opioids

On Page 22, Laurel Hamers reports on efforts to design opioids and other new pain drugs that come with fewer downsides.

BARBARA DAVIDSON/GETTY IMAGES

problems, constant crying. The condition is known as neonatal abstinence syndrome, or NAS.

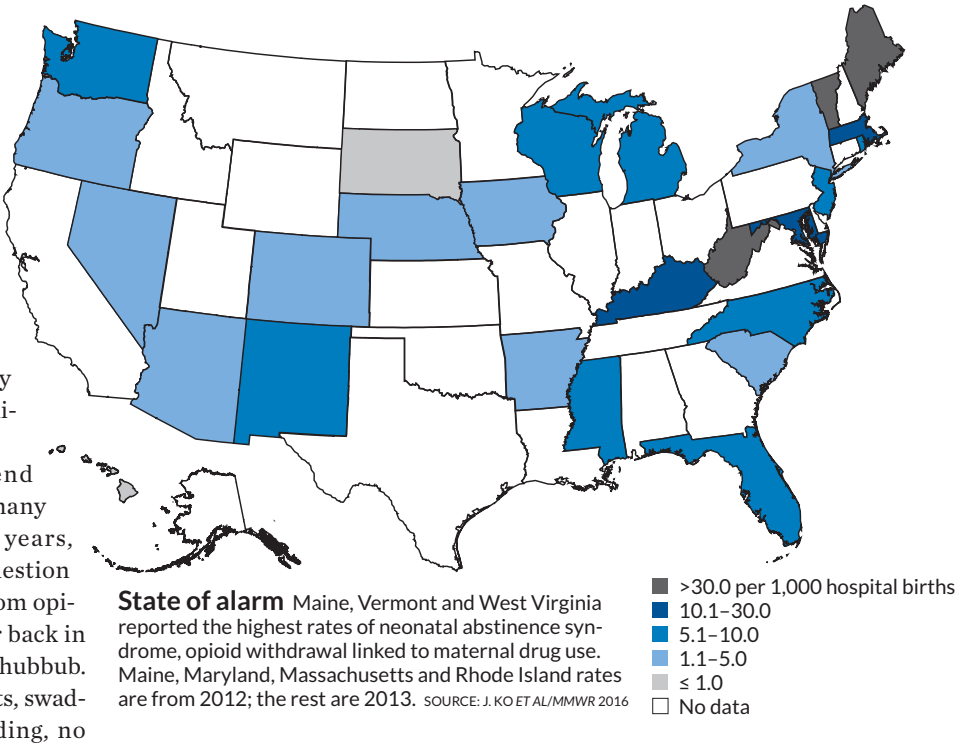
But there's no clear consensus on how to care for these struggling babies, Grossman says. Usually they're whisked off to the NICU and treated with opioids. The drugs ease symptoms, but they prolong exposure to "really powerful and potentially dangerous medications," he says.

At Yale, NAS babies used to spend weeks in the NICU — they still do in many U.S. hospitals. But in the last few years, Grossman and others have begun to question this method of care. Infants suffering from opioid withdrawal might actually do better back in parents' arms, away from the high-tech hubbub. Comfort is key. Quiet, dark environments, swaddling, breastfeeding, rocking and holding, no unnecessary tests — it's baby care 101.

That's hard to do in the busy, loud NICU, says Grossman. Plus, there's no place for parents to stay. They can visit, perched on folding chairs wedged between beds, says Yale pediatrician Rachel Osborn, but moms and dads "often feel like they're extraneous and in the way."

Faced with these and other obstacles, Grossman, Osborn and others are radically redefining their methods. They're examining traditional practices, testing new ideas and getting back to basics. The results have been dramatic.

"We're treating the families with respect and the babies like babies," Grossman says. The parents have everything the baby needs, he says. "It's not a whole lot more complicated than that."



State of alarm Maine, Vermont and West Virginia reported the highest rates of neonatal abstinence syndrome, opioid withdrawal linked to maternal drug use. Maine, Maryland, Massachusetts and Rhode Island rates are from 2012; the rest are 2013. SOURCE: J. KO *ET AL*/*MMWR* 2016

Tough going

Families today are much more likely to deal with opioid use — and its consequences for newborns — than they were a decade ago.

In 2004, NAS rates were consistently low across the country: For every 1,000 babies born, roughly one was diagnosed with NAS. By 2013, when pediatrician Nicole Villapiano and colleagues examined rural versus urban data, rates were up across the board. But rural areas had been hit the hardest, with nearly 8 per 1,000 babies diagnosed with NAS, the researchers reported in February in *JAMA Pediatrics*.

In an urban hospital near Rhode Island's Providence River, Villapiano witnessed infant opioid withdrawal firsthand. She was first assigned to the newborn nursery service at Women and Infants Hospital in Providence in 2011. "I imagined it'd be a joyful time, seeing babies going off with their families, having wonderful lives."

Reality quickly dashed that hopeful picture. On any given day, she might see several babies at a time struggling with withdrawal. "These children were miserable," says Villapiano, now at the University of Michigan in Ann Arbor. "Their cries were persistent and their irritability was profound."

NAS isn't easy to define. Babies suffer a wide range of symptoms. They're sweating, shaking, stiff. Stools are loose, eating and sleeping are difficult, and crankiness is common. Babies with NAS can also have breathing problems, seizures and low birth weights.

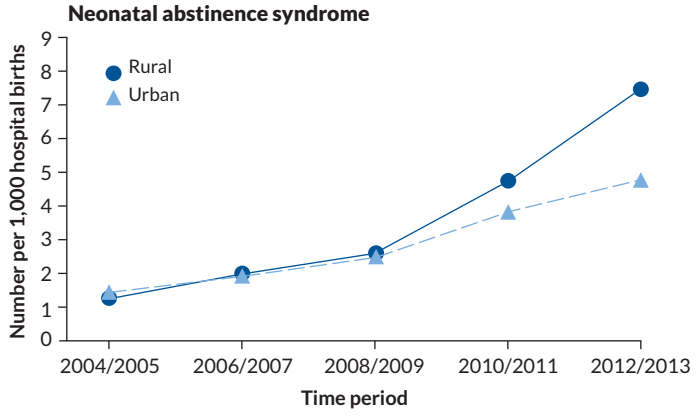
The syndrome was first described in heroin-exposed infants. Scientists now know that all sorts of opioids used during pregnancy can trigger the condition, including "maintenance" drugs like methadone or buprenorphine used to treat opioid addiction, and even painkillers commonly prescribed during pregnancy, such as codeine and hydrocodone.

Not all infants exposed to opioids in utero go through withdrawal — and exactly what conditions lead to NAS is still unclear. The particular opioid and how much a pregnant woman uses, whether she takes certain antidepressants and even the number of cigarettes she smokes per day all seem to factor in, Stephen Patrick of Vanderbilt University in Nashville and colleagues reported in *Pediatrics* in 2015. A nonsmoking woman on oxycodone for a few weeks, for example, might have roughly a 1 percent chance of delivering a

"These children were miserable. Their cries were persistent and their irritability was profound."
NICOLE VILLAPIANO

J. HIRSHFELD

Troubling rise In the United States, as maternal opioid use has risen, the rate of newborns who develop neonatal abstinence syndrome has also gone up. Rural areas (circles) have seen bigger increases than urban areas (triangles).



baby with NAS. For a pack-a-day smoker on antidepressants and buprenorphine for six months, the risk could be more than 30 percent.

Because opioids are such a broad family of addictive drugs, opioid-using moms don't fit neatly into one category, says Ju Lee Oei, a neonatologist at the University of New South Wales in Sydney. "We need to be aware that Mrs. Smith down the road who's getting a bit of codeine for her back pain could have a baby with NAS," Oei says.

Some women give birth to NAS babies while recovering from opioid addiction — even though they're doing everything doctors advise, says pediatrician Alison Holmes of Children's Hospital at Dartmouth-Hitchcock in Lebanon, N.H.

