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How Cranberries Could Improve Memory, Boost Brain Function, and Ward Off Dementia

Adding cranberries to your diet could help improve your memory and brain function, and lower 'bad' cholesterol (LDL) – according to new research from the University of East Anglia (UK).

A new study published on May 19, 2022, highlights the neuroprotective potential of cranberries. The research team studied the benefits of consuming the equivalent of a cup of cranberries a day among people aged 50 to 80 years old. They hope that their findings could have implications for the prevention of neurodegenerative diseases such as dementia.

Lead researcher Dr. David Vauzour, from UEA's Norwich Medical School, said: "Dementia is expected to affect around 152 million people by 2050. There is no known cure, so it is crucial that we seek modifiable lifestyle interventions, such as diet, that could help lessen disease risk and burden.

"Past studies have shown that higher dietary flavonoid intake is associated with slower rates of cognitive decline and dementia. And foods rich in anthocyanins and proanthocyanidins, which give berries their red, blue, or purple color, have been found to improve cognition. "Cranberries are rich in these micronutrients and have been recognized for their antioxidant and anti-inflammatory properties. "We wanted to find out more about how cranberries could help reduce age-related neurodegeneration."

The research team investigated the impact of eating cranberries for 12 weeks on brain function and cholesterol among 60 cognitively healthy participants. Half of the participants consumed freeze-dried cranberry powder, equivalent to a cup or 100 grams of fresh cranberries, daily. The other half consumed a placebo.

The study is one of the first to examine cranberries and their long-term impact on cognition and brain health in humans.

The results showed that consuming cranberries significantly improved the participants' memory of everyday events (visual episodic memory), neural functioning, and delivery of blood to the brain (brain perfusion).

Dr. Vauzour said: "We found that the participants who consumed the cranberry powder showed significantly improved episodic memory performance in combination with improved circulation of essential nutrients such as oxygen and glucose to important parts of the brain that support cognition – specifically memory consolidation and retrieval.

"The cranberry group also exhibited a significant decrease in LDL or 'bad' cholesterol levels, known to contribute to atherosclerosis – the thickening or hardening of the arteries caused by a build-up of plaque in the inner lining of an artery. This supports the idea that cranberries can improve vascular health and may in part contribute to the improvement in brain perfusion and cognition.

"Demonstrating in humans that cranberry supplementation can improve cognitive performance and identifying some of the mechanisms responsible is an important step for this research field.

"The findings of this study are very encouraging, especially considering that a relatively short 12-week cranberry intervention was able to produce significant improvements in memory and neural function," he added. "This establishes an important foundation for future research in the area of cranberries and neurological health."

Reference: "Chronic consumption of Cranberries (Vaccinium macrocarpon) for 12 weeks improves episodic memory and regional brain perfusion in healthy older adults: A randomised, placebo-controlled, parallel-groups study" by Emma Flanagan, Donnie Cameron, Rashed Sobhan, Chloe Wong, Matthew G. Pontifex, Nicole Tosi, Pedro Mena, Daniele Del Rio, Saber Sami, Arjan Narbad, Michael Müller, Michael Hornberger and David Vauzour, 19 May 2022, Frontiers in Nutrition. DOI: 10.3389/fnut.2022.849902

The study was supported by a grant from The Cranberry Institute. It was led by the University of East Anglia in collaboration with researchers at the Leiden University

Medical Center (Netherlands), the University of Parma (Italy), and the Quadram Institute (UK).

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Dust Avalanche on Mars

For decades, scientists have been observing dark landslides on Mars called slope streaks.

By Nancy Atkinson, Universe Today

First seen by the Viking orbiters in the 1970s, every orbiter mission since has observed them, but the mechanism behind the slope streaks has been hotly debated: could they be caused by water activity on the Red Planet, or are they the result of some form of dry mechanics?

These dark streaks, also known as "slope streaks," resulted from dust avalanches on Mars. The HiRISE camera aboard NASA's Mars Reconnaissance Orbiter captured them on December 26, 2017. **Credit: NASA/JPL-Caltech/University of Arizona**

It turns out, that the leading candidate is "dry." But scientists with the Mars Odyssey mission have verified an additional culprit behind the slope streaks: carbon dioxide frost.

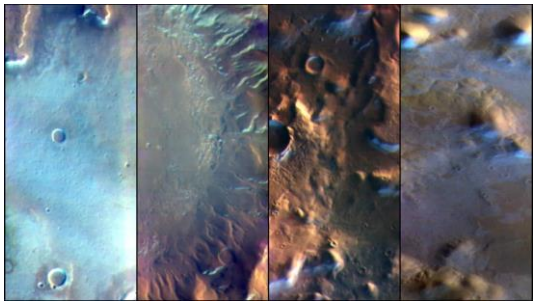
Slope streaks usually appear on the walls of craters or the sides of hills or mountains. Previous studies have determined that the Martian dust and rocks on a slope can be dislodged by something as small as a passing dust devil, or even an impact event in just the right place. These events cause dry dust avalanches on Mars.

Other studies hinted that the sublimation of carbon dioxide frost can dislodge rocks, causing an avalanche, but now images and data from the Odyssey spacecraft have found definitive proof.

Odyssey has been in orbit since 2001, making it the longest-running Mars mission. The spacecraft's current orbit provides a unique look at the planet at 7 a.m. local Mars time, which – like on Earth – is the perfect time to observe frost activity.

Last year, scientists were surprised to see ghostly blue and white colored frost illuminated by the rising Sun in images taken by the visible light camera on board Odyssey. But Odyssey also carries the Thermal Emission Imaging System (THEMIS), and this heat-sensitive camera showed that the frost appeared more widely, including in areas where none was seen by the visible light camera.

"Odyssey's morning orbit produces spectacular pictures," said Sylvain Piqueux of NASA's Jet Propulsion Laboratory in Southern California, who led the paper. "We can see the long shadows of sunrise as they stretch across the surface."



Martian surface frost, made up largely of carbon dioxide, appears blueish-white in these images from the Thermal Emission Imaging System (THEMIS) camera aboard NASA's 2001 Odyssey orbiter. THEMIS takes images in both visible light perceptible to the human eye and heat-sensitive infrared. **Credit: NASA/JPL-Caltech/ASU**

NASA says that because Mars has so little atmosphere (just 1% the density of Earth's), the Sun quickly warms frost that builds up overnight. Instead of melting, dry ice vaporizes into the atmosphere within minutes.

Lucas Lange, an intern at the Jet Propulsion Laboratory working with Piqueux, first noticed the cold-temperature signature from THEMIS of frost in many places where it couldn't be seen on the surface. These temperatures were appearing just tens of microns underground – less than the width of a human hair "below" the surface.

"Our first thought was ice could be buried there," Lange said in a press release. "Dry ice is plentiful near Mars' poles, but we were looking closer to the equator of the planet, where it's generally too

warm for dry ice frost to form."

In those same areas, slope streaks or even larger landslides were observed. The team explains in their paper:

"At sunrise, sublimation-driven winds within the regolith are occasionally strong enough to displace individual dust grains, initiating and sustaining dust avalanches on steep slopes, forming ground features known as slope streaks. This model suggests that the CO2 frost cycle is an active geomorphological agent at all latitudes and not just at high or polar latitudes, and possibly a key factor maintaining mobile dust reservoirs at the surface."

The authors said they were seeing what they called "dirty frost" – dry ice frost mixed with fine grains of dust that obscured it in visible light but not in infrared images. They suspect dirty frost might also explain some of the dark streaks that can stretch 3,300 feet (1,000 meters) or more down Martian slopes. They knew the streaks resulted from, essentially, dust avalanches that slowly reshape mountainsides across the planet, which show up in orbital images.

What if you were there to witness such an avalanche taking place? The scientists said they think these dust avalanches probably look something like a ground-hugging river of dust releasing a trail of fluffy material behind. As the dust travels downhill over several hours, it exposes streaks of darker material underneath.

"Every time we send a mission to Mars, we discover exotic new processes," said Chris Edwards, a paper co-author at Northern Arizona University in Flagstaff. "We don't have anything exactly like a slope streak on Earth. You have to think beyond your experiences on Earth to understand Mars."

Originally published on Universe Today. *For more on this research, see Solving the Mysteries of Invisible Frost and Dust Avalanches on Mars.*

Reference: "Gardening of the Martian Regolith by Diurnal CO2 Frost and the Formation of Slope Streaks" by L. Lange, S. Piqueux, C. S. Edwards, 27 March 2022, Journal of Geophysical Research: Planets. DOI: 10.1029/2021JE006988

https://bit.ly/3ximrXW

Artificial 'inventors' are pushing patent law to its limits

AI programs have played an important role in other patented inventions

1. Toby Walsh* 2. Alexandra George**

It was the veritable search for a needle in a haystack. With drug-resistant bacteria on the rise, researchers at MIT were sifting through a database of more than 100 million molecules to identify a few that might have antibacterial properties. Fortunately, the search proved successful. But it wasn't a human who found the promising molecules. It was a machine learning program.

One compound has been patented under the name Halicin in homage to HAL, the artificial intelligence (AI) in Arthur C Clarke's classic 2001: A Space Odyssey. Halicin works differently from existing antibiotics, disrupting the bacteria's ability to access energy, and researchers hope bacteria may struggle to develop resistance to it.

Halicin might be the first antibiotic discovered using AI, but AI programs have played an important role in other patented inventions from electrical circuits, through meta-materials and drugs, to consumer products such as toothbrushes. As we argue in a recent article in Nature, society urgently needs to consider the impact of AI on the innovation system, particularly on laws regarding intellectual property and patents.

AI patents in court

Can software be an "inventor"? This question has been the focus of some recent high profile court cases about an AI system called DABUS (Device for the Autonomous Bootstrapping of Unified Sentience), created by Stephen Thaler, president and chief executive of US-based AI firm Imagination Engines.

