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Humans Can Learn to 'Echolocate' in Just 10 Weeks, Experiment Shows

With enough training, most humans can learn how to echolocate, using their tongue to make clicking sounds and interpreting the echoes that come back, reflected from the surrounding environment.

Carly Cassella

In as few as 10 weeks, researchers have been able to teach participants how to navigate obstacles and recognize the size and orientation of objects using the rebounding calls of their clicks.

The experiment, the results of which were published in 2021, involved 12 participants who'd been diagnosed as legally blind during their childhood, and 14 sighted people.

Echolocation is a skill we usually associate with animals such as bats and whales, but some blind humans also use the echoes of their own sounds to detect obstacles and their outlines. Some use the tapping of a cane or the snapping of their fingers to make the necessary noise, while others use their mouths to make a clicking sound.

Despite how useful this skill can be, very few blind people are currently taught how to do it. Expert echolocators have been trying to spread the word for years, and this study suggests a simple training schedule is all that's needed. "I cannot think of any other work with blind participants that has had such enthusiastic feedback," said psychologist Lore Thaler from Durham University in the UK in June last year when the results were published.

Over the course of 20 training sessions, which were about 2 to 3 hours long, researchers found that blind and sighted participants, both old and young, all improved considerably at click-based echolocation.

For weeks, participants were trained to navigate virtual mazes – corridors arranged in T-intersections, U bends, and zig-zags – and identify the size and orientation of objects using mouth clicks.

In the final two sessions, participants had their new navigation skills tested in a virtual maze they'd never tackled before. Even while blinded in this unknown environment, collisions were fewer than they had been at the start of the program.

Clearly, the echoes of their own clicks were helping people navigate the course with greater ease than before.

In fact, the authors found these newly trained echolocators performed nearly as well in the maze as seven expert echolocators who had been using this skill for years. In additional tests to determine the shape and orientation of certain surfaces, participants in the study actually performed equally to the experts.

Previous studies have also found sighted individuals can learn click-based echolocation in a series of training sessions, but this was the first study to test whether the results extend to blind people and people of various ages as well.

The visual parts of the brain are what allow echolocators to 'see' the world around them, and it's been unclear if those who grow up without vision can use the same neural networks to the same degree. What's more, many people lose their vision and hearing as they age, and the older a person is, the less plastic their brain.

This can make learning new skills more difficult as you get older, but the research suggests that's not a limiting factor in learning echolocation. In the study, blind individuals as old as 79 were able to pick up the skill with the right training.

When the authors analyzed their results (of their admittedly small experiment), they found older age in itself was not linked to more collisions in the maze task.

"Importantly, when we quantified the degree to which participants improved from session 1 to session 20 in their abilities across each of the tasks, there was no evidence for an association between age

and performance in the practical tasks," the authors wrote.

Younger age did allow some participants to finish the mazes faster, but practically, the authors said, "training led to remarkable behavioral changes for all participants", regardless of age.

Three months after the training sessions ended, blind participants said they had experienced improved mobility using echolocation. In a follow-up survey, 10 out of the 12 participants said the skill had benefited their independence and wellbeing.

"We are very excited about this," said Thaler," and feel that it would make sense to provide information and training in click-based echolocation to people who may still have good functional vision, but who are expected to lose vision later in life because of progressive degenerative eye conditions."

The study was published in *PLOS One*.

https://bit.ly/3OnmNmy

Scientists Have Created a Method To Prevent Deadly Infections Without Antibiotics

UCLA researchers have created a new surface treatment that prevents bacteria from sticking to medical devices such as catheters and stents.

A hospital or medical clinic may seem like the last place you'd expect to get a bad infection, yet almost 1.7 million Americans do each year, resulting in nearly 100,000 deaths from infection-related complications and $30 billion in direct medical expenditures.

According to specialists, medical equipment such as catheters, stents, heart valves, and pacemakers are the primary culprits, accounting for two-thirds of all infections. Their surfaces often become coated with dangerous bacterial films. However, a unique surface treatment developed by a team led by the University of California, Los Angeles (UCLA) scientists could help improve the safety of these devices while also reducing the financial strain on the healthcare system.

The new technique, which has been tested in both laboratory and clinical settings, involves depositing a thin coating of zwitterionic* material on the surface of a device and permanently bonding that layer to the underlying substrate using ultraviolet light irradiation. The resultant barrier prevents germs and other potentially dangerous organic materials from adhering to the surface and infecting people.

The team's results were published in the journal *Advanced Materials* on May 19th, 2022.

In the laboratory, researchers applied the surface treatment to several commonly used medical device materials, then tested the modified materials' resistance to various types of bacteria, fungi, and proteins. They found that the treatment reduced biofilm growth by more than 80% — and in some cases up 93%, depending on the microbial strain.

"The modified surfaces exhibited robust resistance against microorganisms and proteins, which is precisely what we sought to achieve," said Richard Kaner, UCLA's Dr. Myung Ki Hong Professor of Materials Innovation and senior author of the research. "The surfaces greatly reduced or even prevented biofilm formation.

"And our early clinical results have been outstanding," Kaner added.

The clinical research involved 16 long-term urinary catheter users who switched to silicone catheters with the new zwitterionic surface treatment. This modified catheter is the first product made by a company Kaner founded out of his lab, called SILQ Technologies Corp., and has been cleared for use in patients by the Food and Drug Administration.

Ten of the patients described their urinary tract condition using the surface-treated catheter as "much better" or "very much better," and 13 chose to continue using the new catheter over conventional latex and silicone options after the study period ended.

"One patient came to UCLA a few weeks ago to thank us for

changing her life — something that, as a materials scientist, I never thought was possible," Kaner said. "Her previous catheters would become blocked after four days or so. She was in pain and needed repeated medical procedures to replace them. With our surface treatment, she now comes in every three weeks, and her catheters work perfectly without encrustation or occlusion — a common occurrence with her previous ones."

Such catheter-related urinary tract problems are illustrative of the issues plaguing other medical devices, which, once inserted or implanted, can become breeding grounds for bacteria and harmful biofilm growth, said Kaner, a member of the California NanoSystems Institute at UCLA who is also a distinguished professor of chemistry and biochemistry, and of materials science and engineering. The pathogenic cells pumped out by these highly resilient biofilms then cause recurring infections in the body.

In response, medical staff routinely give strong antibiotics to patients using these devices, a short-term fix that poses a longer-term risk of creating life-threatening, antibiotic-resistant "superbug" infections. The more widely and frequently antibiotics are prescribed, Kaner said, the more likely bacteria are to develop resistance to them. A landmark 2014 report by the World Health Organization recognized this antibiotic overuse as an imminent public health threat, with officials calling for an aggressive response to prevent "a post-antibiotic era in which common infections and minor injuries which have been treatable for decades can once again kill."

"The beauty of this technology," Kaner said, "is that it can prevent or minimize the growth of biofilm without the use of antibiotics. It protects patients using medical devices — and therefore protects all of us — against microbial resistance and the proliferation of superbugs."

The surface treatment's zwitterion polymers are known to be extremely biocompatible, and they absorb water very tightly, forming a thin hydration barrier that prevents bacteria, fungi, and other organic materials from adhering to surfaces, Kaner said. And, he noted, the technology is highly effective, non-toxic, and relatively low in cost compared with other current surface treatments for medical devices, like antibiotic- or silver-infused coatings.

Beyond its use in medical devices, the surface treatment technique could have non-medical applications, Kaner said, potentially extending the lifetimes of water-treatment devices and improving lithium-ion battery performance.

Funding sources for the study included the National Institutes of Health, the National Science Foundation, the Canadian Institutes of Health Research, SILQ Technologies Corp, and the UCLA Sustainability Grand Challenge.

Reference: "A Readily Scalable, Clinically Demonstrated, Antibiofouling Zwitterionic Surface Treatment for Implantable Medical Devices" by Brian McVerry, Alexandra Polasko, Ethan Rao, Reihaneh Haghniaz, Dayong Chen, Na He, Pia Ramos, Joel Hayashi, Paige Curson, Chueh-Yu Wu, Praveen Bandaru, Mackenzie Anderson, Brandon Bui, Aref Sayegh, Shaily Mahendra, Dino Di Carlo, Evgeniy Kreydin, Ali Khademhosseini, Amir Sheikhi and Richard B. Kaner, 22 March 2022, Advanced Materials.

DOI: 10.1002/adma.202200254

*A zwitterion is **an ion that contains two functional groups**. In simple terms, it is as ion possessing both positive and negative electrical charges. Therefore, zwitterions are mostly electrically neutral (the net formal charge is usually zero). Zwitterions are sometimes referred to as "inner salts".

https://bit.ly/3yhOS97

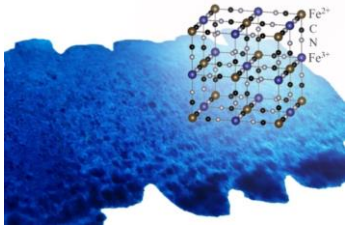
Picasso's favorite pigment may one day recycle metals from your cell phone

Prussian blue binds with gold- and platinum-group metals thanks to jungle-gym structure.

Jennifer Ouellette

Gold and certain other precious metals are key ingredients in computer chips, including those used in consumer electronics such as smart phones. But it can be difficult to recover and recycle those metals from electronic waste. Japanese researchers have found that

a pigment widely used by artists, called Prussian blue, can extract gold- and platinum-group metals from e-waste much more efficiently than conventional bio-based absorbents, according to a recent paper published in the journal Scientific Reports.



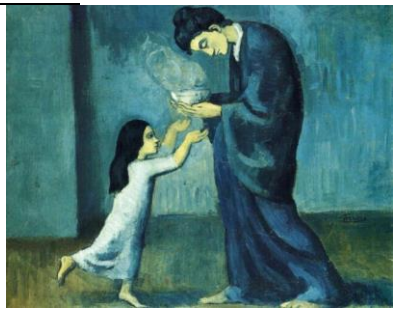
***Enlarge* / A new method helps recover gold from e-waste at a higher rate than it can be extracted from fresh ore. Reiko Matsushita/Shinta Watanabe**

"The amount of gold contained in one ton of mobile phones is 300-400 grams, which is much higher by 10-80 times than that in one ton of natural ore," the authors wrote. "The other elements have a similar situation. Consequently, the recovery of those precious elements from e-wastes is much more effective and efficient when compared to their collections from natural ore."

Prussian blue is the first modern synthetic pigment. Granted, there was once a pigment known as Egyptian blue used in ancient Egypt for millennia; the Romans called it caeruleum. But after the Roman Empire collapsed, the pigment wasn't used much, and eventually the secret to how it was made was lost. (Scientists have since figured out how to recreate the process.) Before Prussian blue was discovered, painters had to use indigo dye, smalt, or the pricey ultramarine made from lapis lazuli for deep-blue hues.

It's believed that Prussian blue was first synthesized by accident by a Berlin paint maker named Johann Jacob Diesbach around 1706. Diesbach was trying to make a red pigment, which involved mixing potash, ferric sulfate, and dried cochineal. But the potash he used was apparently tainted with blood—one presumes from a cut finger or similar minor injury. The ensuing reaction created a distinctive blue-hued iron ferrocyanide and eventually came to be called Prussian blue (or Berlin blue).