"Sometimes people think, 'Oh, these mothers are such horrible addicts,' " Holmes says. But a lot of the time, "they're staying on their methadone, they're staying on their buprenorphine, they're keeping symptoms under control — but their babies are still going to withdraw."

Babies withdrawing from opioids used to stay in the NICU at Yale New Haven Children's Hospital (shown), but now the infants stay in a quiet room with mom and dad.

No one knows exactly what opioid exposure does to fetal brains, or how these kids will fare in the future. Certain brain regions may not grow correctly, previous studies have suggested. Children can also have vision trouble and may develop behavior and attention problems. One long-term Australian study published in February linked a diagnosis of NAS with poor academic performance — all the way up to age 12 or 13.

Whether that's caused by NAS is hard to say, says Oei, a coauthor of the study. Poverty, poor childhood nutrition and prenatal exposure to alcohol or other drugs could also come into play. But the results are a red flag for all those newly diagnosed babies. "You expect your baby to go to school and get good grades," Oei says. But from as early as third grade, "these kids don't seem to be able to do that."

Still, research on NAS outcomes and potential treatments remains full of gaps, a 2015 report from the U.S. Government Accountability Office found. And there's no nationally accepted treatment protocol for NAS. "Everyone's doing it their own way," says Scott Wexelblatt, a pediatrician at Cincinnati Children's Hospital Medical Center.

Time for a change

The traditional way to assess NAS was published more than 40 years ago by neonatologist Loretta Finnegan, now at the College on Problems of Drug Dependence in Philadelphia. Every four to eight hours, sometimes more frequently, nurses evaluate symptoms using a detailed scoring list: the Finnegan Neonatal Abstinence Scoring System. Hit a certain score, and doctors will start up the withdrawal-easing opioids, typically morphine or methadone.

But there's a push and pull between managing withdrawal and dosing babies with more drugs, Wexelblatt says. "We don't want to expose babies to opioids unless we really need to."

Care of NAS babies varies widely in hospitals across the United States, according to a study in the May–June *Academic Pediatrics*. Some newborns may be getting too much opioids. To see if standardizing care could help infants get off the drugs faster, Wexelblatt and colleagues trained nurses on Finnegan scoring and outlined a detailed protocol for weaning.

That simple step made a big difference. Hospitals that adopted the protocol cut infant stays from an average of 31.6 days before the intervention to 23.7 days afterward, Wexelblatt's team reported in 2015 in *Pediatrics*. Duration of opioid

FROM TOP: N. VILLAPIANO *ET AL/JAMA PEDIATRICS* 2017; YALE NEW HAVEN CHILDREN'S HOSPITAL

treatment dropped as well. By 2016, hospital stays were down to 20 days, he says.

Now, 54 hospitals — almost all delivery hospitals in Ohio — use the weaning protocol, Wexelblatt says. The team has since refined its methods, focusing on family support and nonmedication options for care, like swaddling and breastfeeding. And as of 2013, every delivering mom in the Cincinnati region gets urine-tested for opioids upon admission so that care can start early, if needed. Ohio's strategy is paying off: Doctors are using fewer opioids to treat NAS babies and the infants are getting out of the hospital faster too, early results suggest.

31.6
days
Average time opioid-exposed babies spent in Ohio hospitals before 2013 treatment change

23.7
days
Average time spent in same hospitals in 2013–2014

20
days
Average time spent in same hospitals in 2016

SOURCES: E.S. HALL *ET AL/ PEDIATRICS* 2015; S.L. WEXELBLATT

Researchers at Yale and Dartmouth-Hitchcock have also taken a hard look at the hospitals' methods, starting with the Finnegan scoring system. Some aspects just didn't make sense, Holmes and colleagues reported last June in *Pediatrics*. Nurses sometimes woke sleeping babies or removed them from family members' arms for scoring, and they gave hungry babies points for crying.

"We said, 'This is crazy,'" Holmes remembers. It makes more sense to just score the babies after they eat and while they're being held. That way, she says, nurses might be able to sift the actual signs of withdrawal from the normal whines and wails of a hungry or tired baby.

Grossman and colleagues at Yale were skeptical too. Finnegan's system looks for warning signs like vomiting and fever, but also gives points for sneezing and yawning. The final score guides doctors' decision to dial meds up or down. "Is it truly best to give morphine to an infant who yawned 4 times instead of 3, as the [scoring system] guides us to do?" they asked in a *Hospital Pediatrics* commentary in February.

Grossman scoured the scientific literature, searching for clues to improve treatment. But research results bounced all over the place. "We ended up questioning everything," he says. "It turned out there wasn't really a good answer for anything we were doing."

Family first

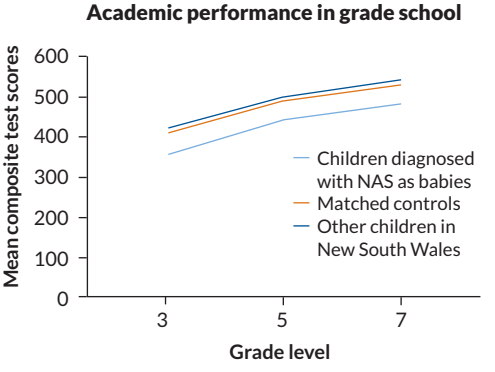
Around the same time Grossman was digging into research on opioid withdrawal in newborns, he had his first child, who screamed constantly. "I'm pacing in the middle of the night, thinking, if this was an NAS baby, he'd be on medication immediately."

Instead, Grossman paced and rocked and held his son — all of the tricks parents use to soothe a cranky newborn. As he found ways to settle the baby, he thought, what if NAS babies needed something similar?

The idea jibed with his experiences at the hospital. Sometimes withdrawing infants would do great for days — their moms were there, and Finnegan scores stayed low. But if moms had to leave, babies would backslide, and scores would rocket up again. "Do these kids need more mom or more meds?" Grossman and colleagues wondered. "We started to think, 'Well, maybe it's more mom.'"

At Dartmouth-Hitchcock, Holmes and her crew were coming up with their own ideas. The team stopped interpreting Finnegan scores so rigidly, for one. But their biggest change was keeping mothers and babies together, 24-7. It's called "rooming-in," and previous studies in Canada and other countries had suggested it might ease babies' transition from the womb to the world.

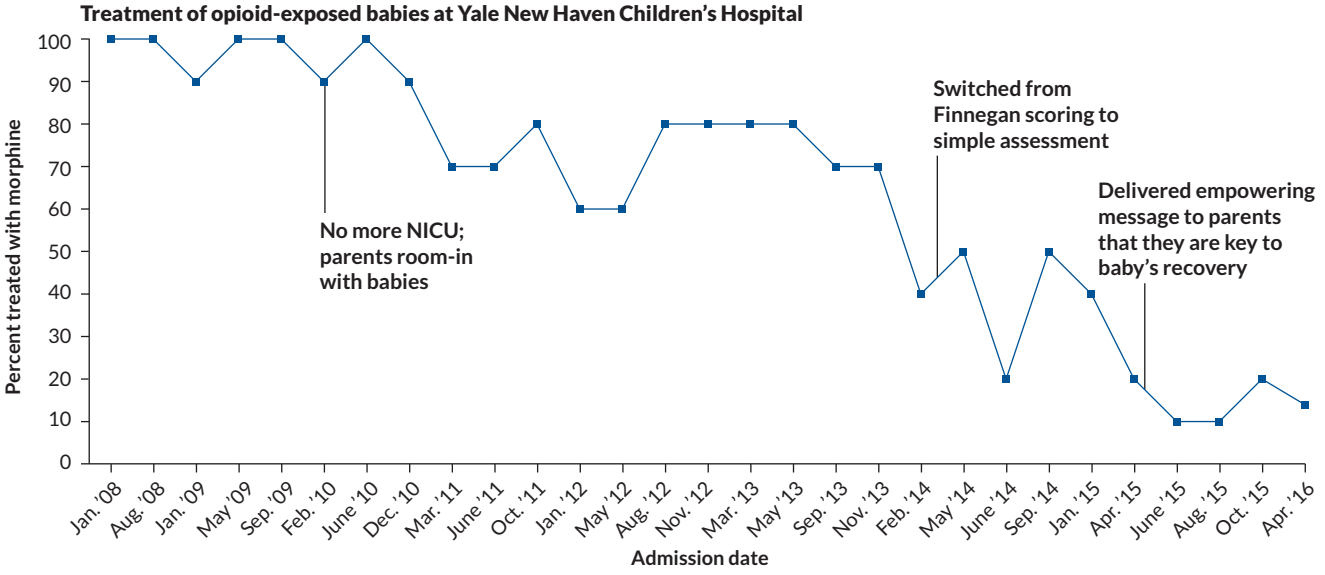
"What withdrawing babies need is a calm, quiet, dark place where they can be held by a caring individual," Holmes says. Her team focused on involving moms and families (and even volunteer cuddlers), and the hunch paid off. From 2012 to 2015, the average length of stay for morphine-treated NAS babies dropped from 16.9 days to 12.3 days. The fraction of babies given morphine plummeted too, from 46 percent to 27 percent. Now, two years later, that number has fallen even further — to just 20 percent, she says.