Thaler claims DABUS is the inventor of a new type of food container with a specially patterned surface, as well as a light that

flashing with a special pattern of pulses for attracting attention in emergencies. The inventions are perhaps not very noteworthy, but the attempts to patent them certainly are.

Thaler's international legal team, led by Ryan Abbott from the University of Surrey, has filed applications to patent offices around the world in which DABUS is named as the sole inventor. These cases are likely the first to test whether an AI system can be recognised as an inventor under existing intellectual property laws.

For now, inventors must be human

Patent registration offices have rejected the DABUS patent applications in multiple jurisdictions, including the United Kingdom, United States, the European Patent Office, Germany, South Korea, Taiwan, New Zealand and Australia. The one outlier is South Africa, where a patent has been granted but without substantive examination of the patent application having yet occurred.

In Australia, a challenge against the rejection was initially accepted but overturned on appeal. Thaler has sought "special leave to appeal" the case to the High Court of Australia, though it remains to be seen whether this will be granted.

In Germany, the Federal Patent Court set aside the initial patent refusal, instead accepting a compromise position in which "Stephen L. Thaler, PhD who prompted the artificial intelligence DABUS to create the invention" was listed as the inventor. Meanwhile, DABUS cases continue to be fought in other jurisdictions around the world.

For now at least, it seems courts have largely concluded that, for the purposes of patentability, inventors must be human. Nevertheless, the cases have thrown up a range of important questions we need to answer as AI takes on ever more roles in our lives.

Can an AI invent?

Given the ever-increasing power of AI, it's not a wild leap to suppose that AI will take on a greater role in coming up with inventions. We don't claim that computer-aided design (CAD) software "invents". But such software lacks the increasing autonomy that AI is starting to have.

Can an AI be named as an inventor?

Patent systems are currently premised on a (human) inventor who owns or assigns the rewards coming from the patent.

Who might own the rewards from an AI patent? The programmer? The owner of the computer on which it runs? And what about the owner(s) of the data on which the AI might be trained?

Will AI change invention?

AI might speed up the rate at which inventions are made, potentially overwhelming the patent system. This might widen inequality between the haves who possess AI systems that can invent, and the have-nots who don't.

It might also change the character of invention. Under well-established patent principles, an "inventive step" occurs when an invention is considered "non-obvious" to a "person skilled in the art". But an AI system might be more knowledgeable and skilled than any one person on the planet.

A path forward

In response to these sort of questions, we argue that the patent system must be re-examined to ensure it remains fit for purpose, and that it continues to reward and encourage innovation appropriately.

We suggest society might benefit from a new type of intellectual property designed specifically to deal with AI inventions (which we call "AI-IP").

The principles underpinning patent legislation are more than 500 years old and have evolved to deal with fresh technological changes from genetic sequencing to human-made living organisms. However, the fresh tests presented by AI inventiveness might be so

significant that they push those patent principles to breaking point.

AI presents a watershed challenge that requires us to think once again carefully about how to reward and encourage innovation.

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https://go.nature.com/3NYcfK1

Fix the process that led to Alzheimer's drug fiasco

Reforms to accelerated approval should focus on securing reliable information in the present and clinical evidence for the future.

Jason Karlawish

The morning of 7 June 2021 was a shock. The US Food and Drug Administration (FDA) approved aducanumab, the first treatment targeting β-amyloid, a protein associated with Alzheimer's disease.

Although some celebrated the approval of the first Alzheimer's drug in nearly 20 years, many were aghast at the lack of demonstrated efficacy: ten members of a panel of experts assembled by the FDA had voted against approving it, with the one remaining member voting 'uncertain'. Three quit in protest when the drug was approved.

I'm among many Alzheimer's specialists who agree with the FDA's statistical reviewers and advisory committee that the late-stage clinical trials were contradictory and incomplete. The reasonable next step was another trial, not approval. A well-intended policy to speed drugs to market has gone awry. One year on, it's past time to fix it.

Both the FDA and the US House of Representatives have launched efforts to reform the accelerated-approval process, mostly focused on empowering the FDA to rescind approval after a drug is authorized. That's essential, but in my opinion, the key is to ensure that assessment is transparent and that companies are committed to assessing actual clinical benefit. The FDA must be more careful and forthcoming about the information it collects and the decisions it makes.

The accelerated-approval programme fast-tracks medicines for serious, life-threatening diseases that lack effective treatments. Instead of relying on evidence that a drug extends lives or reduces disease symptoms, US regulators base accelerated approval on a 'surrogate' marker — such as tumour shrinkage — that is thought to be 'reasonably likely' to indicate clinical benefit. The advisory panel that recommended against approving aducanumab was not consulted (or even notified) about the agency using accelerated approval or whether β-amyloid was an appropriate surrogate, although FDA officials had discussed using this strategy with Biogen, the drug company in Cambridge, Massachusetts, that is developing the drug. What is more, the initial 'label' the FDA wrote to advise physicians on prescribing aducanumab was broader than how the drug had been tested. It did not specify that patients should be assessed for disease stage or evidence of amyloid.

One-third of people who take aducanumab experience swelling and bleeding in the brain, which can be fatal. The FDA is supposed to consider patient input on how they feel unproven benefits stack up against potential risks. The FDA approval came shortly after a 'listening session' with patients and caregivers, for which no public report exists. It was organized by the Alzheimer's Association, a non-profit organization in Chicago, Illinois, which has received funds from Biogen and other companies developing similar treatments. (US government inquiries are under way to consider whether there were improprieties in interactions between Biogen and the FDA; both organizations say the process followed was appropriate. It is not unusual for patient-advocacy groups to receive

funds from drug companies working on relevant diseases.)

Launched in the 1990s to speed HIV drugs that reduced viral load to market, accelerated approval's use — and scepticism about it — is growing. From 2005 to 2010, there were about five such approvals per year. In 2020, a dozen new drugs were approved this way. A 2019 assessment found that, of 93 accelerated approvals for cancer treatments from 1992 to 2017, only 19 led to improved overall survival (B. Gyawali *et al. JAMA Intern Med.* **179**, 906–913; 2019). In 2020, the FDA ignored advisers when it approved a drug for Duchenne muscular dystrophy. Companies can charge upwards of US$100,000 a year for drugs without showing whether patients receiving them will live longer.

Under standard approval, the FDA determines whether a drug is safe and effective. The premise of accelerated approval is quite different. Patients accept uncertainty about whether a drug works to get faster access. (In other countries, such access is patient-by-patient; 'compassionate use' regulations allow clinicians to make the case for individual prescriptions). Accelerated approval balances incomplete information with innovation that could serve unmet medical needs. In negotiating this balance, the FDA must avoid being co-opted to serve commercial interests and unwarranted enthusiasm for accruing approvals.

To minimize that risk, the FDA should recast itself as the guardian of information by providing more transparency about its decision-making and ensuring drug companies produce information about clinical benefit. Announcements and labels of drugs receiving accelerated approval should lead with a plain statement that clinical benefit is not proven. (The label of aducanumab states: "Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).") But drug companies have little incentive to complete those confirmatory trials.

The FDA needs to be open with its advisory committees about plans for accelerated approval, and to thoroughly explain any decisions that go against recommendations by advisory committees. The process shouldn't be a backup for the failure to gain a supportive vote on standard approval. All accelerated approvals must be accompanied by a plan for a confirmatory trial that will assess whether the change in the surrogate marker translates into clinical value. That is how we can better ensure that treatments will lead to a longer or more fulfilling life.

Nature ***606****, 9 (2022) doi: https://doi.org/10.1038/d41586-022-01507-3*

Competing Interests

J.K. has been a site investigator on clinical trials sponsored by Biogen and Lilly; and is a member of AARP's Global Council on Brain Health.

https://wb.md/3NmG5ry

Coffee Drinkers — Even Those With a Sweet Tooth — Live Longer

Moderate consumption of coffee, with or without sugar, is associated with a reduced risk of death, according to prospective cohort study.

Will Pass

Among more than 170,000 people in the United Kingdom, those who drank about two to four cups of coffee a day, with or without sugar, had a lower rate of death than those who didn't drink coffee, reported lead author Dan Liu, MD, of the department of epidemiology at Southern Medical University, Guangzhou, China.

"Previous observational studies have suggested an association between coffee intake and reduced risk for death, but they did not distinguish between coffee consumed with sugar or artificial sweeteners and coffee consumed without," Liu, who is also of the department of public health and preventive medicine, Jinan University, Guangzhou, China, and colleagues wrote in Annals of Internal Medicine.

To learn more, the investigators turned to the UK Biobank, which recruited approximately half a million participants in the United

Kingdom between 2006 and 2010 to undergo a variety of questionnaires, interviews, physical measurements, and medical tests

Out of this group, 171,616 participants completed at least one dietary questionnaire and met the criteria for the present study, including lack of cancer or cardiovascular disease upon enrollment.

Results from these questionnaires showed that 55.4% of participants drank coffee without any sweetener, 14.3% drank coffee with sugar, 6.1% drank coffee with artificial sweetener, and 24.2% did not drink coffee at all. Coffee drinkers were further sorted into groups based on how many cups of coffee they drank per day.

Coffee Drinkers Were Significantly Less Likely To Die From Any Cause

Over the course of about 7 years, 3,177 of the participants died, including 1,725 who died from cancer and 628 who died from cardiovascular disease.

After accounting for other factors that might impact risk of death, like lifestyle choices, the investigators found that coffee drinkers were significantly less likely to die from any cause, cardiovascular disease, or cancer, than those who didn't drink coffee at all. This benefit was observed across types of coffee, including ground, instant, and decaffeinated varieties.

The protective effects of coffee were most apparent in people who drank about two to four cups a day, among whom death was about 30% less likely, regardless of whether they added sugar to their coffee or not. Individuals who drank coffee with artificial sweetener did not live significantly longer than those who drank no coffee at all; however, the investigators suggested that this result may have been skewed by higher rates of negative health factors, such as obesity and hypertension, in the artificial sweetener group.