The earliest known painting to employ Prussian blue is currently Pieter van der Werff's *Entombment of Christ* (1709), but the recipe was published in 1734, and Prussian blue was soon widespread among artists. Hokusai's famous artwork, *The Great Wave off Kanagawa*, is among the most famous works to use the pigment, along with Vincent van Gogh's *The Starry Night* and many of the paintings from Pablo Picasso's "Blue period."



***Enlarge* / Pablo Picasso's La Soupe (The Soup), from the artist's Blue period, makes extensive use of Prussian blue. Public domain**

The pigment has other uses. It's often used to treat heavy-metal poisoning from thallium or radioactive cesium because its lattice-like network structure—similar to a jungle gym—can trap metal ions from those metals and prevent them from being absorbed by the body. Prussian blue helped remove cesium from the soil around the Fukushima power plant after the 2011 tsunami. Prussian blue nanoparticles are used in some cosmetics, and it's used by pathologists as a stain to detect iron in, for example, bone marrow biopsy specimens.

So it's a very useful substance, which is why the Japanese authors of this latest paper decided to explore other potential practical applications. They analyzed how Prussian blue uptakes multi-valent metals—like platinum, ruthenium, rhodium, molybdenum, osmium, and palladium, among others—using X-ray and ultraviolet spectroscopy. They were surprised at how well the pigment retained its jungle-gym structure while substituting iron ions in the framework—the secret to its impressive uptake efficiency compared to bio-based absorbents. That's great news for e-waste recycling.

Prussian blue could also solve one of the challenges of disposing of nuclear waste, according to the authors. Current practice involves converting radioactive liquid waste into a glass-like state at a

reprocessing plant prior to disposal. But platinum-group metals can accumulate on the walls of the melters, eventually causing an uneven distribution of heat. So the melters must be flushed after each use, which in turn increases costs. Prussian blue could remove those deposits with no need for flushing the melters after every use.

DOI: Scientific Reports, 2022. 10.1038/s41598-022-08838-1 (About DOIs).

https://go.nature.com/3bjU8jv

These cancer cells wake up when people sleep

Researchers make 'striking' discovery that breast cancer cells are more likely to jump into the blood when people are resting.

Freda Kreier

Cancer is at its deadliest when a tumour's cells worm their way into the bloodstream and travel to a new location in the body to set up shop — a process called metastasis. Now, a study finds that for people with breast cancer, these rogue cells — called circulating tumour cells, or CTCs — are more likely to jump into the blood at night than during the day. The discovery reveals some basic human physiology that has so far flown under the radar and could lead to better ways of tracking cancer's progression, says Qing-Jun Meng, a chronobiologist at the University of Manchester, UK.

The research community has been discussing for decades how the body's circadian rhythm influences cancer. With this study, it has become clear that "tumours wake up when patients are sleeping", says co-author Nicola Aceto, a cancer biologist at the Swiss Federal Institute of Technology in Zurich, Switzerland. It's a "step forward" in understanding metastasis, he says. "And steps forward are a good thing for patients in the long-term". The research was published on 22 June in *Nature*[1].

Cancer on the clock

In 2007, the International Agency for Research on Cancer listed disrupted circadian rhythm as a "probable" carcinogen after long-term studies concluded that people who work odd hours — such as flight attendants and night nurses — were at a higher risk of developing breast cancer[2]. Why this happens remains an open question.

A person's circadian clock, controlled by various genes that express specific molecules on a 24-hour timetable, influences many processes in the body, including metabolism and sleep. Most researchers, however, had initially thought that cancer cells were "so screwed up, so highly mutated" that they wouldn't conform to such a schedule, Aceto says.

For metastasis, the first hint that this might not be strictly true came when Aceto and his colleagues noticed that levels of CTCs in mice with tumours varied depending on the time of day that their blood was drawn. That observation led Aceto to collect blood from 30 women hospitalized with breast cancer, once at 4 a.m. and again at 10 a.m..

The researchers found that the bulk of the CTCs they detected in the blood samples — almost 80% — appeared in the portion collected at 4 a.m., when the patients were still resting. At first, "I was surprised because the dogma is that tumours send out circulating cells all the time", Aceto says. "But the data were very clear. So, soon after being surprised, we started being very excited."

The next step for the researchers was to confirm whether this was true beyond these few people. To do this, the team grafted breast cancer tumours into mice and tested the animals' CTC levels throughout the day. Compared with humans, mice have an inverted circadian rhythm, meaning that they are most active at night and tend to rest during the day. The team found that the animals' CTC levels peaked during the day — sometimes at a concentration that was up to 88 times higher than baseline — when the animals were in their resting state.

Furthermore, the researchers collected CTCs from the mice, both while the animals were resting and while they were active. They

added different fluorescent tags to the two sets of cells, and then injected them back into the mice. Most of the cells that grew into new tumours were those collected when the mice were resting, suggesting that these CTCs are somehow better at metastasizing.

This revelation is “striking”, says Chi Van Dang, a cancer biologist at the Ludwig Institute for Cancer Research in New York City. Physicians measure CTC levels in the blood — a type of liquid biopsy — to help see how people with cancer are progressing, so “the first lesson for me is that the time of day you take a blood sample can give you misleading information”, he says. This means that physicians might want to rethink when they track cancer, he adds.

Sleep is not the enemy

Why breast cancer cells in humans are more active at night probably depends on a multitude of factors that still need to be investigated, Aceto says. Hormones, which are one tool the body uses to signal that it’s time to wake up or go to bed, might play a part. The team found that treating mice with hormones such as testosterone or insulin had an impact on CTC levels — lowering or raising them, depending on when the hormones were administered.

Understanding how this process works could one day lead to better cancer treatments, Dang says, but that reality is probably still a long way off. More studies are needed first, to untangle the complicated web connecting circadian rhythms and cancers, he adds.

In the meantime, Meng cautions against thinking of sleep as the enemy for people with breast cancer. Some studies have shown that people who have cancer and who commonly get less than seven hours of sleep per night are at higher risk of death[3], and messing with circadian rhythms in mice can make cancer move faster[4]. The findings aren’t an indication that “you don’t need sleep, or that you need less sleep”, he says. “It simply means these cells prefer a specific phase of the 24-hour cycle to go into the bloodstream.”

doi: https://doi.org/10.1038/d41586-022-01724-w

***Updates & Corrections Correction 23 June 2022**: An earlier version of this story spelled chronobiologist Qing-Jun Meng’s name incorrectly.*

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https://bit.ly/3HWpCZm

A blueprint for life forms on Mars?

The extremely salty, very cold, and almost oxygen-free environment under the permafrost of Lost Hammer Spring in Canada's High Arctic is a good place to look

The extremely salty, very cold, and almost oxygen-free environment under the permafrost of Lost Hammer Spring in Canada's High Arctic is the one that most closely resembles certain areas on Mars. So, if you want to learn more about the kinds of life forms that could once have existed—or may still exist—on Mars, this is a good place to look. After much searching under extremely difficult conditions, McGill University researchers have found microbes that have never been identified before. Moreover, by using state-of-the-art genomic techniques, they have gained insight into their metabolisms.

In a recent paper in *The ISME Journal*, the scientists demonstrate, for the first time, that microbial communities found living in Canada's High Arctic, in conditions analogous to those on Mars, can survive by eating and breathing simple inorganic compounds of a kind that have been detected on Mars (such as methane, sulfide, sulfate, carbon monoxide, and carbon dioxide). This discovery is so compelling that samples of the Lost Hammer surface sediments were selected by the European Space Agency to test the life detection capabilities of the instruments they plan to use on the next ExoMars Mission.

Developing a blueprint for life on Mars

Lost Hammer Spring, in Nunavut in Canada's High Arctic, is one of the coldest and saltiest terrestrial springs discovered to date. The water which travels up through 600 meters of permafrost to the surface is extremely salty (~24% salinity), perennially at sub-zero temperatures (~−5 °C) and contains almost no oxygen (<1ppm dissolved oxygen). The very high salt concentrations keep the Lost Hammer spring from freezing, thus maintaining a liquid water habitat even at sub-zero temperatures. These conditions are analogous to those found in certain areas on Mars, where widespread salt deposits and possible cold salt springs have been observed. And while earlier studies have found evidence of microbes in this kind of Mars-like environment—this is one of a very few studies to find microbes alive and active

To gain insight into the kind of life forms that could exist on Mars, a McGill University research team, led by Lyle Whyte of the Department of Natural Resource Sciences, has used state-of-the-art genomic tools and single cell microbiology methods to identify and characterize a novel, and more importantly, an active microbial community in this unique spring. Finding the microbes and then sequencing their DNA and mRNA was no easy task.

It takes an unusual life form to survive in difficult conditions

"It took a couple of years of working with the sediment before we were able to successfully detect active microbial communities," explains Elisse Magnuson, a Ph.D. student in Whyte's lab, and the first author on the paper. "The saltiness of the environment interferes with both the extraction and the sequencing of the microbes, so when we were able to find evidence of active microbial communities, it was a very satisfying experience."

The team isolated and sequenced DNA from the spring community, allowing them to reconstruct genomes from approximately 110 microorganisms, most of which have never been seen before. These genomes have allowed the team to determine how such creatures survive and thrive in this unique extreme environment, acted as blueprints for potential life forms in similar environments. Through mRNA sequencing, the team were able to identify active genes in the genomes and essentially identify some very unusual microbes actively metabolizing in the extreme spring environment.

No need for organic material to support life

"The microbes we found and described at Lost Hammer Spring are surprising, because, unlike other microorganisms, they don't depend on organic material or oxygen to live," adds Whyte. "Instead, they survive by eating and breathing simple inorganic compounds such as methane, sulfides, sulfate, carbon monoxide and carbon dioxide, all of which are found on Mars. They can also fix carbon dioxide and nitrogen gasses from the atmosphere, all of which makes them highly adapted to both surviving and thriving in very extreme environments on Earth and beyond."

The next steps in the research will be to culture and further characterize the most abundant and active members of this strange microbial ecosystem, to better understand why and how they are thriving in the very cold, salty, muck of the Lost Hammer Spring. The researchers hope that this, in turn, will help in the interpretation of the exciting but enigmatic sulfur and carbon isotopes that were very recently obtained from the NASA Curiosity Rover in the Gale Crater on Mars.

More information: *Elisse Magnuson et al, Active lithoautotrophic and methane-oxidizing microbial community in an anoxic, sub-zero, and hypersaline High Arctic spring, The ISME Journal (2022).* *DOI: 10.1038/s41396-022-01233-8*

https://bit.ly/3NhW0Xl

Squirrels Could Make Monkeypox a Forever Problem

If the virus finds a new animal host, it could settle in for the long run—and cause more outbreaks in the future.

By Katherine J. Wu

In the summer of 2003, just weeks after an outbreak of monkeypox sickened about 70 people across the Midwest, Mark Slifka visited "the super-spreader," he told me, "who infected half of Wisconsin's cases."

Chewy, a prairie dog, had by that point succumbed to the disease, which he'd almost certainly caught in an exotic-animal facility that he'd shared with infected pouched rats from Ghana. But his owners' other prairie dog, Monkey—named for the way he clambered about his cage—had contracted the pathogen and survived. "I was a little worried," said Slifka, an immunologist at Oregon Health & Science University. All the traits that made Monkey a charismatic pet also made him an infectious threat. He cuddled and nibbled his owners; when they left the house, he'd swaddle himself in their clothing until they returned. "It was sweet," Slifka told me. "But I was like, 'Can Monkey be in his cage when we come over?'"