Falling behind Children from New South Wales, Australia, diagnosed with NAS, neonatal abstinence syndrome, as babies tended to score lower on academic performance tests than the general population of kids from New South Wales. They also scored lower than children in a control group matched for gestation age, year of birth, socioeconomic status and sex. SOURCE: J.L. OEI *ET AL/PEDIATRICS* 2017

J. HIRSHFELD

Taking the plunge From 2008 to 2016, the proportion of opioid-withdrawing infants treated with morphine at Yale New Haven Children's Hospital dropped from 98 percent to 14 percent, a drastic reduction in the number of babies given the medication. SOURCE: M. GROSSMAN *ET AL*/*PEDIATRICS* 2017



Holmes says her own kids joke about her work: "Babies like their mothers — surprise, surprise! What a discovery!" She laughs, and then adds, "They're kind of right."

Grossman's team at Yale has pushed the family-focused approach even further. "Our mind-set is rooming-in on steroids," he says. For NAS, parental care is considered more important — and more effective — than medication. Doctors ask parents: "How do we get you here or dad here or grandma here?" Grossman says. "Because that's what your baby needs."

Parental care is considered more important — and more effective — than medication.

His team rolled in other ideas too, like fortifying formula and pumped breast milk with extra calories. And hospital personnel stopped using Finnegan scores to guide medication dosing. Today, they base assessments on three simple parameters: whether an infant can eat, sleep and be consoled.

The patient rooms where parents can bunk with their babies are a world apart from the NICU. One room at Yale has a couch that converts into a bed and ceiling tiles with pictures of Elmo and Tweety Bird. Monitors are muted, nothing beeps incessantly and natural light pours in from the window. There's plenty of space for parents to walk around and tend to their baby. In these rooms, "it feels like the parent is a necessary part of the care team," Yale's Osborn says.

In 2016, babies with NAS stayed in the Yale hospital just 5.9 days — a cliff dive compared with the 2008–2010 average of 22.4 days, Grossman, Osborn and colleagues reported online May 18 in *Pediatrics*. Even more staggering is the fraction of these babies treated with morphine: just 14 percent in 2016, down from 98 percent in 2008–2010.

Yale's approach basically comes down to common sense, Grossman says: a quiet room, lots of holding, feeding when hungry and simply keeping babies with mom and dad. "It's not rocket science," he says. Medication became more of a plan B.

Still, other doctors looking to transform NAS treatment may run into barriers. Not all U.S. hospitals are set up like Dartmouth-Hitchcock or Yale New Haven, Wexelblatt says. There's not always room for mom to stay with her baby once she's released. And universal drug testing of moms won't work everywhere, he warns. In Tennessee, a law passed in 2014 allowed new mothers to be prosecuted for using illegal drugs while pregnant if the newborn was harmed. The law expired last July, but such legislation drives women away from medical care, Wexelblatt says.

It could be that the best care for babies begins with care and compassion for moms. Rather than blame mothers, Holmes says, "We need to do as much as we can to support them in being good parents." ■

Explore more

■ Matthew Grossman *et al*. "An initiative to improve the quality of care of infants with neonatal abstinence syndrome." *Pediatrics*. June 2017.

Meghan Rosen is a science writer based in Rockville, Md.

J. HIRSHFELD

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ScienceNews

Beyond Today's Opioids

Scientists search for better pain drugs

By Laurel Hamers

Last year, Joan Peay slipped on her garage steps and smashed her knee on the welcome mat. Peay, 77, is no stranger to pain. The Tennessee retiree has had 17 surgeries in the last 35 years — knee replacements, hip replacements, back surgery. She even survived a 2012 fungal meningitis outbreak that sickened her and hundreds of others, and killed 64. This knee injury, though, "hurt like the dickens."

When she asked her longtime doctor for something stronger than ibuprofen to manage the pain, he treated her like a criminal, Peay says. His response was frustrating: "He's known me for nine years, and I've never asked him for pain medicine other than what's needed after surgery," she says. She received nothing stronger than over-the-counter remedies. A year after the fall, she still lives in constant pain.

Just five years ago, Peay might have been handed a bottle of opioid painkillers for her knee. After all, opioids — including codeine, morphine and oxycodone — are some of the most powerful tools available to stop pain.

But an opioid addiction epidemic spreading across the United States has soured some doctors on the drugs. Many are justifiably concerned that patients will get hooked or share their pain pills with friends and family. And even short-term users risk dangerous side effects: The drugs slow breathing and can cause constipation, nausea and vomiting.

A newfound restraint in prescribing opioids is in many cases warranted, but it's putting people like Peay in a tough spot: Opioids have become harder to get. Even though the drugs are far from perfect, patients have few other options.

Many drugs that have been heralded as improvements over existing opioids are just old opioids repackaged in new ways, says Nora Volkow, director of the National Institute on Drug Abuse. Companies will formulate a pill that is harder to crush, for instance, or mix in another drug that prevents an opioid pill from working if it's crushed up and snorted for a quick high. Addicts, however, can still sidestep these safeguards. And the newly packaged drugs have the same fundamental risks as the old ones.

The need for new pain medicines is "urgent," says Volkow.

Scientists have been searching for effective alternatives for years without success. But a better understanding of the way the brain sends and receives specific chemical messages may finally boost progress.

Scientists are designing new, more targeted molecules that might kill pain as well as today's opioids do — with fewer side effects. Others are exploring the potential of tweaking existing opioid molecules to skip the negative effects. And some researchers are steering clear of opioids entirely, testing molecules in marijuana to ease chronic pain.

FEDERICO GASTALDI

Opioid action

Humans recognized the potential power of opioids long before they understood how to control it. Ancient Sumerians cultivated opium-containing poppy plants more than 5,000 years ago, calling their crop the "joy plant." Other civilizations followed suit, using the plant to treat aches and pains. But the addictive power of opium-derived morphine wasn't recognized until the 1800s, and scientists have only recently begun to piece together exactly how opioids get such a stronghold on the brain.

Opioids mimic the body's natural painkillers — molecules like endorphins. Both endorphins and opioids latch on to proteins called opioid receptors on the surface of nerve cells. When an opioid binds to a receptor in the peripheral nervous system, the nerve cells outside the brain, the receptor changes shape and sets in motion a cellular game of telephone that stops pain messages from reaching the brain.