Liu and colleagues noted that their findings align with previous studies linking coffee consumption with survival. Like those other studies, the present data revealed a "U-shaped" benefit curve, in which moderate coffee consumption was associated with longer life, whereas low or no consumption and high consumption were not.

Experts Caution Against Drinking Sweetened Beverages Despite New Findings

Although the present findings suggested that adding sugar did not eliminate the health benefits of coffee, Liu and colleagues still cautioned against sweetened beverages, citing widely known associations between sugar consumption and poor health.

In an accompanying editorial, Christina C. Wee, MD, MPH, deputy editor of Annals of Internal Medicine, pointed out a key detail from the data: the amount of sugar added to coffee in the U.K. study may be dwarfed by the amount consumed by some coffee drinkers across the pond.

"The average dose of added sugar per cup of sweetened coffee [in the study] was only a little over a teaspoon, or about 4 grams," Wee wrote. "This is a far cry from the 15 grams of sugar in an 8-ounce cup of caramel macchiato at a popular U.S. coffee chain."

Still, Wee, an associate professor of medicine at Harvard Medical School, Boston, and director of the obesity research program in the division of general medicine at Beth Israel Deaconess Medical Center, Boston, suggested that your typical coffee drinker can feel safe in their daily habit.

"The evidence does not suggest a need for most coffee drinkers – particularly those who drink it with no or modest amounts of sugar – to eliminate coffee," she wrote. "So drink up – but it would be prudent to avoid too many caramel macchiatos while more evidence brews."

Estefanía Toledo, MD, MPH, PhD, of the department of preventive medicine and public health at the University of Navarra, Pamplona, Spain, offered a similar takeaway.

"For those who enjoy drinking coffee, are not pregnant or lactating, and do not have special health conditions, coffee consumption could be considered part of a healthy lifestyle," Toledo said in a written comment. "I would recommend adding as little sugar as possible to coffee until more evidence has been accrued."

Toledo, who previously published a study showing a link between coffee and extended survival, noted that moderate coffee consumption has "repeatedly" been associated with lower rates of "several chronic diseases" and death, but there still isn't enough evidence to recommend coffee for those who don't already drink it.

More long-term research is needed, Toledo said, ideally with studies comparing changes in coffee consumption and health outcomes over time. These may not be forthcoming, however, as such trials are "not easy and feasible to conduct."

David Kao, MD, assistant professor of medicine-cardiology and medical director of the school of medicine at the University of Colorado at Denver, Aurora, said that the study conducted by Liu and colleagues is a "very well-executed analysis" that strengthens our confidence in the safety of long-term coffee consumption, even for patients with heart disease.

Kao, who recently published an analysis showing that higher coffee intake is associated with a lower risk of heart failure, refrained from advising anyone to up their coffee quota. "I remain cautious about stating too strongly that people should increase coffee intake purely to improve survival," Kao said in a written comment. "That said, it does not appear harmful to increase it some, until you drink consistently more than six to seven cups per day."

The study was supported by the National Natural Science Foundation of China, the Young Elite Scientist Sponsorship Program by CAST, the Guangdong Basic and Applied Basic Research Foundation, and others. Toledo and Kao disclosed no relevant conflicts of interest.

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https://bbc.in/3MqtPYj

Transplant success: Liver survives out of body for days

Surgeons say they have successfully transplanted a donor liver kept warm and alive outside the body for three days, using a special machine.

By Michelle Roberts Digital health editor

The normothermic perfusion method gives the organ a continuous blood supply, which experts say is better than the traditional way of putting it on ice. It might even be possible to stretch viability to 10 days, the Swiss team told the journal Nature Biotechnology.

The patient who received the warm liver is doing well a year on.

Experts hope the advance could help reduce the number of donor organs that have to be discarded, since preserving tissues and organs at low temperatures can cause substantial cell damage.

Extending how long a donor liver can be kept would allow more flexibility in the timing of the transplant operation too. Cooled livers only keep for up to 12 hours. The machine can also deliver drugs or other nutrients, as well as blood, to make sure the organ is in the best condition ahead of the transplant.

The man who received the liver - which was plumbed into the perfusion machine for 68 hours - needed a new one because he had cancer. His transplant operation was done four days after the donor organ was removed from its original owner - a 29-year-old woman who died in May 2021. The man was able to go home from hospital 12 days after the surgery.

His doctors say more research - with more patients and longer observation periods - is still needed, but the results so far look very promising. "We think that this first transplantation success...can open new horizons in the treatment of many liver disorders," they told Nature Biotechnology journal. Some of the UK's seven liver transplant units have also started using the same type of technology, and experts at Oxford University plan to assess the outcomes as

part of a trial called the PLUS study.

https://bit.ly/3910mnL

4 hostile alien civilizations may lurk in the Milky Way, a new study suggests

But Earth is 100 times more likely to be destroyed by an asteroid than invaded by aliens.

By Brandon Specktor

The Milky Way is home to millions of potentially habitable planets — and approximately four of them may harbor evil alien civilizations that would invade Earth if they could, new research posted to the preprint database arXiv *(opens in new tab)* suggests.

Artist's impression of an alien spaceship near Earth **(Image credit: Devrimb via Getty IMages)**

The new paper, which has not yet been peer-reviewed, poses a peculiar question: What are the odds that humans could one day contact a hostile alien civilization that's capable of invading our planet?

To answer this, sole study author Alberto Caballero — a doctoral student in conflict resolution at the University of Vigo in Spain — began by looking back at human history before looking out to the stars.

"This paper attempts to provide an estimation of the prevalence of hostile extraterrestrial civilizations through an extrapolation of the probability that we, as the human civilization, would attack or invade an inhabited exoplanet," Caballero wrote in the study.

(Caballero is not an astrophysicist, but he has published a study on the infamous Wow! signal — a potential sign of extraterrestrial life — in the peer-reviewed International Journal of Astrobiology *(opens in new tab)*.)

To reach his estimation, Caballero first counted the number of countries that invaded other countries between 1915 and 2022. He found that a total of 51 of the world's 195 nations had launched some sort of invasion during that period. (The U.S. sat at the top of the list, with 14 invasions tallied in that time.) Then, he weighted each country's probability of launching an invasion based on that country's percentage of the global military expenditure. (Again, the U.S. came top with 38% of global military spending.)

From there, Caballero added each country's individual probability of instigating an invasion, then divided the sum by the total number of countries on Earth, ending up with what he describes as "the current human probability of invasion of an extraterrestrial civilization."

According to this model, the current odds of humans invading another inhabited planet are 0.028%. However, Caballero wrote, that probability refers to the current state of human civilization — and humans aren't currently capable of interstellar travel. If current rates of technological advancement hold, then interstellar travel wouldn't be possible for another 259 years, Caballero calculated using the Kardashev scale *(opens in new tab)* — a system that categorizes how advanced a civilization is based on its energy expenditure.

Assuming the frequency of human invasions continues to decline over that time at the same rate that invasions have declined over the last 50 years (an average of minus 1.15% per year, according to Caballero's paper), then the human race has a 0.0014% probability of invading another planet when we potentially become an interstellar , or Type 1, civilization 259 years from now.

That may sound like very slim odds — and it is, until you start multiplying it by the millions of potentially habitable planets in the Milky Way. For his final calculation, Caballero turned to a 2012 paper published in the journal Mathematical SETI *(opens in new tab)*, in

which researchers predicted that as many as 15,785 alien civilizations could theoretically share the galaxy with humans.

Caballero concluded that less than one of the Type 1 civilizations — 0.22, to be precise — would be hostile toward humans who make contact. However, the number of malicious neighbors increases to 4.42 when accounting for civilizations that, like modern humans, are not yet capable of interstellar travel, Caballero told Vice News *(opens in new tab)*.

"I don't mention the 4.42 civilizations in my paper because 1) we don't know whether all the civilizations in the galaxy are like us… and 2) a civilization like us would probably not pose a threat to another one since we don't have the technology to travel to their planet," Caballero told Vice. Four hostile alien powers doesn't seem like a lot to worry about. Furthermore, the probability that humans might contact one of these malicious civilizations — and then be invaded by them — is vanishingly small, Caballero added.

"The probability of extraterrestrial invasion by a civilization whose planet we message is… around two orders of magnitude lower than the probability of a planet-killer asteroid collision," he wrote in his paper — adding that planet-killing asteroids, like the one that doomed the dinosaurs, are 1-in-100-million-year events.

Though Caballero's study poses an interesting thought experiment, the author admits his model has limitations. The invasion probability is based on a very narrow slice of human history, and it makes many assumptions about the future development of our species. The model also presumes that alien intelligence will have brain compositions, values and senses of empathy similar to those of humans, which may simply not be the case, Caballero told Vice.

"I did the paper based only on life as we know it," he said. "We don't know the mind of extraterrestrials."

And by the looks of things, it'll be at least a few hundred more years until we do.

https://bit.ly/3Nm9XUV

Staying 'Conscious' Under Anesthesia May Be Much More Common Than We Realized

In rare cases, some people are responsive to their surrounds under general anesthesia

Clare Watson

General anesthesia is a marvelous thing, knocking us out and blocking our sense of pain in a matter of seconds before surgery.

But in rare cases, some people are responsive to their surrounds under general anesthesia, yet they cannot remember what happened afterwards.

This is called 'connected consciousness', and now the largest study of its kind to date on the phenomenon suggests that it's more common than first thought, affecting 1 in 10 young adults, and women more than men. The findings highlight the need to better understand how different people respond to anesthetic drugs, the researchers say. Even after 170 years of use, we still don't have a firm grasp on how general anesthesia works – and now age and sex seem to be another factor in the mix.

"There is an urgent need for further research on the biological differences, particularly sex, that may influence sensitivity to anesthetic medication," says study author Robert Sanders, an anesthetist and neuroscientist at the University of Sydney in Australia. If the results of the new study can be replicated, it might put us one step closer to understanding who is more likely to experience 'connected consciousness' and how anesthetists can reduce the odds of it happening.