Slifka made it home pox-free, and the 2003 outbreak fizzled out. But that rash of cases was a close call: an opportunity for the virus to set up shop in a new animal host. One lasting interspecies hop, akin to the one that SARS-CoV-2 has made into white-tailed deer, and monkeypox will be "with us forever" in the U.S., says Barbara Han, a disease ecologist at the Cary Institute, in New York. In Central and West Africa, where the virus is endemic, scientists suspect that at least a couple of rodent species intermittently slosh it into humans. And as the largest-ever epidemic of monkeypox outside of Africa in history continues to unfurl—more than 2,700 confirmed and suspected cases have been reported across roughly three dozen countries—the virus is now getting plenty more shots on goal. This time, we may not get so lucky; the geography of monkeypox might soon change.

Any new leaps could reshape the future for this virus, and for us. Experts consider the possibility unlikely—"low risk, but it is a risk," says Jeffrey Doty, a disease ecologist at the CDC. Existing animal reservoirs make some diseases near impossible to snuff out; the emergence of new ones could seed future outbreaks in places where they're not currently common. If researchers can ID some of those animals, and keep them from mingling with us, we could head off a few of those issues. But that's a big *if*. With so many susceptible animals out there, figuring out which ones harbor the virus could send researchers on a yearslong race, without a clear finish line.

Scientists first discovered monkeypox in the 1950s, in two species of monkeys housed at a Danish animal facility; hence the name, which will likely change soon. But in the decades since, the best evidence of the virus lingering in animals has been tugged from rodents in Central and West Africa, including rope squirrels, sun squirrels, Gambian pouched rats, and dormice. All signs point to rodents being "responsible for maintaining this virus in the wild," Doty told me, and so he and his colleagues worry most about those mammals when they ponder what animals in non-endemic regions may pose the most future risk.

But a *lot* of rodents scurry the planet—about 2,500 species, which together make up roughly 40 percent of known mammals. Though not all species are capable of carrying monkeypox—for example, guinea pigs, golden hamsters, and common mice and rats usually don't—many of them can.

Building the case for an animal reservoir tends to require years of fieldwork, rigorous safety protocols, and a good deal of luck. For a few viruses, the reservoir narrative is relatively neat: Hendra virus, an often-fatal respiratory infection, typically moves from bats to horses to people; most hantaviruses, which can cause lethal fevers, set up shop in one rodent species each. Monkeypox, however, is far less picky than that. Experts suspect that multiple animals keep the virus percolating in the wild. Just how many, though, is anyone's

guess.

The gold standard for establishing a reservoir requires isolating active virus—proof that the pathogen was xeroxing itself inside of a viable host. But in the wilds of nature, "you can break your back and end up getting only five animals from a species," Han, who's been using machine learning to try to predict potential monkeypox reservoirs, told me. "And what's five animals?" They may lack the virus in question, even if other members of their population harbor it; they may have been caught at an age, or during a season, when the pathogen's not present. And among the animals that host the virus, a reservoir might not always be the most obvious species: Rodents might be among the most commonly detected carriers of monkeypox, but zoo outbreaks and laboratory experiments have shown the virus to be capable of infiltrating anteaters, rabbits, and a hefty handful of primates, along with other un-mousy mammals. In several of these species and others, scientists have found antibodies that recognize poxviruses, hinting at past exposures; they've even uncovered the virus's DNA. Only twice, though, has anyone found active virus in wild animals: a rope squirrel from the Democratic Republic of Congo in the 1980s, and a sooty mangabey, found in Côte d'Ivoire about a decade ago.

Even those cases weren't slam dunks. It takes more to "figure out which one is a reservoir, versus which ones get infected, but aren't actually responsible for maintaining circulation of the virus" in nature, then spilling it into human communities, Jamie Lloyd-Smith, a disease ecologist at UCLA, told me. Just because an animal could bop the virus into us doesn't mean that it will.

For that to happen, humans need to have enough contact with the animals to make exposure likely—on routine hunts for bushmeat, for instance, or in fractured landscapes where animals forage for food in and around people's homes. Lloyd-Smith, who has been analyzing surveys of residents of the Congo, said parsing what's risky and what's not is tougher than it sounds: Most everyone in these areas interacts with forest creatures all the time. "It's not like, 'Oh, it was the people who ate the salmon mousse at the church breakfast,'" he told me. To complicate matters further, wild and domesticated animals can act as intermediaries between humans and a true reservoir, says Stephanie Seifert, a disease ecologist at Washington State University. Researchers sometimes have to traverse webs of interaction, moving through Kevin Bacon–esque degrees of separation, to pinpoint the original source.

Unveiling those natural origins is key to blocking the virus from moving onto new real estate—and, perhaps, breaking existing tenancies. In Central and West Africa, for instance, where some people's livelihoods depend on hunting and eating wild game, "You can't just say, 'Don't interact with rodents,'" Seifert told me. But with more investigation, says Clement Meseko, a veterinarian and virologist studying the human-wildlife interface at Nigeria's National Veterinary Research Institute, perhaps experts could eventually pinpoint just a couple of species, then recommend sustainable alternatives in their place. Improved sanitation to keep rodent pests away from humans could also help. So could doling out vaccines to people who live in the high-risk regions of endemic countries—or perhaps to worrisome wild animals themselves. (Immunizing animals is a pretty lofty goal, but may still be a better alternative to culling animals, which "often doesn't work," Lloyd-Smith said.)

In the U.S., amid the current rash of monkeypox cases, the CDC has recommended that infected people avoid interacting with pets, livestock, and other animals altogether. Though no cat or dog has ever been known to contract the infection, "we basically know nothing about monkeypox in common companion animals," Doty said. For now, it's best to play it safe.

And the most meaningful way to keep the virus from surging into a

new animal species, Han said, “is to control the human outbreak.” Already, monkeypox’s species range is formidable, and in today’s world, humans and animals are colliding more frequently. Amid the ongoing outbreak, Meseko, who is spending the year completing a fellowship in St. Paul, Minnesota, has been taking note of “how squirrels are just free all over the place.” Whatever threat they might pose to us, “animals are also in danger from humans,” he told me.

Human activity, after all, brought monkeypox to the U.S. in 2003, and into a coterie of prairie dogs that included Chewy and Monkey. “They would not have been exposed geographically without us moving around this virus,” Seifert said. And the human desire for pets brought those prairie dogs into dozens of midwestern homes. People mobilize disease; our species, too, poses an immense infectious threat to the planet. The current monkeypox outbreak, for instance, is more sprawling and human-centric than those documented in the past. And the more opportunity the virus has to infiltrate new hosts, the more opportunity it has to expand its species range. Any trickle into animals might not be detected until too late; perhaps, some experts pointed out, it already occurred long ago, seeding a reservoir that helped the ongoing epidemic erupt. “We have no evidence of that right now,” says Grant McFadden, a poxvirus expert at Arizona State University. “But that could change on a dime.”

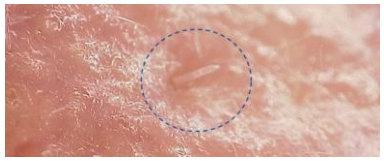
https://bit.ly/3xPz8ss

Skin Mites That Mate on Our Faces at Night Are Slowly Merging With Humans

If you are reading this, you are probably not alone.

Michelle Starr

Most people on Earth are habitats for mites that spend the majority of their brief lives burrowed, head-first, in our hair follicles, primarily of the face. In fact, humans are the only habitat for *Demodex folliculorum*. They are born on us, they feed on us, they mate on us, and they die on us.



Their entire life cycle revolves around munching your dead skin cells before kicking the teeny tiny bucket.

Microscope image showing Demodex folliculorum on human skin. **(University of Reading)**

So reliant is *D. folliculorum* on humans for their survival, new research suggests, that the microscopic mites are in the process of evolving from an ectoparasite into an internal symbiont – and one that shares a mutually beneficial relationship with its hosts (that's us). In other words, these mites are gradually merging with our bodies so that they now live permanently within us.

Scientists have now sequenced the genomes of these ubiquitous little beasts, and the results show that their human-centered existence could be wreaking changes not seen in other mite species.

"We found these mites have a different arrangement of body part genes to other similar species due to them adapting to a sheltered life inside pores," explained invertebrate biologist Alejandra Perotti of the University of Reading in the UK. "These changes to their DNA have resulted in some unusual body features and behaviors."

D. folliculorum is actually a fascinating little creature. Human skin detritus is its sole food source, and it spends the majority of its two-week lifespan in pursuit thereof.

The individuals emerge only at night, in the cover of darkness, to crawl painstakingly slowly across the skin to find a mate, and hopefully copulate before returning to the safe darkness of a follicle. Their tiny bodies are just a third of a millimeter in length, with a cluster of tiny legs and a mouth at one end of a long, sausage-shaped body – just right for scooching down human hair follicles to get at the tasty noms therein.

The work on the genome of the mite, co-led by Marin and

geneticist Gilbert Smith of Bangor University in the UK, revealed some of the fascinating genetic characteristics that drives this lifestyle. Because their lives are so cruisy – they have no natural predators, no competition, and no exposure to other mites – their genome has reduced down to just the bare essentials.

Their legs are powered by three, single-cell muscles, and their bodies have the absolute minimum number of proteins, only what is needed for survival. It's the smallest number ever seen in its wider group of related species.

This pared-down genome is the reason for some of *D. folliculorum*'s other strange peccadilloes, too. For instance, the reason it only comes out at night. Among the genes lost are those responsible for protection against UV radiation, and those that wake animals up at daylight.

They are also unable to produce the hormone melatonin, found in most living organisms, with varying functions; in humans, melatonin is important for regulating the sleep cycle, but in small invertebrates, it induces mobility and reproduction.

This hasn't seemed to have hindered *D. folliculorum*, however; it can harvest melatonin secreted by the skin of its host at dusk.

Unlike other mites, their reproductive organs of *D. folliculorum* have moved towards the front of their bodies, with male mites' penises pointing forwards and upwards from their backs. This means he has to arrange himself underneath the female as they perch precariously on a hair for mating, which they do all night, AC/DC-style (presumably).

But although mating is pretty important, the potential gene pool is very small: there is very little opportunity for expanding genetic diversity. This could mean that the mites are on track for an evolutionary dead end.

Interestingly, the team also found that, at the nymph stage of development, between larva and adult, is when the mites have the greatest number of cells in their bodies. When they move on to the adult stage, they lose cells – the first evolutionary step, the researchers said, in the march of an arthropod species to a symbiotic lifestyle.

One might wonder what possible benefits humans can gain from these peculiar animals; something else the researchers found might partially hint at the answer. For years, scientists have thought that *D. folliculorum* doesn't have an anus, instead accumulating waste in its body to explode out when the mite dies, and thus causing skin conditions.

The team found that this is simply not the case. The mites do indeed have tiny little buttholes; your face probably isn't full of mite poop expelled posthumously.

"Mites have been blamed for a lot of things," said zoologist Henk Braig of the University of Bangor and the National University of San Juan in Argentina. "The long association with humans might suggest that they also could have simple but important beneficial roles, for example, in keeping the pores in our face unplugged."

The research has been published in *Molecular Biology and Evolution*.

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Bonobos' tolerant, peaceful group relationships paved way for human peacemaking

How did humans get our capacity for tolerance and cooperation among social groups?