> "No matter how much I say I want to avoid opioids, half of my patients will get some kind of opioid."
>
> CHRISTOPHER WU

The danger comes because opioid receptors scattered throughout the body and in crucial parts of the brain can cause far-reaching side effects when drugs latch on. For starters, many opioid receptors are located near the base of the brain — the part that controls breathing and heart rate. When a drug like morphine binds to one of these receptors in the brain stem, breathing and heart rate slow down. At low doses, the drug just makes people feel relaxed. At high doses, though, it can be deadly — most opioid overdose deaths occur when a person stops breathing. And high numbers of opioid receptors in the gut — thanks in part to all the nerve endings there — can trigger constipation and sometimes nausea.

Plus, opioids are highly addictive. These drugs mess with the brain's reward system, triggering release of dopamine at levels higher than what the brain is used to. Gradually, the opioid receptors in the brain become less sensitive to the drugs, so the body demands higher and higher doses to get the same feel-good benefit. Such tolerance can reset the system so the body's natural opioids no longer have the same effect either. If a person tries to go without the drugs, withdrawal symptoms like intense sweating and muscle cramps kick in — the body is physically dependent on the drugs. Addiction is a more complex phenomenon than dependence, involving physical cravings so strong that a person will go to extreme lengths to get the next dose. Long-term users of prescription opioids might be dependent on the drugs, but not necessarily addicted. But dependence and addiction often go together.

Despite their risks, opioids are still widely used because they work so well, particularly for moderate to severe short-term pain.

"No matter how much I say I want to avoid opioids, half of my patients will get some kind of opioid. It's just unavoidable," says Christopher Wu, an anesthesiologist at Johns Hopkins Medicine.

In the late 1990s and early 2000s, more doctors began doling out the drugs for long-term pain, too. Aggressive marketing campaigns from Purdue Pharma, the maker of OxyContin, promised that the drug was safe — and doctors listened. Opioid overdoses nearly quadrupled between 2000 and 2015, with almost half of those deaths coming from opioids prescribed by a doctor, according to data from the U.S. Centers for Disease Control and Prevention.

Opioid prescriptions have dipped a bit since 2012, thanks in part to stricter prescription laws and prescription registration databases. U.S. doctors wrote about 30 million fewer opioid prescriptions in 2015 than in 2012, data from IMS Health show. But restricting access doesn't make pain disappear or curb addiction. Some people have turned to more dangerous street alternatives like heroin. And those drugs are sometimes spiked with more potent opioids such as fentanyl (*SN: 9/3/16, p. 14*) or even carfentanil, a synthetic opioid that's used to tranquilize elephants. Overdose deaths from fentanyl and heroin have both spiked since 2012, CDC data reveal.

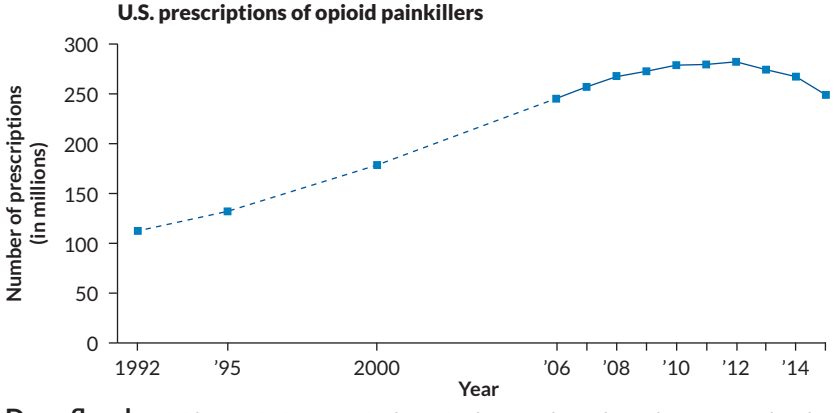
A sharper target

Scientists have been searching for a drug that kills pain as successfully as opioids without the side effects for close to a hundred years, with no luck, says Sam Ananthan, a medicinal chemist at Southern Research in Birmingham, Ala. He is newly optimistic.

"Right now, we have more biological tools, more information regarding the biochemical pathways," Ananthan says. "Even though prior efforts were not successful, we now have some rational hypotheses."

Scientists used to think opioid receptors were simple switches: If a molecule latched on, the receptor fired off a specific message. But more recent studies suggest that the same receptor can send multiple missives to different recipients.

The quest for better opioids got a much-needed jolt in 1999, when researchers at



Drug flood Opioid prescriptions rose in the United States throughout the 1990s and early 2000s. Physicians have begun to back off in the last few years. SOURCE: IMS HEALTH

L. LO

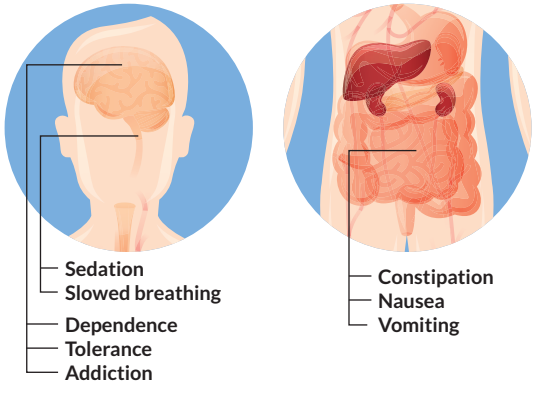
Duke University showed that mice lacking a protein called beta-arrestin 2 got more pain relief from morphine than normal mice did. And in a follow-up study, negative effects were less likely. "If we took out beta-arrestin 2, we saw improved pain relief, but less tolerance development," says Laura Bohn, now a pharmacologist at the Scripps Research Institute in Jupiter, Fla. Bohn and colleagues figured out that mu opioid receptors — the type of opioid receptor targeted by most drugs — send two different streams of messages. One stops pain. The other, which needs beta-arrestin 2, drives many of the negatives of opioids, including the need for more and more drug and the dangerous slowdown of breathing.

Since that work, Bohn's lab and many others have been trying to create molecules that bind to mu opioid receptors without triggering beta-arrestin 2 activity. The approach, called biased agonism, "has been around some time, but now it's bearing the fruit," says Susruta Majumdar, a chemist at Memorial Sloan Kettering Cancer Center in New York City. Scientists have identified dozens of molecules that seem to avoid beta-arrestin 2 in mice. But only a few might make good drugs. One, called PZM21, was described in *Nature* last year.

Another one has shown promise in humans — a much higher bar. The pharmaceutical company Trevena, headquartered in King of Prussia, Pa., has been working its way through the U.S. Food and Drug Administration's drug approval process with a molecule called oliceridine. In studies reported in April in San Francisco at the Annual Regional Anesthesiology and Acute Pain Medicine Meeting, oliceridine was as effective as morphine in patients recovering from bunion removal and others who had tummy tuck surgeries. Over the short term, people taking a moderate dose of the drug got pain relief comparable to that of morphine, but reported fewer side effects, such as vomiting and breathing problems.

Unintended effects

Hitting opioid receptors in the peripheral nervous system keeps pain messages from reaching the brain. But opioids can cause problems by overstimulating the brain's reward system and binding to receptors in the brain stem and gut.



Oliceridine is an intravenous opioid, not an oral one. That means it would be administered in the short term in hospitals, during and after surgeries. It's not a replacement for the pills people can go home with, says Jonathan Violin, Trevena's cofounder. And it's not perfect: More side effects cropped up at higher doses. But it's the first opioid using this targeted approach to get this far in human studies. The company hopes to submit an application for FDA approval by the end of 2017, Violin says.

Avoiding the beta-arrestin 2 pathway isn't the only approach to targeted opioids — just one of the best studied. Ananthan's lab is taking a different tack. His team showed that mice lacking a different opioid receptor, the delta receptor, tended not to show negative effects in response to the drugs. Now, the researchers are trying to find molecules that can activate mu opioid receptors while blocking delta receptors.