Past estimates had suggested around 5 percent of people going under general anesthesia experienced 'connected consciousness'. But Sanders' team had suspected, based on other research, that it might have been more common in younger people.

The results of the new study suggest that a larger than expected

amount of young adults are still responsive under general anesthesia, before surgery begins.

Roughly one in 10 of the 338 young adults in the study, aged between 18 and 40 years, responded to commands asking them to squeeze the researchers' hand once if they understood, and twice if they were in pain while under general anesthesia. An hour after waking up, participants were asked to recall 16 words that they had heard under anesthesia, to see what they remembered of the experience. Women were between two to three times more likely than men to experience 'connected consciousness', the study found.

The odds of 'connected consciousness' were also lower if a continuous level of anesthesia was maintained in the minutes after anesthesia was induced and before intubation, the point where a plastic tube is inserted down a person's windpipe to maintain airflow and deliver anesthetic drugs during surgery.

It's important to note that 'connected consciousness' is different to the unintended awareness that an even smaller fraction of people – just 0.1 percent – experience during anesthesia, after which they can recall specific details about the procedure.

'Connected' in this instance refers to parts of the brain still being capable of processing sensations from their environment, half-paying attention but not fully aware.

"Patients expect to be unconscious under anesthesia, and not be in pain, and this demonstrates why research into anesthesia is so important," Sanders says.

Around 13 percent of women in the study responded to commands under anesthesia, compared to only 6 percent of men, even though they received the same weight-adjusted amounts of propofol, a drug used to start and maintain general anesthesia.

"Differences in dosing, if present, were small and do not explain why females experienced connected consciousness more often than males," write the researchers in their paper.

About half of the 37 people who responded to commands also indicated they were in pain, which would have been swiftly rectified by adjusting the dose of anesthetic drugs. One person also clearly recalled the experience of surgery after the procedure ended.

"In our opinion, this is a higher level of consciousness than patients (or their anesthesiologists) anticipate during general anesthesia," Sanders and colleagues write in the paper.

While it may feel like anesthetics knock us out with a slug-punch of drugs that hit before you can count to ten, being in a state of anesthesia only requires a person to be disconnected from their environment, not necessarily involving a full loss of consciousness.

However, that clearly seems to be very fine line for anesthetists to tread, and one which appears to vary greatly from person to person.

At least now, anesthetists might have a better understanding of how maintaining continuous anesthesia in the first few minutes (which is already standard practice in many countries) may help reduce the incidence of 'connected consciousness'.

"It is very important to note that patients did not remember responding to the commands," says Sanders, noting that overall, general anesthetics are very safe. "It was also reassuring to see that if anesthetic drugs are administered continuously in the time period between induction of anesthesia and intubation, the risk of connected consciousness was greatly reduced," he says.

The study was published in the *British Journal of Anaesthesia*.

https://bbc.in/3xjr6sE

Oesophageal cancer: Andy Goram diagnosis brings 'don't ignore symptoms' warning

Former Rangers and Scotland goalkeeper Andy Goram has revealed he has oesophageal cancer and been given about six months to live.

Goram, 58, told the Daily Record he turned down chemotherapy as it would only extend his life by three months.

Two people who have been treated for the disease, sometimes known as a "silent killer", have spoken to BBC Scotland about their experience.

'It felt like I had wind'

Paul Sinclair, from Kirkcaldy in Fife, started to experience what "felt like wind at the bottom of my rib-cage" in September 2020 and had a sensation that he had "eaten too much in one mouthful".

"I ignored it like everyone else does," he told BBC Radio's Good Morning Scotland. "It just felt like I had wind. I was eating fine, I had no pain. "It was just an annoying niggle at the bottom of my rib-cage. It went on for about a week-and-a-half and then I thought 'I'm going to see someone about this'. "I went to the doctor and he sent me straight for an endoscopy. That confirmed I had a tumour at the top of my stomach."

His experience is similar to that of Goram, who said he ignored heartburn symptoms after being unable to book a face-to-face GP appointment. Paul went through four sessions of chemotherapy over an eight-week period before a six-week break. Then he had an 11-hour operation, which also included the removal of his spleen, before another six-week break prior to more "very aggressive chemotherapy".

"I was very ill with both sessions of chemo," he said. "The second one was worse because you are already weak after the operation.

"As you recover you have to start learning to eat again, how to chew your food properly, have small portions and a lot of meals throughout the day."

Three years later, he is able to get back to the gym to do light training - but things will never be "totally normal". "You have just got to stay positive and be thankful for every day you wake up," he said. "The important thing is it wasn't particularly major symptoms I had, but it is really important not to ignore it and to get it checked."

What are the symptoms of oesophageal cancer?

The oesophagus is the long tube that carries food from the throat to the stomach. The main symptoms of the cancer are:

- ***having problems swallowing (dysphagia)***
- ***feeling or being sick***
- ***heartburn or acid reflux***
- ***symptoms of indigestion, such as burping a lot***

Others include:

- ***a cough that is not getting better***
- ***a hoarse voice***
- ***loss of appetite or losing weight without trying to***
- ***feeling tired or having no energy***
- ***pain in your throat or the middle of your chest, especially when swallowing***

Source: **www.nhs.uk**

'You're never fully recovered'

Linda Moffat, from Auchterarder, Perth and Kinross, considered herself a fit 48-year-old who rode horses every day until December 2014.

Then she "started to feel my food go down - it was just kind of sticking," she recalled. "The pain progressed and the food was getting stuck. "I was having to be sick to un-block it. I just thought it was an ulcer. We just thought 'Ach, it is going to be nothing'."

After a while she "plucked up the courage to speak to the doctor" and was put on antacids. But the symptoms continued and she was sent for an endoscopy.

That revealed a "very advanced tumour" at the junction of her oesophagus and the start of a "very long, difficult journey".

"It's a very aggressive cancer and really brutal surgery - eight hours in theatre," she said. "You've got chemotherapy before and after. You have to learn to eat again.

"You have lots of problems with sickness and diarrhoea and pain. I

don't think you're ever fully recovered. "I am very lucky. My cancer was very advanced and I was only given a 20% chance of survival.
"But I'm nearly seven years on now and I'm very happy to be alive and very grateful to everyone who helped me to be here."
Ms Moffat said reading about Goram's diagnosis and others suffering with oesophageal cancer was "absolutely heart-breaking".
"It's often called the silent killer because the symptoms vary so much," she added. "You just hope and pray people get to the doctor early enough."

'Earlier the better'

Caroline Geraghty, a specialist nurse at Cancer Research UK, said the risk of oesophageal cancer rises with "the usual things" such as smoking, alcohol and weight gain, as well as chewing tobacco.
"But having an increased risk doesn't mean you will definitely go on and get cancer," she pointed out. "For most people, we don't know why they get oesophageal cancer."
Ms Geraghty urged anyone who thinks they may have symptoms to go to their GP "to be on the safe side". "As we know, the earlier you get to a cancer, the better the chances you have," she added.
Statistics from Public Health Scotland released on Tuesday showed 155,405 NHS patients were waiting to be seen for the eight key diagnostic tests on 31 March.
Numbers have gone up 10% in the first three months of the year and are 75% higher than the average before the pandemic.
David Ferguson, of Cancer Research UK in Scotland, said it was "unacceptable" that people were waiting too long for tests to determine whether they have cancer.
Ms Geraghty added that for the majority of patients, their symptoms will not be cancer-related. "You can understand why some GPs won't go straight to endoscopy to investigate - some people just need antacids," she said. "But there will be some individuals who maybe need to be sent for investigation quicker."

https://bit.ly/3thCset

Scientists May Have Found a Way to Inject Oxygen Into The Bloodstream Intravenously

Oxygen may now be able to be added directly, and the patient's blood can stay where it is

David Nield

There are many illnesses and injuries, including COVID-19, where the body struggles to get the amount of oxygen into the lungs necessary for survival. In severe cases, patients are put on a ventilator, but these machines are often scarce and can cause problems of their own, including infection and injury to the lungs.
Scientists may have now found a breakthrough, and it's one that that could significantly impact how ventilators are used.
In addition to traditional mechanical ventilation, there's another technique called Extracorporeal Membrane Oxygenation (ECMO), where blood is carried outside the body so that oxygen can be added and carbon dioxide can be removed.
Thanks to a new discovery, oxygen may now be able to be added directly, and the patient's blood can stay where it is. With a condition like refractory hypoxemia, which can be brought on by being on a ventilator, having this approach available could save lives. "If successful, the described technology may help to avoid or decrease the incidence of ventilator-related lung injury from refractory hypoxemia," the researchers write in their new paper.
The new technique works by channeling an oxygen-laden liquid through a series of nozzles that get smaller and smaller. By the time the process is finished, the bubbles are smaller than red blood cells – and that means they can be directly injected into the bloodstream without blocking blood vessels.
A lipid membrane is used to coat the bubbles before they're added to the blood, which prevents toxicity and stops the bubbles from clumping together. After the solution is injected, the membrane

dissolves and the oxygen is released.

In experiments on donated human blood, blood oxygen saturation levels could be lifted from 15 percent to over 95 percent within just a few minutes. In live rats, the process was shown to increase saturation from 20 percent to 50 percent. "Importantly, these devices allow us to control the dosage of oxygen delivered and the volume of fluid administered, both of which are critical parameters in the management of critically ill patients," the researchers write.

The researchers are keen to emphasize that this is a "proof of concept" for now and it has yet to be tested on people. However, they seem to have found a potentially effective formula with the size of the bubbles and the coating used.

Getting oxygen into the body like this is a difficult balancing act, because complications can quickly ensue if too much or too little is added, or it's added in the wrong way. The researchers now want to test their technology on larger animals before moving on to human trials. While it's not able to completely replace ventilators or ECMO life support in its current form, it's hoped the new device may be able to better prepare the body to be put on these machines, or keep the lungs going until a ventilator becomes available.