Humans display a capacity for tolerance and cooperation among social groups that is rare in the animal kingdom, our long history of war and political strife notwithstanding. But how did we get that way?

Scientists believe bonobos might serve as an evolutionary model. The endangered primates share 99% of their DNA with humans and have a reputation for generally being peace-loving and sexually

active—researchers jokingly refer to them "hippie apes." And interactions between their social groups are thought to be much less hostile than among their more violent cousins, the chimpanzees.

Some, however, have challenged this because of a lack of detailed data on how these groups work and how they separate themselves. A new study led by Harvard primatologists Liran Samuni and Martin Surbeck on the social structure of bonobos may begin to fill in some of the blanks.

The research, published in *PNAS*, shows that four neighboring groups of bonobos they studied at the Kokolopori Bonobo Reserve in the Democratic Republic of Congo maintained exclusive and stable social and spatial borders between them, showing they are indeed part of distinct social groups that interact regularly and peacefully with each other.

"It was a very necessary first step," said Samuni, a postdoctoral fellow in Harvard's Pan Lab and the paper's lead author. "Now that we know that despite the fact that they spend so much time together, [neighboring] bonobo populations still have these distinct groups, we can really examine the bonobo model as something that is potentially the building block or the state upon which us humans evolved our way of more complex, multilevel societies and cooperation that extends beyond borders."

The study is a result of three consecutive years of observing the bonobo community in the Kokolopori reserve from 2017 to 2019. Previous research showed evidence of the 59 bonobos forming four separate groups that routinely crossed paths to interact, groom each other, and share meals. What hasn't been clear is the extent to which the behavior of these bonobo groups resembles that of chimpanzee subgroups that form within one larger community.

Primatologists refer to chimp subgroups, which are highly territorial and hostile to those in different communities, as neighborhoods. Essentially, members of these subgroups don't spend all their time together as part of one large group but are all still part of it, maintaining relationships with each other and (most importantly) not battling each other when they meet.

Bonobos have been far less studied than chimps due to political instability and logistical challenges to setting up research sites in the forests of the Democratic Republic of Congo, the only place where the primates are found. In addition, studying relationships among and between Bonobo groups has been further complicated by the fact that subgroups appear to intermingle with some frequency.

"There aren't really behavioral indications that allow us to distinguish this is group A, this is group B when they meet," Samuni said. "They behave the same way they behave with their own group members. People are basically asking us, how do we know these are two different groups? Maybe instead of those being two different groups, these groups are just one very large group made up of individuals that just don't spend all their time together [as we see with chimpanzee neighborhoods]."

To get at the answer, at least two observers from the reserve followed each bonobo group daily from dawn to dusk, recording behavioral and location data that was then analyzed.

The researchers primarily tracked how much time individual bonobos spent together, with whom, and what activities they engaged in. This helped the researchers perform a statistical method called a cluster analysis. This method groups data points in a cluster so that points from the same group are clustered closely on a plot, while data points not in the same group are clustered in another space.

Essentially, they tracked which bonobos shared significant associations with one another, which ones tended to come together for meals more often, which ones tended to stick together when faced with a choice of whom to go with, and which ones interacted

more in the same home range. This helped them draw clear distinctions between what bonobos were part of the same group and when members of one group were peacefully interacting with neighboring groups across each other's borders.

They compared this to data collected on 104 chimpanzees that lived in the Ngogo community in Uganda's Kibale National Park between 2011 and 2013.

The researchers found the bonobo clusters were overall more consistent and stable than the subgroups of chimps. This suggests that the bonobos within each cluster had a stronger social preference for one another than was seen within chimpanzee subgroups.

When it comes to the Kokolopori bonobos, this helped the researchers not only confirm the four groups—which they named the Ekalakala, the Kokoalongo, the Fekako, and the Bekako—but also come up with a reliable way to predict which bonobos were most likely to stick together when the different groups of bonobos met and separated.

Samuni and Surbeck, an assistant professor in the Department of Human Evolutionary Biology and the paper's senior author, say the results show that bonobos, like humans, are capable of complicated relationships outside their immediate core network.

Now that the researchers have firmly established that these bonobos have distinct groups, they want to dig further into what cooperation and trade look between these groups and whether it can potentially represent what it looked like in our common ancestor. This would help explain how humans, to an extent, overcame antagonism between different groups and developed peaceful cooperation.

Surbeck, who founded and directs the Kokolopori Bonobo Research Project, points out the window to gain these powerful insights is closing as bonobos near extinction.

"There are very few left," he said. "We gather here information that potentially will not be available anymore in 50 years if things continue the way they do."

More information: *Liran Samuni et al, Characterization of Pan social systems reveals in-group/out-group distinction and out-group tolerance in bonobos, Proceedings of the National Academy of Sciences (2022).* *DOI: 10.1073/pnas.2201122119*

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Side Effects May Include … A Completely New Hair Color?

An experimental therapy helped patients with a rare disease feel better. It also led to an accidental makeover.

By Sarah Zhang

In October 2019, Jordan Janz became the first person in the world to receive an experimental therapy for cystinosis, a rare genetic disease. The treatment was physically grueling. Doctors extracted blood stem cells from Janz's bone marrow and genetically modified them in a lab. Meanwhile, he underwent chemotherapy to clear out the remaining faulty cells in his bone marrow before he got the newly modified ones. The chemo gave Janz sores in his mouth so painful that he couldn't eat. He lost his head full of pale-blond hair.

But Janz, then a 20-year-old from Alberta, Canada, had signed up for this because he knew that cystinosis was slowly killing him. The mutated gene behind this disease was causing toxic crystals of a molecule called cystine to build up everywhere in his body. He threw up constantly as a kid. Visible crystals accumulated in his eyes. And his kidneys were now failing. Cystinosis patients live, on average, to 28.5 years old.

Fortunately, the experimental gene therapy seemed to work; Janz began to feel better. His hair grew back in a stubble, but to his shock, it came in a different color: dark, almost black. In the two and half years since, his hair has settled into a dark blond, which is still markedly different from the "almost white blond" of before. "My girlfriend actually said the other day that she feels like she's

dating a different person," Janz told me.

Of all the things the experimental gene therapy was expected to alter—such as the severity of his cystinosis symptoms—hair color was not one of them. "That was very surprising," Stephanie Cherqui, a stem-cell scientist at UC San Diego and the principal investigator of the gene-therapy trial, told me. But as she and her colleagues dug into the literature on the disease, they found that darker hair wasn't a sign of something going awry; instead it might be a very visible sign of the gene therapy *working*.

Doctors had observed years ago that cystinosis patients tend to be paler than their families. Many—though certainly not all—have blond hair and pale skin. One study in mice found that the gene that's mutated in cystinosis patients normally plays a role in the production of the dark-brown pigment melanin. Janz had always been a bit self-conscious about how pale he was. His whole family is "pretty pale," Janz said. "But I'm, like, a whole different pale—or I was." The hair change, as far as he's concerned, was a nice surprise.

But how did genetically modifying his *blood* cells change his hair color? While the mutation that causes cystinosis affects virtually every cell in his body, gene therapy did not change the DNA of every cell in his body, only a tiny fraction of them. Scientists chose to genetically tweak blood stem cells because they have a special ability: Some eventually become white blood cells, which "travel to all different parts of the body," Jeffrey Medin, who studies gene therapy at the Medical College of Wisconsin, told me. White blood cells normally go into all our different tissues and organs to patrol for pathogens.

Janz's new white blood cells were genetically modified to express the gene that is mutated in cystinosis, called *CTNS*. Once they traveled to his eyes, skin, and gut, the white blood cells began pumping out the missing protein encoded by the gene. Cells in the area began taking up the protein and clearing away long-accumulated cystine crystals. In Janz, the anti-cystine proteins from his modified blood cells must have reached the hair follicles in his skin. There, they cleared out the excess cystine that was blocking normal melanin production, and his hair got darker. The same phenomenon has played out in other people: So far in the gene-therapy trial, four of the five patients—all of whom are white—have gotten darker hair. (The fifth patient's hair is just starting to grow back post-therapy.) The investigators have since added hair biopsies to the trial in order to track the color changes in a more systematic fashion.

The sudden hair-color changes were surprising to Cherqui and her colleagues, but they are consistent with the role of the cystinosis gene in hair pigments, says Robert Ballotti, a melanin researcher at the French National Institute of Health and Medical Research. But he has also found that pigmentation and cystinosis can interact in unexpected ways. Not all people with cystinosis are pale, and in particular, Black patients tend not to have skin or hair that is any lighter. "Maybe there is not a strict correlation between the gravity of the disease and pigmentation," Ballotti says.

Hair color is one way in which patients in the clinical trial are teaching scientists about the full scope of the *CTNS* gene, which is still not fully understood. Cherqui had helped discover the gene, as a graduate student more than 20 years ago, and her research has hinted at other functions for it in cell growth and survival, too. "More and more, we understand that there are many functions of the protein that we didn't know," she said.

That's why patients on the standard treatment, a drug called cysteamine, still get sicker and die of their disease, Cherqui said. "Removing cystine is not enough." It doesn't help that cysteamine has some pretty nasty side effects: It causes stomach pain, nausea, and diarrhea. When Janz was very young, he needed a stomach tube

to get the medication around the clock. Cysteamine also has a rotten, fishlike smell. “I had a lot of difficult times as a younger kid,” says Jacob Seachord, another patient in the trial whose hair went from blond to brown. “I smelled really bad from medication, so I didn't make a lot of friends.”

Gene therapy actually replaces the *missing protein*, theoretically filling in all of its functions, known and unknown. All five patients in the gene-therapy trial have gone off their oral cysteamine, and preliminary data show they now have fewer cystine crystals in their eyes, skin, and gut. Their vision has gotten slightly better, too. But improvements in kidney function are more elusive. Seachord had a kidney transplant before the gene therapy and is doing well. Janz had advanced kidney disease before the trial, and he will need a kidney transplant in a few months.

For adults with cystinosis, Cherqui said, it may be too late for gene therapy to help their kidneys. They have already accumulated a lifetime of kidney damage from cystine. Gene therapy can’t reverse the damage that’s been done, but “we can correct it going forward,” Medin said. “We can stop progression.” In diseases like cystinosis, patients may have to get gene therapy at a young age, probably before 10, Cherqui said. If it works, a future kid who has cystinosis might be *cured* through gene therapy—preventing them from needing a lifetime of cysteamine or a kidney transplant. And it just might change their hair color, too.

https://bit.ly/3xWNsPP

Organ storage a step closer with cryopreservation discovery

Australian scientists have taken the first step towards improved storage of human cells, which may lead to the safe storage of organs such as hearts and lungs.

The team's discovery of new cryoprotective agents opens the door to many more being developed that could one day help to eliminate the need for organ transplant waiting lists. Their results are published in the *Journal of Materials Chemistry B*.

Cryopreservation is a process of cooling biological specimens down to very low temperatures so they can be stored for a long time. Storing cells through cryopreservation has had big benefits for the world—including boosting supplies at blood banks and assisting reproduction—but it is currently impossible to store organs and simple tissues.

The lead researcher, Dr. Saffron Bryant from RMIT University, said that in the United States around 60% of all donated hearts and lungs were discarded. While figures vary in other countries, preservation and transport times remain a global issue.

"We have these massive organ shortages, and we only have hours to get an organ from a donor to a recipient," Bryant said.