There may also be a way to direct pain-killing messages specifically to the parts of a person's body that are feeling pain. In one recent study, scientists described a molecule that bound to opioid receptors only when the area around the receptors was more acidic than normal. Inflammation from pain and injury raises acidity, so this molecule could quash pain where necessary, but wouldn't bind to receptors elsewhere in the body, reducing the likelihood of side effects. Rats in the study, published in the March 3 *Science*, didn't find the new molecule as rewarding as fentanyl, so it may be less addictive. And they were less likely to have constipation and slowed breathing.

Drugs face a long uphill climb from even the most promising animal studies to FDA approval for use in humans. Very few make it that far. It's too soon to tell whether PZM21 and other molecules being studied in mice will ever end up as treatments for patients.

Unwilling to wait, some people in pain are turning to substances that are already available — without a doctor's order. And scientists are trying to catch up.

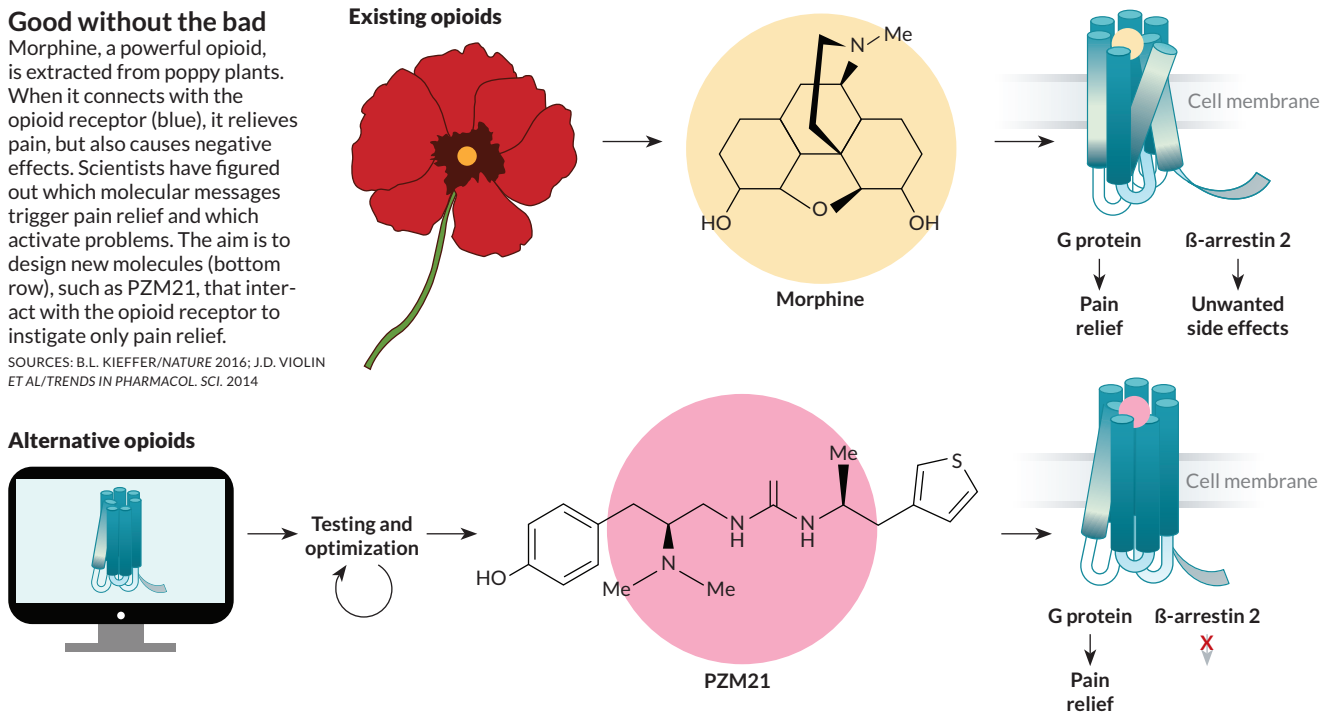
Kratom crackdown

In August 2016, the Drug Enforcement Administration announced that it was cracking down on a supplement called kratom. Officials wanted to put the herb in the same regulatory category as heroin and LSD, labeling it a dangerous substance with no medical value. Members of the public vehemently disagreed. More than 23,000 comments poured in from veterans, cancer survivors, factory workers, lawyers and teachers. Almost all of them said the same thing: Kratom freed them from pain.

Made from the leaves of the tropical plant *Mitragyna speciosa*, kratom is sold in corner convenience stores and through online retailers. Its pain-killing abilities come mainly from two different molecules in the plant's leaves: mitragynine and the structurally similar 7-hydroxymitragynine. Both have a structure that's very different from morphine, but they bind to opioid receptors. That technically makes them opioids, even though they don't look like morphine or oxycodone, Majumdar says. And that's what concerned the DEA.

But just like some of the new opioids that scientists are

FILO/ISTOCKPHOTO, ADAPTED BY L. LO



developing, kratom's active ingredients appear — anecdotally, at least — to deliver pain relief with fewer problems and less risk of tolerance. Some chronic opioid users switch to kratom to wean themselves off of pain pills and ease withdrawal symptoms, says Oliver Grundmann, a medicinal chemist at the University of Florida in Gainesville. Other users have never habitually used opioids but are seeking relief from chronic pain or mental health problems, according to a survey he published online May 10 in *Drug and Alcohol Dependence*. Grundmann hopes the survey results will help guide research into the substance's efficacy for specific medical concerns.

The safety and efficacy of kratom is still up for debate. There's a lack of controlled clinical studies about the leaf's impact on the body, Grundmann says. Plus, the way kratom is regulated — as a supplement — means that people buying it have no guarantee of what they're actually getting.

While kratom has its fans, its active compounds aren't very potent, says Majumdar. He thinks he could make a better drug by modifying these molecules.

Majumdar, Sloan Kettering collaborator András Váradi and colleagues tested a structural cousin of 7-hydroxymitragynine: mitragynine pseudoindoxyl. It binds to mu opioid receptors about 200 times as effectively as mitragynine in mice, the researchers reported in August in the *Journal of Medicinal Chemistry*. Just like Trevena's oliceridine, the new molecule does not activate beta-arrestin 2. The pseudoindoxyl version also blocks the delta opioid receptor, further impeding nonpain-related activities.

Majumdar hopes a DEA ban on kratom won't happen; it would severely restrict access, making research much harder to do. For now, there is no ban — but scientists are wary, he says.

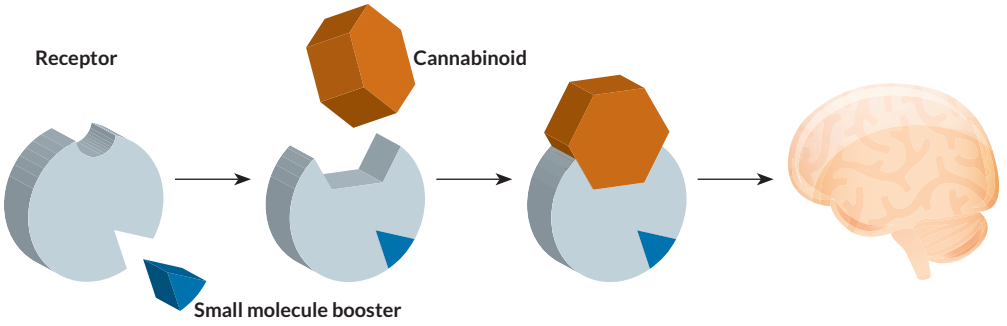
Mix it up

Despite the potential for new, better opioids, other researchers are focused on an altogether different set of pain-killing drugs: the cannabinoids (made famous by marijuana, the dried leaves and other parts of the hemp plant, *Cannabis sativa*).

The active molecules in marijuana don't have the same fast-acting pain-quenching abilities that opioids do. "If I go into

Mitragyna speciosa, a plant from Southeast Asia, contains mild opioids. It is sold as a supplement, called kratom, for pain relief. Scientists are trying to tweak the plant's molecules to make stronger painkillers with fewer side effects than existing drugs.