"It is worth mentioning that our device could potentially be integrated into existing ventilators, allowing for seamless integration into existing clinical workflows," the researchers write.

The research has been published in *PNAS*.

https://bit.ly/3x45nnv

Ancestral Bacteria May Have Invaded Early Eukaryotic Cells

The discovery that a group of cell-infecting bacteria lived roughly 2 billion years ago stirs a longstanding controversy around which came first: phagocytosis or mitochondria.

Clare Watson

The ability of one cell to ingest another, called phagocytosis, was a crucial step in the evolution of eukaryotic cells and may explain how membrane-bound organelles first came to be. But some researchers argue that cells would have needed to evolve mitochondria to fuel phagocytosis. Lionel Guy, a microbiologist at Uppsala University in Sweden, didn't intend to wade into this debate, he says, when he began profiling an understudied group of bacteria called *Legionellales* whose members live inside cells and include the bacterium that causes Legionnaire's disease.

Guy and his colleagues compared a collection of recently published *Legionellales* genomes isolated from environmental samples and noticed that members of the group shared the same molecular tools that protect against being digested, suggesting that the group's common ancestor had adapted to life inside bacteria-eating eukaryotic cells. "That shows phagocytosis already existed at the time of the first *Legionellales*," says Guy.

The team used molecular clock techniques to date the group's last common ancestor to 1.9 billion years ago, plus or minus a few hundred million years—Guy notes that "there is a lot of uncertainty" because their age estimate hinges on a single biomarker. Still, he says, the timing suggests that early eukaryotes could engulf bacteria before they had mitochondria, whose origins have been estimated at between 1.2 billion and 2 billion years ago.

University of Queensland microbiologist Phil Hugenholtz, who was not involved in the work, says that reconstructing bacterial evolution is notoriously difficult because bacteria don't leave fossils, only chemical traces, and because researchers have documented only a tiny fraction of microbial life. These findings, while interesting, do not rule out the possibility that mitochondria evolved before cells could phagocytose, he says, noting that "there's quite a bit of spread in those estimated dates."

E. Hugoson et al. "Host-adaptation in Legionellales is 1.9 Ga, coincident with eukaryogenesis," Mol Biol Evol, 39:msac037, 2022.

https://bit.ly/38TDHK0

Better than CRISPR? Another way to fix gene problems may be safer and more versatile

Epigenome editing flips genetic on-off switches in mouse studies

By Jocelyn Kaiser

Tools such as CRISPR that snip DNA to alter its sequence are moving tantalizingly close to the clinic as treatment for some genetic diseases. But away from the limelight, researchers are increasingly excited about an alternative that leaves a DNA sequence unchanged. These molecular tools target the epigenome, the chemical tags adorning DNA and its surrounding proteins that govern a gene's expression and how it ultimately behaves.

A flurry of studies in the past few years in mice suggests epigenome editing is a potentially safer, more flexible way to turn genes on or off than editing DNA. In one example described last month at a gene therapy meeting in Washington, D.C., an Italian team dialed down expression of a gene in mice to lower the animals' cholesterol levels for months. Other groups are exploring epigenome editing to treat everything from cancer to pain to Huntington disease, a fatal brain disorder.

Unlike DNA editing, where the changes are permanent and can include unintended results, epigenomic edits might be less likely to cause harmful offtarget effects and can be reversed. They can also be more subtle, slightly ramping up or down a gene's activity, rather than blasting it at full force or erasing it altogether. "What's exciting is that there are so many different things you can do with the technology," says longtime epigenome editing researcher Charles Gersbach at Duke University.

Adding or removing the chemical tags on DNA and the histone proteins it coils around (see illustration, p. 1035) can either muffle a gene, or expose its sequence of DNA bases to other proteins that turn it on. Some cancer drugs strip off or add these chemical tags, but as disease fighters they have had limited success. One problem is that the drugs are unfocused, acting on many genes at once, not just cancer related ones, which means they come with toxic side effects.

But epigenome editing can be made precise by harnessing the same enzymes that cells use to turn their genes on and off. Researchers attach key components of those proteins to a gene-editing protein, such as a "dead" version of CRISPR's Cas9 protein, capable of homing in on a specific place in the genome but unable to cut DNA. Their effects can vary: One editor might remove tags from histones to switch a gene on, whereas another might add methyl groups to DNA to repress it.

Two decades ago, the biotech company Sangamo Therapeutics designed an epigenome editor using this method that turned up a gene called *VEGF*, which helps promote blood vessel growth, in hopes of restoring blood flow in people with neuropathy from diabetes. The company injected DNA encoding the editor into the leg muscles of about 70 patients in a clinical trial, but the treatment didn't work very well. "We couldn't deliver it efficiently" to muscle tissue, says Fyodor Urnov, a former Sangamo scientist now at the Innovative Genomics Institute at the University of California (UC), Berkeley.

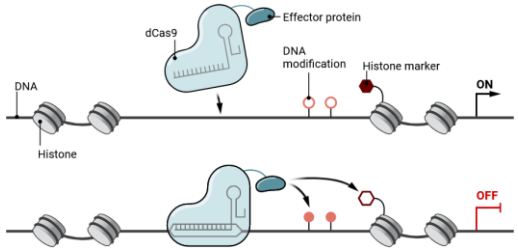
So the company turned to an adeno-associated virus (AAV), a harmless virus long used in gene therapy to efficiently deliver DNA to cells. The cell's protein making machinery, the thinking went, would use DNA encoding an epigenome editor to make a steady supply of it. This strategy is looking more hopeful: In the past 3 years, Sangamo has reported that in mice, it can tamp down brain levels of tau, a protein involved in Alzheimer's disease, as well as levels of the protein that causes Huntington disease.

Other teams working with mice are using the AAV delivery approach to ramp up abnormally low levels of a protein to treat an

inherited form of obesity, as well as Dravet syndrome, a severe form of epilepsy. Last year, a group used epigenome editing to turn off a gene involved in pain perception for months, a potential alternative to opioid drugs. Another team recently turned on a gene with an epigenome editor delivered by a different virus than AAV. They injected it into young rats exposed to alcohol; the alcohol was muffling the activity of a gene, which in turn left the animals anxious and prone to drink. The epigenome editor reawakened the gene and relieved the symptoms, the team reported in May in *Science Advances*.

The AAVs being tested by many groups are expensive, and these DNA carriers, along with the foreign proteins they encode, can trigger an immune response. Another drawback is that the loop of DNA encoding the epigenome editor is gradually lost in cells when they divide.

Taking control



In epigenome editing, a gene-editing tool such as a "dead" version of CRISPR's Cas9 protein homes in on a gene. Next, an attached "effector" protein adds or removes chemical tags on DNA and histone proteins it coils around, turning gene activity up or down. **N. DESAI/*SCIENCE***

Last month at the annual meeting of the American Society of Gene and Cell Therapy in Washington, D.C., gene-editing experts offered an alternative to avoid the downsides of AAVs. A key step for the group, led by Angelo Lombardo at the San Raffaele Telethon Institute for Gene Therapy, came in 2016, when he, Luigi Naldini, and others reported in *Cell* that adding a cocktail of three different epigenome editors to cells in a petri dish repressed gene expression and that this endured as the cells divided.

This meant that instead of relying on AAVs to ferry in DNA for their epigenome editors—and force unending expression—they could use lipid nanoparticles, a kind of fat bubble, to carry its blueprint as messenger RNA (mRNA). In this way, cells make the protein for only a brief time, which is less likely to trigger an immune response or make epigenome edits in unintended places. Such nanoparticles are widely considered safe, especially after having been injected into hundreds of millions of people in the past 2 years to deliver mRNA for COVID-19 vaccines.

It took several more years for the Italian team to convert its lab study into success in an animal. At the genomics meeting, postdoc Martino Cappelluti from Lombardo's lab detailed how the team injected mice with fat particles carrying mRNA encoding epigenome editors designed to silence a live gene, *PCSK9*, that influences cholesterol levels. The strategy worked, with one injection suppressing blood levels of the PCSK9 protein by 50% and slashing low-density lipoprotein, or "bad," cholesterol for at least 180 days.

"I see it as a formidable advance," says Urnov, who hopes the lipid nanoparticle approach will soon be extended to other disease genes. "The key thing here is that you don't have to have continued expression of the epigenome editor," says Jonathan Weissman of the Whitehead Institute. Weissman co-led work reported last year in *Cell* on improved CRISPR-based epigenome editors that make long-lasting changes.

Researchers say epigenome editing could be especially useful for controlling more than one gene, which is harder to do safely with DNA editing. It could treat diseases like Dravet syndrome where a person makes some of a needed protein but not enough, because like a light dimmer, the strategy can modulate gene expression without turning it on or off entirely. Several new companies are hoping to commercialize treatments using epigenome editors. (Gersbach and Urnov founded one, Tune Therapeutics; Lombardo,

Naldini, and Weissman are among the founders of another, Chroma Medicine.)

Despite the excitement, researchers caution that it will take time for epigenome editing to have a broad impact. The editors don't always work as advertised on some genes, says UC Davis epigenetics researcher David Segal. This may be partly because, as epigenetics researcher John Stamatoyannopoulos of the University of Washington, Seattle, worries, researchers don't understand exactly what the editors do once they infiltrate cells. "It's a black box," he says.

Still, Stamatoyannopoulos agrees that epigenome editing has "tremendous promise." Now, researchers need to fine-tune their epigenome editors, try them on other disease genes and tissues, and test them in larger animals for safety before moving to people.

doi: 10.1126/science.add2887

https://bit.ly/3GPy0Jw

Monkeypox is a new global threat. African scientists know what the world is up against

Cases in West and Central Africa have been on the rise for decades

By Jon Cohen

As monkeypox stokes here-we-go-again fears in a pandemic-weary world, some researchers in Africa are having their own sense of déjà vu. Another neglected tropical disease of the poor gets attention only after it starts to infect people in wealthy countries. "It's as if your neighbor's house is burning and you just close your window and say it's fine," says Yap Boum, an epidemiologist in Cameroon who works with both the health ministry and Doctors Without Borders.