About 1,850 people are on the waiting list for an organ transplant in Australia, while more than 100,000 Americans are waiting for a transplant.

Bryant said transplant waiting lists could become a problem of the past, as the RMIT team's discovery of new cryoprotective agents could lead to the development of potentially thousands more that could help keep donated organs viable for years, rather than hours.

"For the past 50 years cryopreservation practices have largely relied on the same two cryoprotective agents, but they don't work for organs and many cell types," she said.

Cryoprotective agents are like the antifreeze that you put in your car to stop the engine freezing as they allow the storage of cells at very low temperatures, Bryant said.

"These agents help to protect against damage during cryopreservation, primarily from dehydration and freezing by preventing the formation of ice crystals that can damage cells," she said. "Ice crystals cause damage inside cells. Cryoprotectants stop ice forming, leading to a glassy structure instead that can solidify

but doesn't cause the same sort of damage as ice crystals."

The research team discovered a cryoprotectant with two agents, proline and glycerol, was effective for all four cell types tested, including skin and brain cells, which were incubated with the cryoprotectant at 37 degrees Celsius before being frozen.

"This cryoprotectant was more effective and less toxic than its individual components," Bryant said. "This is one of the first times that this class of solvents has been systematically tested for cryopreservation of mammalian cells. This study could lead to the development of potentially thousands of new cryoprotective agents that may be tailored to specific cell types."

Bryant said incubating these cells with the cryoprotectant at 37 degrees Celsius for several hours prior to freezing and keeping them viable is a crucial step towards the storage of organs and tissues. "It means we could expose organs to the cryoprotectants for long enough for them to penetrate into the deepest layers of the organ without causing damage," she said.

"We have a long way to go with our research, as we've only looked at single cells and it's a much more complicated process for organs. But if we can develop this approach to store organs, we could eliminate organ shortages—there would be no waiting lists at all."

As a next step, the RMIT team will investigate ways to cryopreserve new cell types, including some that cannot be frozen and kept viable using current methods.

"We're also working with Lifeblood to investigate cryopreservation of blood products such as platelets, which are vital for the treatment of patients who have suffered significant blood loss," Bryant said.

"Current technology only enables the storage of platelets for up to a week, but with successful cryopreservation they could be stored for years."

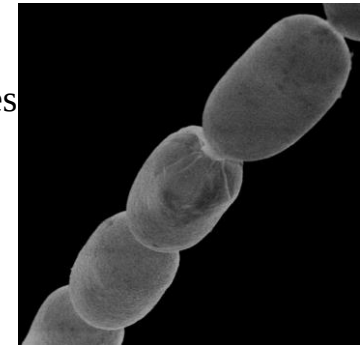
More information: *Saffron J. Bryant et al, Deep eutectic solvents as cryoprotective agents for mammalian cells, Journal of Materials Chemistry B (2022). DOI: 10.1039/D2TB00573E*

https://go.nature.com/39Psv1v

Largest bacterium ever found is surprisingly complex

'Microorganism' is a misnomer when it comes to centimetre-long Thiomargarita magnifica.

Katharine Sanderson



Lurking on rotting leaves sunken in the mangroves of Guadeloupe in the Caribbean live some extraordinary thread-like creatures These filament-like organisms, up to a centimetre in length, are the biggest single-cell bacteria yet to be found. Named *Thiomargarita magnifica*, they live by oxidizing sulfur, and are 50 times bigger than any other known bacteria.

The filamentous Thiomargarita magnifica cells have more complex internal organization than do typical bacteria. **Credit: Olivier Gros/Lawrence Berkeley National Laboratory**

Biologist Olivier Gros found the bacteria in 2009 while exploring the mangroves of Guadeloupe, where he works at the University of the Antilles in the French West Indies. "At the beginning, I thought it was something like a fungi or something — not bacteria, but a eukaryote, maybe," Gros says. Unlike bacteria and archaea, which are simple microorganisms, eukaryotes — which include animals and plants — have complex cells containing a nucleus and organelles such as mitochondria.

When he got back to his laboratory at Pointe-à-Pitre in Guadeloupe, Gros examined his discovery under a microscope. It was then that he realized he wasn't looking at a eukaryote — and that he'd found something special. In 2018, marine biologist Jean-Marie Volland at Lawrence Berkeley National Laboratory in California looked at the bacteria more closely using a range of methods, including transmission electron microscopy and an imaging technique called

fluorescence *in situ* hybridization. In this way, he helped to confirm that it was a single cell. The authors reported their results in a preprint in February, and have now published them in *Science*[1].

There are other whoppers in the *Thiomargarita* bacteria family, but the next-largest is only around 750 micrometres in length. Other filament-like bacteria are also found in the mangroves, but these all consist of tens or hundreds of cells. "What is very unique about the *T. magnifica* is that the entire filament, which is among the longest filaments in the mangrove, is just one cell," says Volland.

Central to the bacterium is its vacuole — an inert, fluid-filled membrane. Around the edge of this are membrane-bound structures, which the authors call pepins and describe as being similar to the organelles found mostly in eukaryotic cells.

Thiomargarita magnifica filaments next to a US 10-cent coin. **Credit: Tomas Tyml/Lawrence Berkeley National Laboratory**

Thiomargarita magnifica is remarkable for more than its size. In other bacteria, genetic material floats freely inside the cell, usually in the form of just one circular chromosome. In *T. magnifica*, the team saw that the genetic information was stored in hundreds of thousands of pepins. Each of these contains DNA and ribosomes, molecular machines that translate instructions from DNA to make proteins. The pepins collectively host up to 700,000 copies of the genome.

Many questions remain. Among these are whether the specific habitat of the mangrove, which has high levels of sulfur-containing molecules and sulfur-eating microbes, is crucial to the existence of this bacterium. And the pepins themselves needs a closer look to determine whether they all contain the same mix of genetic material, ribosomes and proteins. "We have not sequenced individual pepins — we have sequenced the entire cell, which contains hundreds of thousands of pepins," says Volland. In particular, the researchers don't know whether each pepin contains just one copy of the genome, or more than one.

Now that *T. magnifica* has been discovered, Gros expects other teams to go off in search of even larger bacteria — which might be hidden in plain sight, he says. Petra Levin at Washington University in St Louis, Missouri, says that the discovery challenges conventional wisdom that bacteria have lower size limits than eukaryotic cells. "There's probably an upper limit on cell size at some point, but I don't think it will be peculiar to bacteria or archaea or eukaryotes."

"We really should not underestimate evolution, because we can't guess where it's going to go," says Levin. "I would not have guessed this thing exists, but now that I see it, I can see the logic in the evolution to this point."

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https://wb.md/3u5bBCV

Introduce Allergens Early, Say French Allergologists

French Society of Allergology advocates early introduction of allergens for all children, starting at 4 months of age.

Nathalie Raffier

LILLE, France — Although in many cases, food-allergen tolerance can be achieved with oral immunotherapy, primary prevention of food allergies remains crucial, according to the French Society of Allergology. In new recommendations that were presented at a session of the Congress of French Pediatric Societies, the academic society advocated early introduction of allergens for all children, starting at 4 months of age.

The latest prevention data from two major studies, LEAP and EAT (see box), have prompted European and French experts to rethink their stance on food diversification.

The new French proposals were recently published under the coordination of Dominique Sabouraud-Leclerc, MD, Pediatrics Department, Reims University Hospital, France, on behalf of the Food Allergy Working Group of the French Society of Allergology.

For all newborns, regardless of whether they have a history of atopic or nonatopic dermatitis, food diversification is now recommended from 4 months of age instead of 6 months, as was previously recommended. If the child does not develop atopic dermatitis or develops only a mild form, peanuts, eggs, and nuts may be introduced at home.

However, if the child experiences severe atopic dermatitis, an allergy testing panel for peanuts, nuts, eggs, and cow's milk proteins should be performed. An oral food challenge may be conducted at the allergist's discretion.

Regarding peanuts, the working group proposed introducing a purée in the form of either a mixture of peanuts/hazelnuts/cashew nuts (1 level teaspoon five times a week; 2 g of protein/food/week) or a 100% peanut paste (1 scant teaspoon four times a week; 2 g of peanut protein/week). If the family is worried, the allergist can suggest monitoring the child in the clinic waiting room for 30 minutes after the first dose.

"We shouldn't delay the introduction of the primary allergens anymore, regardless of whether children are at risk for a food allergy, and particularly a peanut allergy," explained Stéphanie Lejeune, MD, pediatric pulmonologist and allergist at Lille Regional University Hospital, who presented these new findings at the congress. "In fact, if we only target at-risk children, we overlook children with no family history who will nevertheless develop food allergies.

The idea is to introduce everything, especially peanuts, between 4 and 6 months of age and to no longer do so gradually, one food after another, as was being done until now, beginning at 6 months and over. We must give priority to regularity over quantity."

Although this approach is based on clinical trials, no real-life data are currently available.

LEAP and EAT Studies Support Early Introduction of Peanuts

A study from 2021 summed up the risk factors for peanut allergy. Sixty-one percent of infants (4–11 months) had atopic dermatitis, 18% had a food allergy, 62% had a first-degree relative with a peanut allergy, and 11% had a confirmed peanut allergy. The risk of peanut allergy increased with age and severe eczema.

In 2015, the LEAP study, which was conducted in the United Kingdom with 640 infants aged 4–11 months who had risk factors for peanut allergy, revolutionized peanut-allergy primary prevention. Regardless of whether the children were sensitized or not, the number of children who developed a peanut allergy was systematically lower in the group that ingested the allergen in comparison with the "avoidance" group.

Additionally, the LEAP-ON study showed that protection against peanut allergy persisted for 12 months after cessation of consumption between ages 5 and 6 years among children who had consumed peanuts previously.

Early diversification in the general population was investigated in the EAT study, which involved 1303 breastfed infants. Of these infants, 24% had atopic dermatitis (median SCORAD score, 7.5). They were divided into two arms: avoidance and breast feeding until 6 months (standard introduction) or early introduction at 3 months (boiled egg, milk, peanuts, sesame, white fish, wheat, 2 g of protein twice a week).

In the per protocol analysis, there were 13 cases of peanut allergy in the standard introduction group; there were no cases in the early introduction group.

This article was translated from the Medscape French edition.

https://bit.ly/39Pfu8c

Poliovirus may be spreading in London; virus detected in sewage for months

Vaccine-derived poliovirus spreads with poor hygiene, sanitation, and low vaccination.

Beth Mole

A vaccine-derived version of poliovirus has repeatedly surfaced in London sewage over the past several months, suggesting there may be a cryptic or hidden spread among some unvaccinated people, UK health officials announced Wednesday.

No polio cases have been reported so far, nor any identified cases of paralysis. But sewage sampling in one London treatment plant has repeatedly detected closely related vaccine-derived polioviruses between February and May. This suggests "it is likely there has been some spread between closely-linked individuals in North and East London and that they are now shedding the type 2 poliovirus strain in their feces," the UK Health Security Agency (UKHSA) said.

Though the current situation raises alarm, the agency notes that it's otherwise common to see a small number of vaccine-like polioviruses pop up in sewage from time to time, usually from people who have recently been vaccinated out of the country. This is because many countries use oral polio vaccines that include weakened (attenuated) polioviruses, which can still replicate in the intestines and thus be present in stool. They can also spread to others via poor hygiene and sanitation (i.e., unwashed hands and food or water contaminated by sewage), which can become concerning amid poor vaccination rates.