CLOCKWISE FROM TOP: L. LO; ZUMA PRESS, INC./ALAMY; NINONINOS/SHUTTERSTOCK



Pump up the volume Small molecules that latch on to the body's cannabinoid receptors can make other docking sites on the receptor change shape to fit the body's natural cannabinoids. The better fit may amp up the body's ability to send pain-dulling messages to the brain. SOURCE: R.A. ROSS/*TRENDS IN PHARMACOL. SCI.* 2007

an emergency room with acute pain, give me morphine," says Yasmin Hurd, a pharmacologist at Mount Sinai in New York City. But with medical marijuana legal in 29 states plus the District of Columbia, the plant is getting more attention as a potential pain reliever, especially for chronic pain (*SN: 6/14/14, p. 16*).

Doctors in states where marijuana is legal write fewer prescriptions for opioid painkillers, a 2016 study in *Health Affairs* showed. Those states also had about a 25 percent lower rate of opioid overdose deaths compared with states that didn't legalize marijuana, according to a 2014 study in *JAMA Internal Medicine*. When marijuana becomes legally available, some people might choose it instead of opioids.

There might be some merit to that choice. There are plenty of cannabinoid receptors in parts of the brain that process pain messages. But unlike opioid receptors, few exist in the brain stem. That means cannabinoids are far less likely to influence breathing than opioids, says Joseph Cheer, a neurobiologist at the University of Maryland School of Medicine in Baltimore. Fatal overdoses are nearly unheard of.

As with kratom, though, there's a glut of anecdotal evidence suggesting marijuana's power to cure everything from pain to anxiety to ulcers — but not many controlled clinical trials to back up the assertions (*SN Online: 1/12/17*). The knowledge gap is made even wider by the fact that marijuana has wildly different effects depending on how it's ingested and the relative ratios of certain active molecules in each strain of the plant.

"People think they know how marijuana affects the brain," Hurd says. In reality, "there's been very little evidence-based structural scientific studies done with marijuana."

Aron Lichtman, a pharmacologist at Virginia Commonwealth University in Richmond, agrees. "There's definitely medicine in that plant — that's been proven," he says. "The challenge is that it may not work for everybody and every type of pain."

Scientists who are serious about figuring out marijuana are breaking it down, looking at the plant's active molecules — cannabinoids — one by one. Cannabidiol, or CBD, has garnered particular attention. Because of the way it indirectly interacts with cannabinoid receptors, it doesn't give people the high that's characteristic of tetrahydrocannabinol, or THC, the mind-altering chemical in marijuana. That makes CBD less rewarding and better suited to longer-term use. The molecule can influence signals sent by a number of other receptors in the brain, many involved in pain and inflammation.

But THC might have merit, too. It's already used in a couple of FDA-approved drugs to treat nausea and vomiting from chemotherapy. There's some evidence that those medications might also help relieve pain, though Lichtman calls those studies a "mixed bag."

Alone, cannabinoids might be fairly weak painkillers. But combined with opioids, he's shown, they can amplify the pain relief and reduce the opioid dose needed in mice.

Drugs that might amp up the power of the body's natural cannabinoids are another option. That's what Ruth Ross of the University of Toronto is studying. A few years ago, her team identified a region on a cannabinoid receptor called CB1 that has an interesting property: Small molecules that bind to it act like volume knobs for the body's natural cannabinoids, called endocannabinoids. When a molecule of the right shape locks on to CB1, it makes endocannabinoids naturally present in the body more likely to latch on. That boosts pain relief in a targeted way — when endocannabinoids are already being released by the body, such as after injury or stress.

"You magnify the already existing effects of the compound," Ross says. Her team has identified and patented several of these volume-knob molecules, and is working on improving them.

"For various reasons they wouldn't be good as drugs," she says. They have too many effects on the body beyond their intended one. But she's making slight tweaks to their chemical structures to try to reduce those off-target effects, with the hope that one day the molecules could be studied in patients.

Safer opioids or alternative painkillers would help people deal with their pain without risking addiction or death. Peay has gotten to know people — as a member of social media groups for those living with chronic pain — who are experiencing the crushing results of poorly managed pain. People lose their jobs, she says, or move to Colorado just to get access to legal marijuana. As for her? "I still have my sense of humor, and that helps me get through all the pain." But she's holding out for something better. ■

Explore more

- Nora Volkow and A. Thomas McLellan. "Opioid abuse in chronic pain — misconceptions and mitigation strategies." *New England Journal of Medicine*. March 31, 2016.
- CDC guideline for prescribing opioids for chronic pain: www.cdc.gov/drugoverdose/prescribing/guideline.html

L. LO, BRAIN: FILO/ISTOCKPHOTO

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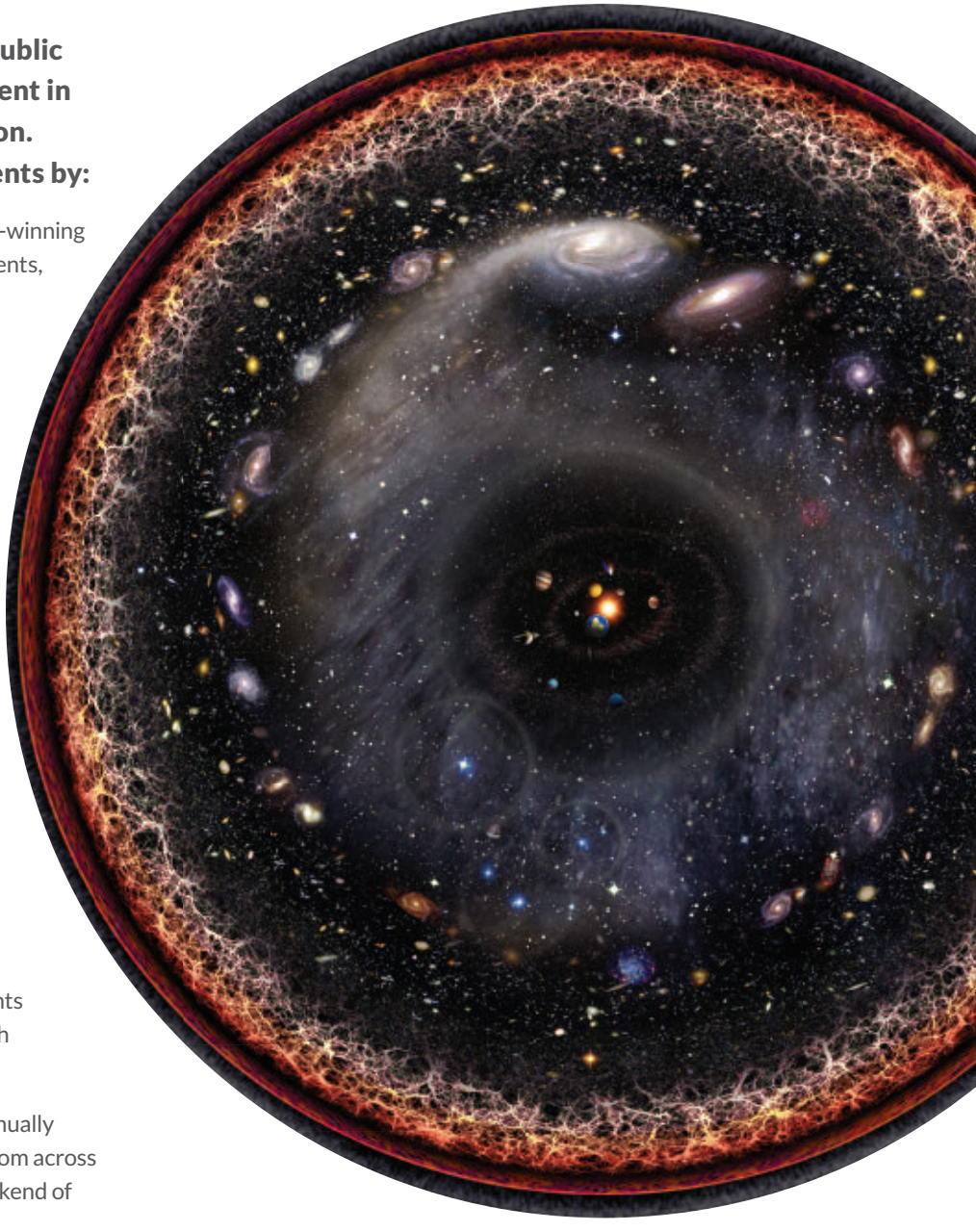