Now, the fire is spreading. The global outbreak of monkeypox, which causes smallpoxlike skin lesions but is not usually fatal, surfaced on 7 May in the United Kingdom. More than 700 suspected and confirmed cases had been reported as of 31 May, from every continent other than Antarctica. It is the largest ever outbreak outside of Africa and is concentrated among men who have sex with men, a phenomenon never seen before. Public health officials and scientists are scrambling to understand how the virus spreads and how to stop it—and they are paying new attention to Africa's long experience with the disease.

"We are interdependent," Boum notes. "What is happening in Africa will definitely impact what is happening in the West and vice versa."

Monkeypox is endemic in 10 countries in West and Central Africa, with dozens of cases this year in Cameroon, Nigeria, and the Central African Republic (CAR). The Democratic Republic of the Congo (DRC) has by far the highest burden, with 1284 cases in 2022 alone. Those numbers are almost certainly underestimates. In the DRC, infections most often happen in remote rural areas; in the CAR, armed conflict in several regions has limited surveillance.

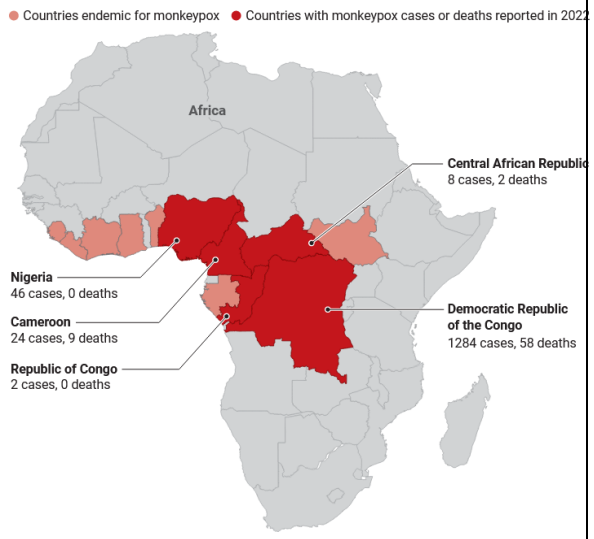
The virus got its name after it was first identified in a colony of Asian monkeys in a Copenhagen, Denmark, laboratory in 1958, but it has only been isolated from a wild monkey—in Africa—once. It appears to be more common in squirrel, rat, and shrew species, occasionally spilling over into the human population, where it spreads mainly through close contact, but not through breathing. Isolating infected people typically helps outbreaks end quickly.

Cases have steadily increased in sub-Saharan Africa over the past 3 decades, driven largely by a medical triumph. The vaccine against smallpox, a far deadlier and more transmissible virus, also protects against monkeypox, but the world stopped using it in the 1970s, shortly before smallpox was declared eradicated. As a result, "There's a huge, huge number of people who are now susceptible to monkeypox," says Placide Mbala, a virologist who heads the genomics lab at the National Institute of Biomedical Research

(INRB) in Kinshasa, DRC.

Mbala says demographic shifts have fueled the rise as well. “People are more and more moving to the forest to find food and to build houses, and this increases the contact between the wildlife and the population,” he says. Studies in the CAR showed cases spike after villagers move into the forest during the rainy season to collect caterpillars that are sold for food. “When they stay in the bush they get in contact easily with the animal reservoir,” says virologist Emmanuel Nakouné, scientific director at the Pasteur Institute of Bangui, which in 2018 launched a program named Afripox with French investigators to better understand and fight monkeypox.

Outbreaks outside Africa, including the current one, have all involved the West African strain, which kills about 1% of those it infects. The Congo Basin strain, found in the DRC and the CAR, is 10 times more lethal, yet despite the relatively high disease burden in the DRC, it has never left Africa. But it has never caused a serious outbreak in a Congolese city either, which underscores the isolation of the areas where it is endemic. “It’s kind of a self-quarantine,” Mbala says. “Those people don’t move from DRC to other countries.”



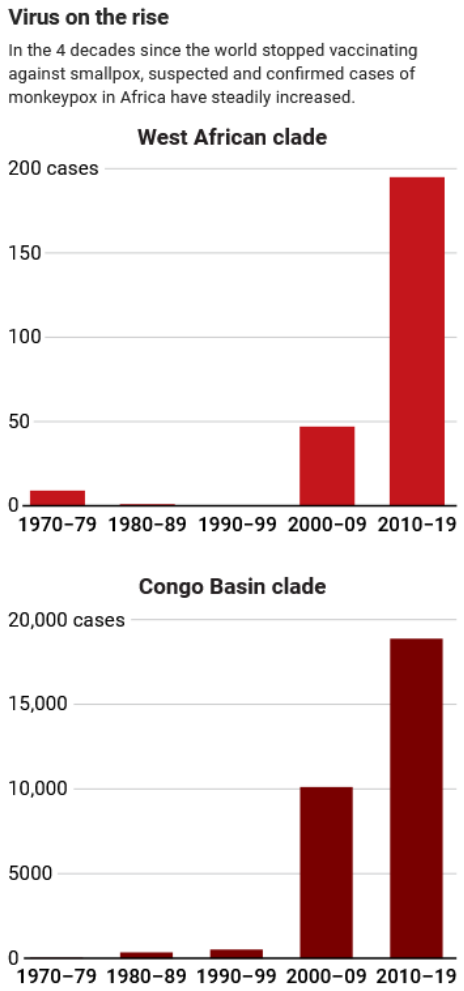
Spilling over ***The monkeypox virus infects squirrel, rat, and shrew species in at least 10 countries in West and Central Africa and occasionally jumps into the human population. So far this year, five countries have reported human cases.*** **(Graphic) K. Franklin/*Science*; (Data) World Health Organization**

Just where the current outbreak started, and how long ago, is unclear. “It’s a little bit like we’ve tuned into a new TV series and we don’t know which episode we’ve landed on,” says Anne Rimoin, an epidemiologist at the University of California, Los Angeles, who has worked on monkeypox in the DRC for 20 years. The first patient with an identified case traveled from Nigeria to the United Kingdom on 4 May, but does not appear to have infected anyone else. Two patients diagnosed later, one in the United States and the other in the United Arab Emirates, had recently traveled to Africa as well, and perhaps imported the virus separately. But none of the other cases identified in recent weeks has links to infected travelers or animals from endemic countries. Instead, many early cases were linked to transmission at gay festivals and saunas in Spain, Belgium, and Canada.

Some suspect the virus may have been imported from Nigeria, Africa’s most populous country, which has good infrastructure connecting rural areas to large cities and two airports that are among the busiest in Africa. But this is “highly speculative,” stresses Christian Happi, who runs Nigeria’s African Centre of Excellence for Genomics of Infectious Diseases. Happi urges people in other countries “not to point fingers,” but to collaborate.

Epidemiologist Ifedayo Adetifa, head of the Nigeria Centre for Disease Control, says the country receives undue attention because it does more surveillance than its neighbors and shares what it finds. “There’s too much emphasis for whatever reasons in Western capitals and news media about trying to hold somebody responsible for a particular outbreak,” he says. “We don’t think those narratives are helpful.” Adetifa says that although Nigeria has recently seen “an uptick in cases,” he is confident it’s not missing a large number of them. “We are literally rattling the bushes to see what comes out.”

African countries' ability to deal with monkeypox was improving even before the current outbreak. The DRC has stepped up its surveillance across the vast country, which is key to isolating infected people and tracking the virus' moves. INRB and a lab in Goma can now diagnose samples using the polymerase chain reaction assay, and researchers ultimately hope to develop rapid tests for use in clinics nationwide. INRB and labs in Nigeria can also sequence the full genome of the virus, and Nigeria plans to make public genomes of several recent monkeypox isolates, Adetifa says. Those and other sequences from Africa could help researchers pinpoint the source of the international outbreak by building viral family trees.



Virus on the rise ***In the 4 decades since the world stopped vaccinating against smallpox, suspected and confirmed cases of monkeypox in Africa have steadily increased.*** **(Graphic) K. Franklin/Science; (Data) E.M. Bunge et al., PLOS Neglected Tropical Diseases, 16(2): e0010141 (2022)**

For now, Africa lacks medicines to prevent and treat monkeypox. In the United Kingdom and the United States, high-risk contacts of cases are being offered a vaccine produced by Bavarian Nordic that was approved for monkeypox by the U.S. Food and Drug Administration in 2019, but it's not available anywhere in Africa. The U.S. Centers for Disease Control and Prevention and collaborators in the DRC are testing the vaccine in health care workers; the 2019 approval was based on animal studies.

In the CAR, 14 people with monkeypox have received an experimental drug, tecovirimat, as part of a trial launched by the University of Oxford in July 2021. "We've had very good results," says Nakouné, who says he expects the data to be published within the next few weeks. The drug's manufacturer, SIGA, has pledged to provide up to 500 treatment courses to the country.

Although the international outbreak has—again—highlighted global health inequities, it has also brought much-needed attention to the smoldering disease in Africa. "It's been really hard to get the resources to do the kind of background work that really needs to be done and that isn't hair-on-fire, in the context of an emergency," Rimoin says. "We cannot keep hitting the snooze button. Now, the stakes are really high."

doi: 10.1126/science.add2880

https://bit.ly/3NSKwtT

Study suggests that most of our evolutionary trees could be wrong

Determining evolutionary trees of organisms by comparing anatomy rather than gene sequences is misleading

New research led by scientists at the Milner Centre for Evolution at the University of Bath suggests that determining evolutionary trees of organisms by comparing anatomy rather than gene sequences is misleading. The study, published in *Communications Biology*, shows that we often need to overturn centuries of scholarly work that classified living things according to how they look.

Since Darwin and his contemporaries in the 19th Century, biologists have been trying to reconstruct the "family trees" of animals by carefully examining differences in their anatomy and structure (morphology).