How and why this happens

Briefly, there are two types of polio vaccines: the attenuated oral vaccines and inactivated vaccines. Many high-income countries that are considered polio-free—including the UK and the US—use the inactivated vaccines, which do not have viruses capable of replicating or spreading. These vaccines are highly effective at preventing paralytic polio, but they do not produce high levels of local immune responses in the gut. So, if a vaccinated person encounters wild poliovirus, the virus may still be able to replicate in their gut and spread. In areas affected by wild polio outbreaks, this means that the virus can continue spreading.

Oral polio vaccines, on the other hand, can not only prevent paralytic polio, they can also produce strong local immune responses in the gut that block the virus from replicating there, thus disrupting its spread. These vaccines can also be more than five times cheaper than the inactivated kind. For all of these reasons, oral polio vaccines are the predominant vaccines used in the long, drawn-out battle to eradicate wild polio. Currently, wild polio is still found in Afghanistan and Pakistan, and Malawi and Mozambique have recently reported single cases.

But, one of the downsides to oral polio vaccines is that vaccinated people can shed the attenuated vaccine virus in their stool for several weeks after vaccination. If this happens in a community with poor sanitation, hygiene, and low vaccination coverage, the vaccine virus can spread from person to person. Over time, as the vaccine virus spreads to more people, it can pick up mutations that make it more like wild-type polio, allowing it to regain the ability to cause disease and, in rare instances, paralysis in unvaccinated people. At this point, the mutated vaccine virus gets dubbed "vaccine-derived poliovirus" or VDPV. Recently, VDPV cases have been reported from several African countries and Israel.

A cautionary tale in London

A VDPV is what health officials are now reporting in London: They found vaccine-like polio virus starting in February—likely from someone who had recently traveled to a different country where oral polio vaccines are used—and, since then, the virus

appears to have continued to evolve and is now classified as a vaccine-derived poliovirus type 2 (VDPV2).

"Vaccine-derived poliovirus is rare and the risk to the public overall is extremely low," Dr. Vanessa Saliba, consultant epidemiologist at UKHSA, said. But, "vaccine-derived poliovirus has the potential to spread, particularly in communities where vaccine uptake is lower. On rare occasions it can cause paralysis in people who are not fully vaccinated, so if you or your child are not up to date with your polio vaccinations, it's important you contact your [doctor] to catch up or if unsure check your [vaccination records]. Most of the UK population will be protected from vaccination in childhood, but in some communities with low vaccine coverage, individuals may remain at risk."

Health experts say that risk in London is exactly why strong childhood vaccination programs and uptake are critical everywhere, even in countries where vaccine-preventable diseases are thought of as bygones. To be clear, polio vaccines protect against both wild and vaccine-derived polio.

"Parents sometimes ask why, when diseases are uncommon in UK, or in the case of polio has been eliminated, do we continue to vaccinate against them," David Elliman, consultant pediatrician at Great Ormond Street Hospital in London, said in a statement. "The answer is that, although we are an island, we are not isolated from the rest of the world, which means diseases could be brought in from abroad. The finding of vaccine-derived polio virus in sewage proves the point."

The Global Polio Eradication Initiative, led by the World Health Organization, put the point more succinctly, saying in a Wednesday announcement: "Any form of poliovirus anywhere is a threat to children everywhere."

Polio outcomes

In the US, travelers occasionally bring polio into the country, which last happened in 1993. But, the last time a polio case originated in the US was in 1979. In the UK, the last wild polio case originating there occurred in 1984, and the country was declared polio-free in 2003.

Most people infected with poliovirus have no symptoms, but about a quarter will develop a flu-like illness that clears on its own, according to the Centers for Disease Control and Prevention. In a smaller proportion—estimated to be between 1- to 5-in-1,000—the virus attacks the central nervous system, leading to more severe symptoms, including tingling in legs and arms, meningitis, and paralysis.

The CDC estimates that about 1-in-200 people infected with poliovirus will develop paralysis. And about 2 percent to 10 percent of people with paralytic polio will die because the paralysis will affect their ability to breathe.

For anyone who survives the infection—whether it's mild or severe—an estimated 25 percent to 40 percent will develop post-polio syndrome, which can cause pain, weakness, and paralysis 15 to 40 years after the initial infection.

https://bit.ly/3OZDKU3

An Ancient Killer Is Rapidly Becoming Resistant to Antibiotics, Scientists Warn

According to new research, the bacterium that causes typhoid fever is evolving extensive drug resistance, and it's rapidly replacing strains that aren't resistant.

Carly Cassella

Typhoid fever might be rare in developed countries, but this ancient threat, thought to have been around for millennia, is still very much a danger in our modern world.

Currently, antibiotics are the only way to effectively treat typhoid, which is caused by the bacterium *Salmonella enterica* serovar Typhi (S Typhi). Yet over the past three decades, the bacterium's

resistance to oral antibiotics has been growing and spreading.

Sequencing the genomes of 3,489 S Typhi strains contracted from 2014 to 2019 in Nepal, Bangladesh, Pakistan, and India, researchers found a recent rise in extensively drug-resistant (XDR) Typhi.

XDR Typhi is not only impervious to frontline antibiotics, like ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole, but it is also growing resistant to newer antibiotics, like fluoroquinolones and third-generation cephalosporins. Even worse, these strains are spreading globally at a rapid rate. While most XDR Typhi cases stem from south Asia, researchers have identified nearly 200 instances of international spread since 1990.

Most strains have been exported to Southeast Asia, as well as East and Southern Africa, but typhoid superbugs have also been found in the United Kingdom, the United States, and Canada.

"The speed at which highly-resistant strains of S. Typhi have emerged and spread in recent years is a real cause for concern, and highlights the need to urgently expand prevention measures, particularly in countries at greatest risk," says infectious disease specialist Jason Andrews from Stanford University.

Scientists have been warning about drug-resistant typhoid for years now, but the new research is the largest genome analysis on the bacterium to date. In 2016, the first XDR typhoid strain was identified in Pakistan. By 2019, it had become the dominant genotype in the nation.

Historically, most XDR typhoid strains have been fought with third-generation antimicrobials, like quinolones, cephalosporins, and macrolides. But by the early 2000s, mutations that confer resistance to quinolones accounted for more than 85 percent of all cases in Bangladesh, India, Pakistan, Nepal, and Singapore. At the same time, cephalosporin resistance was also taking over.

Today, only one oral antibiotic is left: the macrolide, azithromycin. And this medicine might not work for much longer.

The new study found mutations that confer resistance to azithromycin are now also spreading, "threatening the efficacy of all oral antimicrobials for typhoid treatment". While these mutations have not yet been adopted by XDR S Typhi, if they are, we are in serious trouble.

If untreated, up to 20 percent of typhoid cases can be fatal, and today, there are 11 million cases of typhoid a year. Future outbreaks can be prevented to some extent with typhoid conjugate vaccines, but if access to these shots is not expanded globally, the world could soon have another health crisis on its hands.

"The recent emergence of XDR and azithromycin-resistant S Typhi creates greater urgency for rapidly expanding prevention measures, including use of typhoid conjugate vaccines in typhoid-endemic countries," the authors write. "Such measures are needed in countries where antimicrobial resistance prevalence among S Typhi isolates is currently high, but given the propensity for international spread, should not be restricted to such settings."

South Asia might be the main hub for typhoid fever, accounting for 70 percent of all cases, but if COVID-19 has taught us anything, it is that disease variants in our modern, globalized world are easily spread. To prevent that from happening, health experts argue nations must expand access to typhoid vaccines and invest in new antibiotic research. One recent study in India, for instance, estimates that if children are vaccinated against typhoid in urban areas, it could prevent up to 36 percent of typhoid cases and deaths.

Pakistan is currently leading the way on this front. It is the first nation in the world to offer routine immunization for typhoid. Last year, millions of children were administered the vaccine, and health experts argue more nations need to follow suit.

Antibiotic resistance is one of the world's leading causes of death, claiming the lives of more people than HIV/AIDS or malaria. Where available, vaccines are some of the best tools we

have to prevent future catastrophe. We don't have time to waste.

The study was published in *The Lancet Microbe*.

https://bit.ly/3A7dfI4

Encapsulated bacteria show promise as injectable living drugs factories to treat diseases

Engineered bacteria have been injected under the skin of rodents where they functioned as living drug or vaccine factories.

By James Urquhart

The approach, which used modified *Escherichia coli* trapped inside hydrogel microcapsules, holds promise for new therapies to treat diseases such as diabetes and cancer.

Microbes have been modified for decades to produce protein drugs, including insulin. However, because proteins are easily degraded and inactivated, it has been difficult to develop protein drug delivery methods that allow for their sustained release beneath the skin without repeated and regular injections.

Now Hanjie Wang and his colleagues at Tianjin University in China have developed a living therapeutic approach by filling hydrogel capsules with engineered *E. coli* to produce and release protein drugs as 'in vivo drug factories'. The team demonstrated the concept's potential with two engineered *E. coli* strains: one that produced a protein that promotes insulin secretion to reduce blood sugar levels, and another that manufactured a protein 'nanovaccine' against cancer.

Safely trapping engineered bacteria within insoluble capsules that could still allow the therapeutic proteins to escape was crucial to this approach. To do this, the researchers turned to chitosan, a biocompatible polysaccharide derived from the exoskeleton of shellfish such as shrimp and lobster, which is often used in drug manufacturing. The team added engineered *E. coli* to a chitosan solution, which was then treated with sodium tripolyphosphate, resulting in hydrogel capsules containing the bacteria.

However, although the engineered bacteria could produce therapeutic proteins, the researchers needed a way to get them out of the microbes. This was achieved at the engineering stage by adding a gene that would periodically breakdown the bacteria's cell membrane allowing therapeutic compounds to leak out.

This worked by harnessing the quorum sensing abilities of *E. coli*, by which chemical communication signals between bacteria regulate gene expression. This means that the required gene for breaking the bacterial membranes was only triggered when the bacteria's population reached a certain density. As a safety measure and in order to terminate the therapy, the team engineered a kill system into the bacteria that could be triggered by blue light.

In one experiment, *E. coli* containing capsules were injected under the skin of diabetic rats. Results showed that the therapeutic protein was released smoothy over two weeks and reduced blood glucose levels. Another experiment with the 'nanovaccine'-producing strain revealed that immunity was activated in mice to prevent tumour growth. No inflammation or immune response was apparent upon administration.

'The importance, impact and power of this work is derived from the authors' ability to first develop, and then seamlessly stitch together, several design modules which act in synergy,' comments Yuval Elani a synthetic biologist at Imperial College London, UK. 'The concept of using bacteria as in-situ drug factories is compelling and the authors show some of the first steps needed to achieve this goal.'

'As always with "living" therapeutics, significant regulatory and public perception challenges need to be overcome. But it is clear that the underpinning science is reaching an incredible level of sophistication, which this paper showcases,' says Elani. 'Deployment in real-world applications is only a matter of time.'

C Han et al, Biomaterials, 2022, DOI: 10.1016/j.biomaterials.2022.121619

https://wb.md/3A9fo5Q

Vaccines Prevented Nearly 20M COVID Deaths Globally in First Year: Study

Vaccinations prevented nearly 20 million deaths from COVID-19 in 185 countries and territories in the first 12 months the shots were available, a mathematical modeling study calculates.