UNIVERSAL MAP This diagram, made up of stitched together NASA imagery, is essentially a map of the observable universe. The solar system is at center. The scale changes as you move outward so that the distances depicted toward the edge of the circle are enormous. UNMISMOOBJETIVO/WIKIMEDIA COMMONS (CC BY-SA 3.0)

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SCREENTIME

Citizen scientists join the hunt for Planet 9

Astronomers want you in on the search for the solar system's ninth planet.

In the online citizen science project Backyard Worlds: Planet 9, space lovers can flip through space images and search for this potential planet as well as other far-off worlds awaiting discovery.

The images, taken by NASA's Wide-field Infrared Survey Explorer satellite, offer a peak at a vast region of uncharted territory at the far fringes of the solar system and beyond. One area of interest is a ring of icy rocks past Neptune, known as the Kuiper belt. Possible alignments among the orbits of six objects out there hint that a ninth planet exerting its gravitational influence lurks in the darkness (*SN: 7/23/16, p. 9*). The WISE satellite may have imaged this distant world, and astronomers just haven't identified it yet. Dwarf planets, free-floating worlds with no solar system to call home (*SN: 4/4/15, p. 22*) and failed stars may also be hidden in the images.

The WISE satellite has snapped the entire sky several times, resulting in millions of images. With so many snapshots to sift through, researchers need extra eyes. At the Backyard Worlds website, success in spotting a new world requires sharp sight. You have to stare at what seems like thousands of fuzzy dots in a series of four false-color infrared images taken months to years apart and identify faint blobs that appear to move. Spot that movement and you may have found a new world.

By scrutinizing images taken by NASA's WISE satellite (illustrated), volunteers can help a group of astronomers find undiscovered space objects.

But you can't let blurry spots or objects moving in only a couple of the frames fool you: Image artifacts can look like convincing space objects. True detections come from slight shifts in the positions of red or whitish-blue dots. With so many dots to track, it's best to break up an image into sections and then click through the four images section by section. This process can take hours. But think of the payoff — discovering a distant world no one has observed before.

Once you've marked any potential object of interest, the project's astronomers take over. Jackie Faherty of the American Museum of Natural History in New York City and colleagues cross-reference the object's coordinates with databases of celestial worlds. If the object does, in fact, appear to be a newbie, the team requests time on other telescopes to do follow-up. Those studies can reveal whether the object is a failed star or a planet.

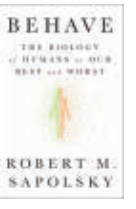
So far, tens of thousands of citizen scientists have scoured images at Backyard Worlds. The team has identified five possible failed stars and had its first paper accepted for publication.

But there's still much more to explore: The elusive Planet Nine might still be out there, disguised as a flash of dots.

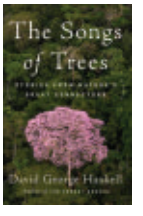
— Ashley Yeager

BOOKSHELF

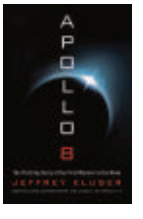
Finding Fibonacci
Keith Devlin
A mathematician and writer recounts his journey to uncover the life story of Italian genius Leonardo of Pisa, aka Fibonacci. Best known for the number sequence named after him, Fibonacci introduced modern arithmetic to the West during the Middle Ages. *Princeton Univ., $29.95*



Behave
Robert M. Sapolsky
Weaving biological research with cultural, environmental and other influences, a neurobiologist sets out to explain humankind's best and worst behavioral traits, from morality and free will to xenophobia. *Penguin Press, $35*



The Songs of Trees
David George Haskell
An olive tree in Jerusalem and a bonsai that survived the Hiroshima bombing are just a couple of the trees profiled in this book, which examines how the plants connect people to the natural world. *Viking, $28*



Apollo 8
Jeffrey Kluger
In retelling the story of NASA's first manned mission to the moon, the author also recounts the lives of the people who made it happen. *Henry Holt, $30*

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– AMY KOCHENSPARGER, EATON HIGH SCHOOL IN EATON, OHIO

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APRIL 29, 2017

When octopuses fly

Eating live octopus can be dangerous, but some dolphins in Australian waters have figured out how to do it safely, **Sarah Zielinski** reported in "How a dolphin eats an octopus without dying" for the *Wild Things* blog (*SN Online: 4/25/17*). Dolphins shook and tossed their prey over and over until the octopus went limp and its sucker-covered arms relaxed. Watch a video of the feeding frenzy at bit.ly/SN_OctopusToss

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Proton puzzler

*Uncertainty over the proton's size, spin and life span could have physicists rethinking standard notions about matter and the universe, **Emily Conover** reported in "The proton puzzle"* (SN: 4/29/17, p. 22).

Readers wondered about the diameter (or size) of the proton, which has three fundamental particles called quarks rattling around inside. "Still scratching my head over how combining three dimensionless quarks ends up forming a proton with a 'diameter,'" online reader **Down_Home** wrote. "Maybe that word doesn't mean what I think it means."

The three quarks within the proton are only apparent when the proton is probed with high-energy particles, **Conover** says. At lower energies, particles "see" the entire proton as one entity. "In that case, the proton just behaves like a sphere of positive charge," she says. Scientists measure the size of this sphere by looking at how electrons are deflected when they come close to the proton. "Researchers disagree on the sphere's diameter, which makes for a bit of an identity crisis for the proton," **Conover** says.

Blooming Arctic

*Nearly 30 percent of ice covering the Arctic Ocean at summer's peak is thin enough to foster sprawling phytoplankton blooms in the waters below, a recent study estimated. These ice-covered blooms were probably uncommon just 20 years ago, **Thomas Sumner** reported in "Thinning ice creates undersea greenhouses in the Arctic"* (SN: 4/29/17, p. 20).

Several online readers wanted to know how the under-ice blooms get the carbon dioxide they need to photosynthesize.

Others wondered about the blooms' potential effect on climate. "I'm not sure if this is good or bad news," reader **Witch Daemon** wrote. More phytoplankton could mean that the Arctic could store more carbon, but the blooms wouldn't exist if it weren't for warming and melting ice, **Witch Daemon** reasoned.

When phytoplankton are trapped under ice, they absorb CO_2 that's dissolved in the upper ocean, says oceanographer and study coauthor **Christopher Horvat** of Harvard University.