However, with the development of rapid genetic sequencing techniques, biologists are now able to use genetic (molecular) data to help piece together evolutionary relationships for species very quickly and cheaply, often proving that organisms we once thought were closely related actually belong in completely different branches of the tree.

For the first time, scientists at Bath compared evolutionary trees based on morphology with those based on molecular data, and mapped them according to geographical location.

They found that the animals grouped together by molecular trees lived more closely together geographically than the animals grouped using the morphological trees.

Matthew Wills, Professor of Evolutionary Paleobiology at the Milner Centre for Evolution at the University of Bath, says that "it turns out that we've got lots of our evolutionary trees wrong.

"For over a hundred years, we've been classifying organisms according to how they look and are put together anatomically, but molecular data often tells us a rather different story."

"Our study proves statistically that if you build an evolutionary tree of animals based on their molecular data, it often fits much better with their geographical distribution." "Where things live—their biogeography—is an important source of evolutionary evidence that was familiar to Darwin and his contemporaries."

"For example, tiny elephant shrews, aardvarks, elephants, golden moles and swimming manatees have all come from the same big branch of mammal evolution—despite the fact that they look completely different from one another (and live in very different ways)." "Molecular trees have put them all together in a group called Afrotheria, so-called because they all come from the African continent, so the group matches the biogeography."

The study found that convergent evolution—when a characteristic evolves separately in two genetically unrelated groups of organisms—is much more common than biologists previously thought.

Professor Wills says that "we already have lots of famous examples of convergent evolution, such as flight evolving separately in birds, bats and insects, or complex camera eyes evolving separately in squid and humans." "But now with molecular data, we can see that convergent evolution happens all the time—things we thought were closely related often turn out to be far apart on the tree of life."

"People who make a living as lookalikes aren't usually related to the celebrity they're impersonating, and individuals within a family don't always look similar—it's the same with evolutionary trees too."

"It proves that evolution just keeps on re-inventing things, coming up with a similar solution each time the problem is encountered in a different branch of the evolutionary tree." "It means that convergent evolution has been fooling us—even the cleverest evolutionary biologists and anatomists—for over 100 years."

Dr. Jack Oyston, Research Associate and first author of the paper, says that "the idea that biogeography can reflect evolutionary history was a large part of what prompted Darwin to develop his theory of evolution through natural selection, so it's pretty surprising that it hadn't really been considered directly as a way of testing the accuracy of evolutionary trees in this way before now."

"What's most exciting is that we find strong statistical proof of molecular trees fitting better not just in groups like Afrotheria, but across the tree of life in birds, reptiles, insects and plants too."

"It being such a widespread pattern makes it much more potentially useful as a general test of different evolutionary trees, but it also shows just how pervasive convergent evolution has been when it comes to misleading us."

More information: *Jack W. Oyston et al, Molecular phylogenies map to biogeography better than morphological ones, Communications Biology (2022). DOI: 10.1038/s42003-022-03482-x*

https://bit.ly/3x5lP72

Your Liver Is Only About Three Years Old, Scientists Say

On average the organ is less than three years old, no matter what the age of the person

David Nield

The human liver stays youthful even while the rest of our bodies grow old, according to new research, and on average the organ is is less than three years old, no matter what the age of the person it's attached to.

Using mathematical modeling and a technique called retrospective radiocarbon birth dating – which dates human cells based on levels of a carbon isotope that spiked in the atmosphere following mid-20th century nuclear testing – scientists have found that liver renewal is largely unaffected as we grow old.

That renewal is key to the liver's primary function, which is clearing toxic substances out of the body. This waste removal takes its toll on the organ, but it has a unique ability to regenerate itself after being damaged.

"No matter if you are 20 or 84, your liver stays on average just under three years old," says molecular biologist Olaf Bergmann from the Dresden University of Technology in Germany.

The team analyzed post-mortem and biopsy tissue samples from more than 50 individuals aged between 20 and 84 years. They found our biology maintains tight control over the mass of the liver throughout our lives, via the continual replacement of liver cells.

As our bodies get older, they're less able to renew cells and carry out repairs. What the new study shows is that this doesn't apply to the hepatocytes, the cells in the liver. Whereas earlier animal studies had given conflicting results, here there's much more clarity.

However, not all liver cells are the same in terms of how quickly they renew: A small fraction can live to be up to 10 years old, the researchers found. This seems to be related to how many sets of chromosomes they're carrying.

Most cells in our body, aside from our sex cells, carry two copies of our entire genome. Liver cells are an odd exception, with a proportion of cells generating even more copies of our whole DNA library on top.

"When we compared typical liver cells with the cells richer in DNA, we found fundamental differences in their renewal," says Bergmann. "Typical cells renew approximately once a year, while the cells richer in DNA can reside in the liver for up to a decade."

"As this fraction gradually increases with age, this could be a protective mechanism that safeguards us from accumulating harmful mutations. We need to find out if there are similar mechanisms in chronic liver disease, which in some cases can turn into cancer."

This is an important new insight into the biological mechanisms underpinning how the liver works – and of course the more we know about the organs in the body, the better we can get at figuring out how to keep them healthy and how to cure them from disease.

The researchers are also looking at other organs, including the heart, to see how fast cells are renewed across the body. The same technique of retrospective radiocarbon birth dating can be used to accurately date cells and work out renewal rates.

It's one of the best methods we've currently got for figuring out the age of human tissue, using the decay rates of radiocarbon in the atmosphere to correspond to traces in the body. As it turns out, your organs might not be as old as you feel.

"Our research shows that studying cell renewal directly in humans is technically very challenging but it can provide unparalleled insights into the underlying cellular and molecular mechanisms of human organ regeneration," says Bergmann.

The research has been published in *Cell Systems*.

https://bit.ly/3Q2He9u

This ancient giraffe relative head-butted rivals with an 'amazing sexual weapon'

Fossil suggests the giraffe's long neck could have evolved for getting mates, not leaves

By Elizabeth Pennisi

How did the giraffe get its long neck? That question has enthralled scientists for centuries. Charles Darwin assumed the driver of natural selection was food, as animals with longer necks could reach higher trees and have their own private food supply with little competition from other species. But a newly analyzed fossil of an ancient giraffe relative suggests there might be more to the story: Competition for mates could have also influenced neck evolution.

"It's a cool story about an amazing sexual weapon," says Ted Stankowich an evolutionary ecologist at California State University, Long Beach, who was not involved with the work.

An artist's impression of the ancient giraffoid Discokeryx xiezhi, which had a thick headpiece adapted for fighting. **Credit: Y. Wang and X. Guo**

In 1996, in a 15-million-year-old rock formation in China's far northwest, paleontologists unearthed an unusual fossil with a braincase and some vertebrae. Its skull was thickened at the base, where it had been attached to an enlarged neck vertebra. Researchers first wondered whether it might be an ancient relative of cows or sheep but weren't sure because its teeth and bones were so large, recalls Tao Deng, a paleontologist at the Chinese Academy of Sciences's (CAS's) Institute of Vertebrate Paleontology and Paleoanthropology. Only years later, when a CT scan revealed the inner ear bones of the "strange beast," did they realize it was a giraffoid, one of a group of animals that includes today's okapi and giraffes and several other extinct giraffelike species.

Deng and a CAS colleague, paleontologist Shi-Qi Wang, did a CT scan to examine how its bones were formed and arranged. In addition to the unusually thick bones of the neck, they found a hand-size bony disk with a horny "helmet" on the top of its head. They analyzed how the vertebrae interlocked and did computer simulations to learn how the head and neck would react to impacts. They even probed the chemistry of the creature's tooth enamel to find out what it ate. "Every angle that the researchers could have explored … was covered," says Rob Simmons, a behavioral ecologist at the University of Cape Town who was not involved with the work.

Deng and Wang then compared the data with those on other giraffoids and animals, including wild sheep and musk ox, which lock horns or butt heads to compete for mates. The fossil's vertebrae were not just thicker than those of other animals, but they also had more surface area in contact with the base of the skull and each other. "It's the thickness of the vertebrae that makes [the fossil] very unusual," says Jin Meng, a co-author at the American Museum of Natural History. The simulations revealed these modifications helped keep the head from snapping forward too far when hit.

The researchers conclude that the creature's horny helmet was a powerful buttress for jousting with other males, they report today in *Science*. The researchers named the fossil *Discokeryx xiezhi*, after a Chinese legendary horned creature that had the power to distinguish right from wrong. "They unequivocally show that this little giraffe must have used its helmeted head for combat," Simmons says.

Other extinct giraffoids had a variety of headgear, including club-shaped, meter-long horns. Modern giraffes have bony headgear, too: The bone that forms the helmet in *D. xiezhi* becomes small horns called ossicones, sometimes used by males to jab the necks of

rivals as they swing their heads and necks like clubs. But among giraffelike animals, *D. xiezhi* is the first example of a head-butter, says María Ríos Ibáñez, a paleontologist at NOVA School of Science and Technology. She describes head-butting as "a much more direct, aggressive form of competitive behavior" than the giraffe's "necking."

If *D. xiezhi* evolved its special headgear to compete for mates, then it's possible sexual selection also played a role in the development of other species' headgear—and necks, Wang says. "Neck evolution is very fast and flexible and depends on the male's fighting style," she says. According to that thinking, the ability of giraffes to eat leaves at the tops of trees could have been a fortuitous side benefit, rather than a driving force, in the evolution of giraffes' long necks. (Simmons has made that argument for years because even though both males and females have long necks, the male's continues to grow bigger with age, whereas the female's does not.)

Researchers can't say whether natural selection or sexual selection made the giraffe such an exotic looking beast. But, Simmons says, "I wish Charles Darwin were alive for this discussion. He'd be bowled over."

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People With Food Allergies Seem to Have Lower Risk of SARS-CoV-2 Infection

Individuals with a food allergy were only about half as likely to become infected

Carly Cassella

Since the start of the global pandemic, researchers have been racing to figure out who is most at risk from SARS-CoV-2, and why.