Marcia Frellick

The study, co-led by Oliver J. Watson, PhD, and Gregory Barnsley, MSc, with the MRC Centre for Global Infectious Disease Analysis, Imperial College London in London, England, was published online Thursday in *The Lancet Infectious Diseases.*

Researchers estimated that vaccines prevented 14.4 million (95% credible interval [Crl], 13.7 - 15.9) deaths from COVID in the countries and territories between December 8, 2020, and December 8, 2021. However, the estimate rose to 19.8 million (95% Crl, 19.1 - 20.4) deaths from COVID averted when excess deaths were added to the equation.

"[W]e used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19.8 million of 31.4 million) during the first year of COVID-19 vaccination," the authors write.

In 1 Year, Nearly Half the World Had Two Doses

The first dose of a COVID vaccine outside of a clinic was given December 8, 2020, and 1 year later, the researchers estimate, 55.9% of the global population had received at least one dose, 45.5% had two, and 4.3% had a booster. However, coverage has vastly varied in different parts of the world.

For the 83 countries in the study covered by the COVAX commitment to affordable vaccines, an estimated 7.4 million deaths were averted out of a potential 17.9 million (41%).

But in countries that failed to meet the COVAX target of fully vaccinating 20% of the population, researchers estimated an additional 156,900 died from COVID.

Though a small part of the global deaths, these preventable deaths were clustered in 31 African nations, where 132,700 deaths could have been averted if those targets had been met, the researchers report. The authors calculate that a further 599,300 lives could have been saved if the World Health Organization's (WHO) target of vaccinating 40% in each country with two or more doses by the end of 2021 had been met.

In an accompanying editorial, Chad R. Wells, PhD, and Alison P. Galvani, PhD, both with the Yale Center for Infectious Disease Modeling and Analysis in New Haven, Connecticut, write, "Meeting these targets, particularly in low-income countries, is challenged by myriad obstacles that require international support to overcome."

Among them are that several high-income countries got advanced purchasing agreements for the vaccines, while low-income countries couldn't afford those prices, they noted. In the United States, the number of doses purchased before production "was enough to fully vaccinate its entire population three times over," they write. Meanwhile, in Burundi, rollout started 10 months after the US, write Wells and Galvani, who were not part of the study.

First to Calculate Deaths Averted Globally

Previous studies have looked at deaths averted by countries or other geographic areas. This is the first to calculate lives saved directly or indirectly on a global scale.

There are several limitations with the study, the authors acknowledge. The calculations rely on assumptions including proportions of which vaccine types were delivered in each country, how they were delivered, and the precise timing of when new virus variants arrived.

Researchers also assumed that the relationship between age and the proportion of COVID-19 deaths occurring among infected people is

the same for each country. Additionally, countries differ in the ways they report deaths from COVID-19. "Our findings offer the most complete assessment to date of the remarkable global impact that vaccination has had on the COVID-19 pandemic.... However, more could have been done. If the targets set out by the WHO had been achieved, we estimate that roughly 1 in 5 of the estimated lives lost due to COVID-19 in low-income countries could have been prevented," said Watson, in a press release.

The study was funded by the Schmidt Science Fellowship in partnership with the Rhodes Trust; WHO; UK Medical Research Council; Gavi, the Vaccine Alliance; the Bill & Melinda Gates Foundation; National Institute for Health Research; and Community Jameel. Authors Watson and Barnsley and editorialists Wells and Galvani have disclosed no relevant financial relationships.

Lancet Infect Dis. Published online June 23, 2022. Full text, Editorial

https://nyti.ms/3xU6AOr

The Sleep Debt Collector Is Here

Recent studies in humans and mice have shown that late nights and early mornings may cause long lasting damage to your brain.

By Oliver Whang

The sleep debt collectors are coming. They want you to know that there is no such thing as forgiveness, only a shifting expectation of how and when you're going to pay them back. You think of them as you lie in bed at night. How much will they ask for? Are you solvent? You fall asleep, then wake up in a cold sweat an hour later. You fall asleep, then wake up, drifting in and out of consciousness until morning.

As most every human has discovered, a couple nights of bad sleep is often followed by grogginess, difficulty concentrating, irritability, mood swings and sleepiness. For years, it was thought that these effects, accompanied by cognitive impairments like lousy performances on short-term memory tests, could be primarily attributed to a chemical called adenosine, a neurotransmitter that inhibits electrical impulses in the brain. Spikes of adenosine had been consistently observed in sleep-deprived rats and humans.

Adenosine levels can be quickly righted after a few nights of good sleep, however. This gave rise to a scientific consensus that sleep debt could be forgiven with a couple of quality snoozes — as reflected in casual statements like "I'll catch up on sleep" or "I'll be more awake tomorrow."

But a review article published recently in the journal Trends in Neurosciences contends that the folk concept of sleep as something that can be saved up and paid off is bunk. The review, which canvassed the last couple of decades of research on long term neural effects of sleep deprivation in both animals and humans, points to mounting evidence that getting too little sleep most likely leads to long-lasting brain damage and increased risk of neurodegenerative disorders like Alzheimer's disease.

"This is really, really important in setting the stage for what needs to be done in sleep health and sleep science," said Mary Ellen Wells, a sleep scientist at the University of North Carolina, who did not contribute to the review.

It has long been known that intense periods of sleep deprivation are bad for your health. Forced insomnia was used for centuries as punishment and torture. In the first experimental study of sleep deprivation, published in 1894 by the Russian scientist Maria Manasseina, puppies were forced to stay awake through constant stimulation; they died within five days. Examining their bodies afterward, Manasseina observed that "the brain was the site of predilection of the most severe and most irreparable changes." Blood vessels had hemorrhaged and fatty membranes had degenerated. "The total absence of sleep is more fatal for the animals than the total absence of food," Manasseina concluded.

But there are many ways to not get enough sleep. You can go entirely without sleep for an extended period of time — what scientists call acute sleep deprivation. (In 1963, a high school

student managed to stay awake for 264 hours.) You can consistently miss out on sleep — chronic sleep deprivation. You can lie awake, mind racing, or relax, watching television all night. Studies like Manasseina's were seen as extreme to the point of being irrelevant to humans.

Research continued, but "that was where it was sort of pigeonholed," said Fabian Fernandez, a neuroscientist at the University of Arizona who did not contribute to the new review. "When are you ever going to keep an animal or human awake until they die?"

Over the past couple of decades, however, the animal research on sleep deprivation has become more nuanced, precise and, possibly, applicable to humans, according to Dr. Sigrid Veasey, a neuroscientist at the University of Pennsylvania, and Zachary Zamore, a researcher in Dr. Veasey's lab, the authors of the new review.

After surveying past studies of sleep-deprived mice, many of which Dr. Veasey conducted, the researchers found that when the animals were kept awake for just a couple of hours more than usual each day, two key parts of the brain were notably affected: the locus coeruleus, which manages feelings of alertness and arousal, and the hippocampus, which plays an important role in memory formation and learning. These regions, which, in humans, are central to sustaining conscious experience, slowed down the animals' production of antioxidants, which protect neurons from unstable molecules that are constantly being produced, like exhaust fumes, by functioning cells. When antioxidant levels are low, these molecules can build up and attack the brain from inside, breaking down proteins, fats and DNA.

"Wakefulness in the brain, even under normal circumstances, incurs penalties," Dr. Fernandez said. "But when you're awake for too long, then the system gets overloaded. At some point, you can't beat a dead horse. If you're asking your cells to remain active for 30 percent more time each day, cells die."

In the brains of mice, sleep deprivation led to cell death after a few days of sleep restriction — a much lower threshold for brain damage than previously thought. It also caused inflammation in the prefrontal cortex and increased levels of tau and amyloid proteins, which have been linked to neurodegenerative diseases like Alzheimer's and Parkinson's, in the locus coeruleus and hippocampus.

After a full year of regular sleep, the mice that previously had been sleep-deprived still suffered from neural damage and brain inflammation. To Dr. Veasey and Mr. Zamore, this suggested that the effects were long-lasting and perhaps permanent.

Nevertheless, many scientists said that the new research should not be cause for panic. "It is possible that sleep deprivation damages rat and mouse brains, but that doesn't mean that you should get stressed about not getting enough sleep," said Jerome Siegel, a sleep scientist at the University of California, Los Angeles, who did not contribute to the review.

Dr. Siegel noted that neural injury comes in degrees, and that the extent of sleep deprivation's effect on the human brain is still largely unknown. He also expressed concern that undue worry about the long-term effects of sleep deprivation could lead people to try to sleep more, unnecessarily and with medication.

"The simplest message is sleep deprivation is bad, but that doesn't mean that sleep is monotonically good," he said.

There is currently no ethical way to measure the degree and kind of cell damage caused by sleep deprivation in the locus coeruleus and hippocampus of a living human. Instead, longitudinal studies published over the past 15 years have relied on behavioral changes and self-reported sleep data to link chronic bad sleep to dementia, depression, metabolic issues, cardiovascular disease, insufficient

immune response and even lower grade-point averages. These experiments can be difficult to confirm, but, taken together with findings in animal models, they hint that there is some sort of long-term relationship between a lack of sleep and physical and cognitive damage.

"Sleep loss can injure the brain, and if it happens in mice, and it has been shown to happen in other species, then it probably does happen in humans," Dr. Veasey said. "It always begs the question: How much sleep loss would cause injuries? But looking at all of this literature together, of around one week of chronic sleep loss, it really does suggest that you injured the brain to some extent."

If a link can be drawn between mice and humans, it could change the way we think about sleep, which is typically in terms of sleepiness rather than neural damage. There is already a known gap between how people perceive their own cognitive capacities after sleep deprivation and how they actually perform on memory and reaction time tests. People can feel fine while their brains are in turmoil, and they can feel exhausted when their brains are fine. "Perception and reality of your sleep can be very, very different," Dr. Wells said.

That disconnect, in turn, "has actually hampered our asking the right questions," Dr. Veasey added. Her hope is that people and scientists will come to understand sleep more fully. And then, informed, we'll no doubt go into sleep debt anyway.

https://bit.ly/3I4G7Cr

Sudden Cardiac Death: Up to 80% of Athletes Who Die Suddenly Had No Symptoms or Family History of Heart Disease

New recommendations published in the European Journal of Preventive Cardiology describe how to use genetic testing to prevent sudden cardiac death in athletes and enable safe exercise.

Recommendations on how to use gene testing to prevent sudden cardiac death in athletes and enable safe exercise were published on June 16, 2022, in the *European Journal of Preventive Cardiology*, a journal of the European Society of Cardiology (ESC).

"Genetic testing for potentially lethal variants is more accessible than ever before and this document focuses on which athletes should be tested and when," said author Dr. Michael Papadakis of St George's, University of London, UK. "Sportspeople should be counseled on the potential outcomes prior to genetic testing since it could mean exclusion or restricted play."

In most cases, clinical evaluation will dictate the need for preventive therapy such as a defibrillator and the advice on exercise and participation in competitive sports. Dr. Papadakis explained: "Even if a genetic abnormality is found, recommendations on treatment and return to play usually depend on how severe the disease is clinically. Is it causing symptoms such as fainting? Is the heart excessively weak or thick? Can we see many irregularities of the heart rhythm (arrhythmias) and do they get worse during exercise? If the answer is 'yes' to any of these questions then play is likely to be curtailed in some way."