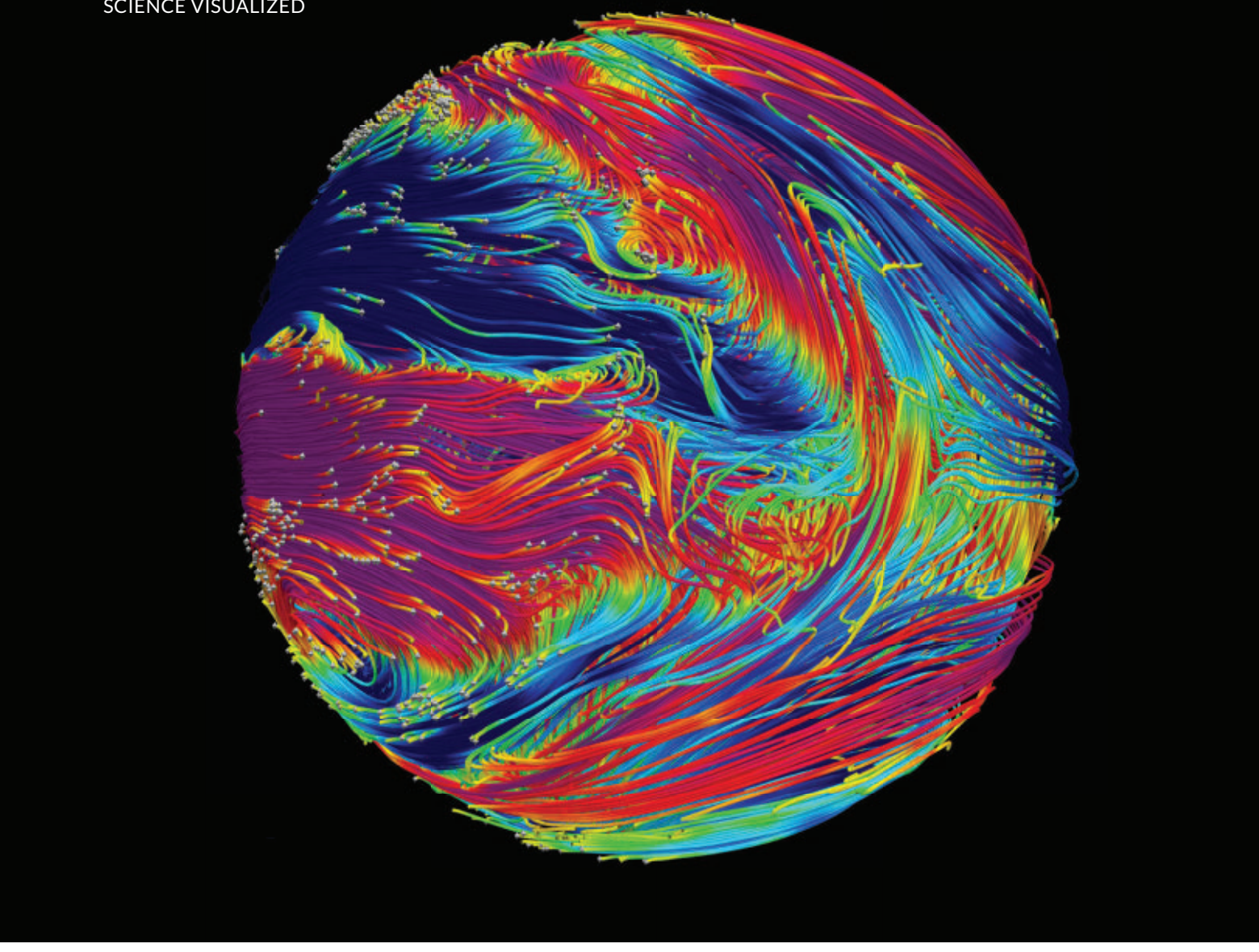
What the blooms might mean for storing carbon in the ocean is uncertain, **Horvat** says. But if these under-ice blooms occur in addition to the familiar blooms along the edges of the ice, then there's a chance that more carbon could be stored away.

Shields up

*Most of the gases in Mars' atmosphere may have been stripped away by solar wind, **Ashley Yeager** reported in "Extreme gas loss dried out Mars"* (SN: 4/29/17, p. 20). *The loss of so much gas may explain how the planet morphed from a wet, warm world to a dry, icy one.*

Online reader **Robert Knox** wondered how long it took for the solar wind to strip Mars of its atmospheric gases. "Earth is closer to the sun, so the solar wind is more intense," **Knox** wrote. "Why did this not happen to Earth?"

Luckily for us, Earth is protected by a magnetic field, **Yeager** says. This field deflects the solar wind and prevents it from picking away at the planet's atmospheric particles. Mars lost most of its global magnetic field about 4.2 billion years ago, which allowed the solar wind to sweep away much of the planet's atmosphere over a few hundred million years, she says.



Exoplanet's magnetism stirs up wild winds

HAT-P 7b is a windy world. Stiff easterlies typically whip through the atmosphere of the distant exoplanet, but sometimes the powerful gales blow in surprisingly varied directions. Now, simulations of the planet's magnetic field lines, illustrated here as a rainbow of scrawled marks, reveal that HAT-P 7b's magnetic field influences the winds, even turning some into westerlies. The result, published May 15 in *Nature Astronomy*, could lead to a better understanding of the atmospheres of other exoplanets.

Known as a "hot Jupiter," HAT-P 7b is a gas giant that orbits its star once every 2.2 Earth days. The exoplanet, located 1,043 light-years away, is also tidally locked: One side always faces toward its star while the other faces away. That orientation pushes temperatures to about 1,900° Celsius on the planet's dayside compared with about 900° C on the nightside. Those extreme temperature differences tend to power strong easterly winds, according to an analysis of data from the Kepler satellite. But that analysis also revealed that over time the winds are surprisingly mercurial.

The magnetic field, which may be generated by the planet's core, is connected to the winds because of high temperatures stripping electrons from atmospheric atoms of lithium, sodium and potassium, making them positively charged. Those particles then interact with the field, creating an electromagnetic force strong enough to disrupt the stout easterly winds, writes study author Tamara Rogers, an astrophysicist at Newcastle University in England.

In the image above, blue lines track strong magnetic field lines directed one way, while those in magenta trace powerful lines in the opposite direction. Weaker parts of the field lines are shown in green and yellow. The stronger the magnetic field, the wilder the winds — with the strongest lines completely reversing the direction the winds blow, Rogers concludes. — *Ashley Yeager*

T.M. ROGERS/*NATURE ASTRONOMY* 2017

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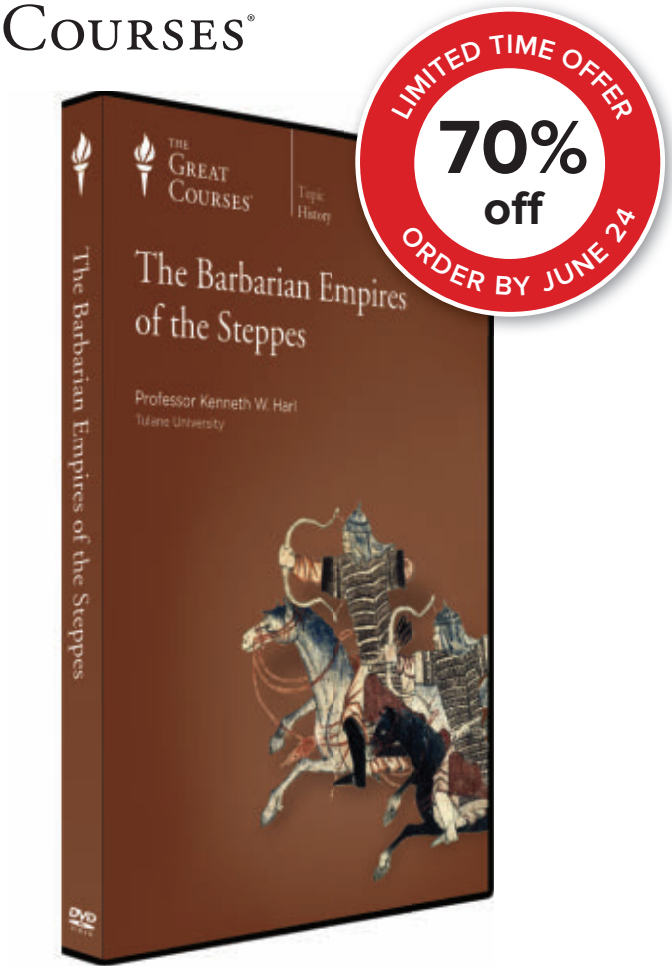

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