One example is an inherited condition that can cause sudden cardiac death in athletes called hypertrophic cardiomyopathy (HCM), where the heart muscle is abnormally thick. Dr. Papadakis noted: "We used to be very conservative but now our advice is more liberal. Athletes with HCM should undergo comprehensive clinical evaluation to assess their risk of sudden cardiac death and then be offered an exercise prescription.

Genetic testing in this condition does not impact management in most cases. Asymptomatic athletes judged to be at low risk can potentially participate in competitive sports after an informed discussion with their doctor. Others at higher risk may be restricted to moderate intensity exercise. The exercise prescription should be

as specific as possible and outline how often, for how long, at what intensity, and which exercise or sport is safe."

In some cases, however, genetic testing can dictate management. One example is long QT syndrome (LQTS), which is an inherited electrical fault of the heart. Identification of different genetic subtypes (LQT 1-3) can inform the risk of arrhythmias, identify potential triggers to be avoided, and help to target medical therapies and plan exercise advice. Dr. Papadakis said: "For instance, sudden immersion in cold water is more likely to cause life-threatening arrhythmias in LQT type 1 rather than types 2 or 3, so one should be more cautious with swimmers who have the type 1 genetic subtype than runners."

The only situation where genetic testing alone may result in exclusion from play is a heart muscle condition called arrhythmogenic cardiomyopathy (ARVC). "Even if an athlete has no clinical evidence of the disease but has the gene for the condition, he or she should abstain from high intensity and competitive sport," said Dr. Papadakis.

"This is because studies show that people with the gene who exercise at a high level tend to develop the disease earlier in life and tend to develop more severe disease which can cause a life-threatening arrhythmia during sport."

Pre-test genetic counseling should be performed to discuss the implications for athletes and their families. As an example, an athlete's mother is clinically diagnosed with ARVC and has the causal gene, the athlete is then screened and all clinical tests are normal. The athlete has two choices: 1) clinical monitoring, probably annually, to check for signs of disease; or 2) genetic testing.

"The athlete needs to know that if the test is positive that may signal the end of his or her career, even if there is no clinical evidence of disease," said Dr. Papadakis. "On the other hand, if genetic testing is refused the condition may get worse. Post-test counseling is critical given the potential psychosocial, financial, and mental health implications, particularly if the athlete is excluded from play."

For child athletes, genetic counseling in an expert pediatric center with assistance from a child mental health specialist may be needed. Dr. Papadakis pointed out: "The psychological impact of a positive genetic test result may be significant for the child, especially if this leads to sports exclusion even in the absence of clinical disease such as in ARVC."

In children with a clinical diagnosis of an inherited condition, genetic testing may confirm the diagnosis and in some cases help predict the risk of sudden death during sports. For example, having the gene for an electrical fault of the heart called catecholaminergic polymorphic ventricular tachycardia (CPVT) may lead to advice for preventive therapies, such as beta blockers, and dictate decisions about exercise.

"This is important as CPVT predisposes to arrhythmias during exercise and can cause sudden death at a very young age," said Dr. Papadakis. "In contrast, the timing of genetic testing in children with a family history of HCM is controversial since in the absence of clinical signs it rarely causes sudden death in childhood."

Reference: "Indications and utility of cardiac genetic testing in athletes" by Silvia Castelletti, Belinda Gray, Cristina Basso, Elijah R. Behr, Lia Crotti, Perry M. Elliott, Cecilia M. Gonzalez Corcia, Flavio D'Ascenzi, Jodie Ingles, Bart Loeys, Antonis Pantazis, Guido E. Pieles, Johan Saenen, Georgia Sarquella Brugada, Maria Sanz de la Garza, Sanjay Sharma, Emeline M. Van Craenebroek, Arthur Wilde and Michael Papadakis, 16 June 2022, European Journal of Preventive Cardiology.

DOI: 10.1093/eurjpc/zwac080

The scientific statement was prepared by the Sports Cardiology and Exercise Section of the European Association of Preventive Cardiology, the European Heart Rhythm Association, the ESC Working group on myocardial and pericardial diseases, the ESC Council on Cardiovascular Genomics, the European Society of Human Genetics and the Association for European Paediatric and Congenital Cardiology.

https://bit.ly/3AwJbpx

Flu Vaccination Linked to 40% Lower Risk of Alzheimer's Disease

A new study finds that flu vaccination was associated with a 40% reduced risk for Alzheimer's disease over a four-year period.

Over the course of four years, those who received at least one influenza vaccine were 40% less likely than their non-vaccinated peers to acquire Alzheimer's disease, according to a new study from the University of Texas Health Science Center at Houston.

Researchers compared the risk of Alzheimer's disease incidence between patients with and without prior flu vaccination in a large nationwide sample of U.S. adults aged 65 and older. The study was led by first author Avram S. Bukhbinder, MD, a recent alumnus of McGovern Medical School at UTHealth Houston, and senior author Paul. E. Schulz, MD, the Rick McCord Professor in Neurology at McGovern Medical School.

An early online version of the paper detailing the findings is available in advance of its publication in the August 2, 2022, issue of the *Journal of Alzheimer's Disease.*

"We found that flu vaccination in older adults reduces the risk of developing Alzheimer's disease for several years. The strength of this protective effect increased with the number of years that a person received an annual flu vaccine – in other words, the rate of developing Alzheimer's was lowest among those who consistently received the flu vaccine every year," said Bukhbinder, who is still part of Schulz's research team while in his first year of residency with the Division of Child Neurology at Massachusetts General Hospital. "Future research should assess whether flu vaccination is also associated with the rate of symptom progression in patients who already have Alzheimer's dementia."

The research study – which comes two years after UTHealth Houston researchers found a possible link between the flu vaccine and reduced risk of Alzheimer's disease – analyzed a much larger sample than previous research, including 935,887 flu-vaccinated patients and 935,887 non-vaccinated patients.

During four-year follow-up appointments, about 5.1% of flu-vaccinated patients were found to have developed Alzheimer's disease. Meanwhile, 8.5% of non-vaccinated patients had developed Alzheimer's disease during follow-up.

These results underscore the strong protective effect of the flu vaccine against Alzheimer's disease, according to Bukhbinder and Schulz. However, the underlying mechanisms behind this process require further study.

"Since there is evidence that several vaccines may protect from Alzheimer's disease, we are thinking that it isn't a specific effect of the flu vaccine," said Schulz, who is also the Umphrey Family Professor in Neurodegenerative Diseases and director of the Neurocognitive Disorders Center at McGovern Medical School. "Instead, we believe that the immune system is complex, and some alterations, such as pneumonia, may activate it in a way that makes Alzheimer's disease worse. But other things that activate the immune system may do so in a different way — one that protects from Alzheimer's disease. Clearly, we have more to learn about how the immune system worsens or improves outcomes in this disease."

Alzheimer's disease affects more than 6 million people living in the U.S., with the number of affected individuals growing due to the nation's aging population. Past studies have found a decreased risk of dementia associated with prior exposure to various adulthood vaccinations, including those for tetanus, polio, and herpes, in addition to the flu vaccine and others.

Additionally, as more time passes since the introduction of the COVID-19 vaccine and longer follow-up data becomes available, Bukhbinder said it will be worth investigating whether a similar

association exists between COVID-19 vaccination and the risk of Alzheimer's disease.

Reference: "Risk of Alzheimer's Disease Following Influenza Vaccination: A Claims-Based Cohort Study Using Propensity Score Matching" by Avram S. Bukhbinder, Yaobin Ling, Omar Hasan, Xiaoqian Jiang, Yejin Kim, Kamal N. Phelps, Rosemarie E. Schmandt, Albert Amran, Ryan Coburn, Srivathsan Ramesh, Qian Xiao and Paul E. Schulz, 13 June 2022, Journal of Alzheimer s Disease. DOI: 10.3233/JAD-220361

https://bit.ly/3y9kGeY

Research Suggests There's a Big Overlooked Benefit of Having Dyslexia

Brains that find it hard to quickly interpret written words could find it easier to explore their environments for useful clues

Mike McRae

The modern world is stitched together by threads of written language. For those with the reading disorder dyslexia, the endless tangle of words can feel like an obstacle to survival.

Long framed purely as a learning disorder, the neurological condition that makes the decoding of text so difficult could also benefit individuals and their community in a world full of unknowns.

University of Cambridge psychologists Helen Taylor and Martin David Vestergaard reexamined the traditional view of developmental dyslexia as a disadvantage, proposing its neurological characteristics could carry advantages under different circumstances.

Specifically, they suggest brains that find it hard to quickly interpret written words could find it easier to explore their environments for useful clues that improve decision-making.

"The deficit-centered view of dyslexia isn't telling the whole story," says Taylor. "This research proposes a new framework to help us better understand the cognitive strengths of people with dyslexia."

Developmental dyslexia is characterized by difficulties turning the visual format of a written word into a meaningful set of sounds – what they call in the literacy business 'phonemes'.

Thought to affect anywhere between 5 and 20 percent of the population, it generally sets reading ability back by a year or so, interfering with ongoing opportunities to learn as their peers progress. The knock-on effect of this delay in a standardized education system can be profound, reducing confidence and self-esteem and potentially feeding into a slew of social problems.

Reading recruits a complex variety of visual, linguistic, and attentional networks in the brain. With as much as 80 percent of the condition's traits dependent on inherited factors, it's likely something in a person's genes changes how these networks operate as a whole.

Since dyslexia affects such a wide diversity of the world's population, and is so heavily influenced by our genes, it stands to reason evolution favored it in some way.

Against the backdrop of human evolution, the culture of reading and writing is shockingly recent. Our general reliance on effective literacy skills is even more recent, meaning the detrimental influences dyslexia has on individual cognition would have been negligible until recent generations.

Over the decades, psychologists have noted those who present signs of having dyslexia also tend to be better at global abstract and spatial reasoning. They also tend to be more inventive, and are better at predicting outcomes.

This could be a coping strategy in a world that values abilities to pull information from walls of text. Though Taylor and Vestergaard don't think this is the case. "We believe that the areas of difficulty experienced by people with dyslexia result from a cognitive trade-off between exploration of new information and exploitation of existing knowledge, with the upside being an explorative bias that could explain enhanced abilities observed in certain realms like discovery, invention and creativity," says Taylor.

Psychologically speaking, our minds are constrained by a constant tug-of-war called the exploration-exploitation trade-off. To make a decision, we need to be comfortable that the information we have is accurate and likely to result in a predictable outcome.

We could wait until we have better information, at the risk of losing that meal (or worse, becoming lunch ourselves). Act too quickly, however, and we might not learn why our decision is a mistake.

"Striking the balance between exploring for new opportunities and exploiting the benefits of a particular choice is key to adaptation and survival and underpins many of the decisions we make in our daily lives," says Taylor.

In another lifetime, dyslexia wouldn't manifest as an inability to transform scratches into sounds in our heads – it would enhance those rapid decision-making skills that could make a life-or-death difference for our community. The framework reflects a wider trend in pathology that views neurodiversity as heavily contextualized by pressures within a changing environment.

The significance isn't that any one disorder is a superpower in disguise, but that the biggest impediments are factors we have direct control over. Changing how we educate, for instance, or how we discuss an ability purely as a detriment, could be a far more effective 'cure' than any pill or therapy.

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