Now, a new population-based study from the National Institutes of Health (NIH) has found evidence of a curious coronavirus advantage for those with allergies.

In an analysis of more than 4,000 people who all lived in households that included minors, researchers noted several curious trends in terms of SARS-CoV-2 infection, including that individuals with a food allergy were only about half as likely to become infected.

The findings match other recent research, which found allergic conditions, like asthma, might offer some protection against severe cases of COVID-19.

Somewhat similarly, the new NIH study found that asthma was not linked to increased risk of SARS-CoV-2 infection, despite asthma being a condition that impacts the respiratory system.

On the other hand, obesity and a high BMI index were factors that increased risk of SARS-CoV-2 infection, as was the age of children and teens sharing the living space. But the finding with regard to food allergies might be the most remarkable discovery.

"[T]he observed association between food allergy and the risk of infection with SARS-CoV-2, as well as between body-mass index and this risk, merit further investigation," says Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases.

Researchers aren't sure why food allergies seem to make people less vulnerable to SARS-CoV-2, but there are a few possible explanations. Half of all the participants in the study claimed they had been diagnosed with a food allergy, asthma, eczema, or allergic rhinitis. These self-reports were then backed up by a subset of blood tests, which revealed antibodies linked to allergic disease.

Researchers then tracked the spread of SARS-CoV-2 in participant households from May 2020 to February 2021.

People with eczema and asthma didn't show extra vulnerability to the virus, but they also didn't seem to be any more protected.

Those with food allergies, meanwhile, were at a 50 percent lower risk of SARS-CoV-2 infection. Not all forms of asthma are atopic (aka highly allergic), and previous studies have shown that only

those with atopic asthma express lower airway levels of the ACE2 receptor, which is what SARS-CoV-2 attaches to.

This suggests that the virus does not have as many ways to invade cells in the lungs of those with respiratory allergies.

Something similar could be occurring among people with food allergies, although the authors only looked at SARS-CoV-2 infection, and not the severity of the infection.

"It is not known whether this is also the case in food allergic individuals, but it is tempting to speculate that type 2 inflammation, a characteristic of food allergy, may reduce airway ACE2 levels and thus the risk of infection," the researchers write.

"Supporting this possibility, we found significantly greater levels of general atopy among those with self-reported food allergy, relative to both those without food allergy, and even those with asthma."

Interestingly, while some studies suggest allergic asthma protects from severe cases of COVID-19, the current study found the condition does not protect from the initial contraction of the virus.

What's more, when a participant with asthma or food allergies did contract the novel coronavirus, they were no more likely to be asymptomatic.

Further research is needed to tease apart the mechanisms behind the new findings, but the authors are hopeful that their research can offer new avenues for COVID-19 prevention. The study was published in the *Journal of Allergy and Clinical Immunology*.

https://bit.ly/3xlDc4N

Studying schizophrenia in plants? Researchers are giving it a shot

What if scientists could study human psychiatric illness in plants?

by Mallory Locklear, Yale University

Yale researchers think it's possible and they've taken an important first step. In a study published June 2 in *Cellular and Molecular Life Sciences*, they investigated a gene very similar in both plants and mammals and looked at how it affects behavior in each.

Tamas Horvath, the Jean and David W. Wallace Professor of Comparative Medicine and senior author of the study, has been thinking about this possibility for some time.

"Years ago, I started to become interested in this idea that every living organism must have some homology, some similarity in how they are or what they do," he said.

As he began to study behavior and mitochondria—specialized structures within cells that generate energy—this idea kept coming back to him. He thought that if one could alter mitochondrial genes in animals and see what behaviors changed, and then try the same thing to similar genes in plants, it might eventually be possible to better understand human behavior through the study of plants. If you take that idea another step, said Horvath, perhaps it's possible to, for example, develop a schizophrenic-like plant.

"If you could develop such a model, then that means you would have alternative species, not just mammals, with which to probe aspects of human behavior," said Horvath, who noted that this is the goal of comparative medicine, to see how non-human models can be used for studying human conditions.

For this study, Horvath and his colleagues studied a mitochondrial gene (Friendly Mitochondria, or FMT) found in a small flowering plant called Arabidopsis thaliana and a very similar gene (Clustered mitochondria homolog, or CLUH) found in mice.

Mitochondria regulate important functions like metabolism and are critical for maintaining health. In both plants and humans, dysfunctional mitochondria can affect development and lead to disease, including neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, and schizophrenia in humans.

For the study, the researchers compared typical plants, plants without FMT, and plants with overactive FMT to better understand

the gene's role. They found that it affects many important characteristics, including germination, or seed sprouting, root length, flowering timing, and leaf growth.

They also looked at two important plant behaviors.

The first was the salt stress response. Too much salt can kill plants, so they've developed behaviors to avoid it. When there's excess salt in their environment, plants tend to halt germination, delay flowering, and disrupt root growth. The researchers found that FMT is critical for these salt-avoiding behaviors.

The second type of plant behavior they investigated is known as hyponastic behavior—movements based on circadian rhythms. "Plants are tremendously impacted by circadian rhythms because light is the critical energy source for them," said Horvath.

For Arabidopsis, hyponastic behaviors include the way its leaves move throughout the day and night. During the day, its leaves are flatter and more exposed to the sun. At night, when there's no sunlight to absorb, the leaves angle upwards. Horvath and his colleagues found that FMT plays an important role in this behavior as well, regulating both how much and how quickly the leaves moved.

To start to connect this to mammals, the researchers assessed a variety of mouse behaviors, comparing typical mice to those with reduced CLUH, a gene very similar to FMT. Using a behavioral test in which mice are placed in an open environment, they observed that mice with less CLUH were slower and traveled shorter distances than their counterparts.

"The mice had a similar response as the plants, with altered speed and altered overall locomotive activity," said Horvath. "It's rudimentary but it still indicates that you can have mitochondrial-related mechanisms that decode similar functions in plants and animals."

While there's more work to do, it's an exciting first step, he said. Plants like Arabidopsis and mammals share several similar genes and cellular processes, not just FMT and CLUH.

"The long-term goal is to develop a sort of dictionary that catalogs these similarities between plants and animals and to use it to ask research questions more robustly," said Horvath. "It's possible this plant can serve as a complementary model organism for behavioral research in the future."

More information: *Alexandra Ralevski et al, Plant mitochondrial FMT and its mammalian homolog CLUH controls development and behavior in Arabidopsis and locomotion in mice, Cellular and Molecular Life Sciences (2022). DOI: 10.1007/s00018-022-04382-3*

https://bit.ly/3xbPA68

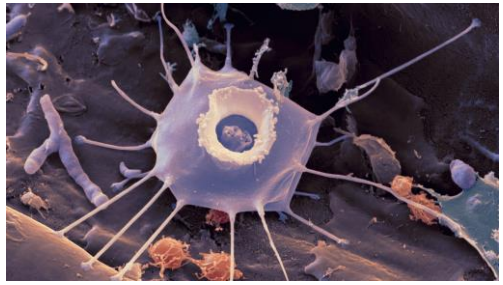
Brain-Signal Proteins Evolved Before Animals Did

Some animal neuropeptides have been around longer than nervous systems.

Viviane Callier

Our human brains can seem like a crowning achievement of evolution, but the roots of that achievement run deep: The modern brain arose from hundreds of millions of years of incremental advances in complexity.

Evolutionary biologists have traced that progress back through the branch of the animal family tree that includes all creatures with central nervous systems, the bilaterians, but it is clear that fundamental elements of the nervous system existed much earlier.



This microbe, called a choanoflagellate, is one of the single-celled organisms most closely related to the animal kingdom. New work shows that its ancestors made proteins that were later repurposed by the nervous systems of the first animals. **Eye of Science/Science Source**

How much earlier has now been made dramatically clear by a

recent discovery by a team of researchers at the University of Exeter in the United Kingdom. They found that the chemical precursors of two important neurotransmitters, or signaling molecules used in nervous systems, appear in all the major animal groups that preceded creatures with central nervous systems.

The big surprise, however, is that these molecules are also present in single-celled relatives of animals, called choanoflagellates. This finding shows that animal neuropeptides originated before the evolution of even the very first animals.

The discovery "solves a long-standing question about when and how animal neuropeptides evolved," said Pawel Burkhardt, who studies the evolutionary origin of neurons at the Sars International Center for Marine Molecular Biology in Norway. It also indicates that at least some of the signaling molecules fundamental to the operation of our brains first evolved for an entirely different purpose in organisms that consisted of only a single cell.

Animal nervous systems are made of neurons that connect to each other, zipping information across synapses with a variety of small peptide neurotransmitters. These peptides are the language with which neurons speak to each other.

But when evolutionary biologists tried to deduce which animal cells first started to use that language, the murkiness of early animal evolution interfered. A variety of molecules very similar to neuropeptides are made by nearly all the early animal groups, including the ctenophores (comb jellies) and the cnidaria (jellyfish, corals and sea anemones). Even the extremely simple animals called placozoans, which have no cells resembling neurons, make neuropeptides. Sponges seemed to be the only exception, which is why it was generally thought that animal neuropeptides originated in cnidarians or ctenophores, after sponges branched away from the rest of the animal tree.

The problem with that theory, though, is that the amino acid sequences of the neuropeptides in the early animal groups are so different from bilaterian neuropeptides that none seemed similar enough to be ancestral to them. Worse, a wide variety of unrelated neuropeptides are also made by many single-celled animals, or protozoans. The evolutionary trail for brain neuropeptides seemed to vanish into a thicket.

This impasse was broken recently by Luis Yañez-Guerra, who studies evolutionary neurobiology in the lab of Gáspár Jékely at the University of Exeter. To trace the origin and evolution of various animal neuropeptides, Yañez-Guerra mapped neuropeptides onto the evolutionary tree of early-branching animals and their close relatives, the choanoflagellates.

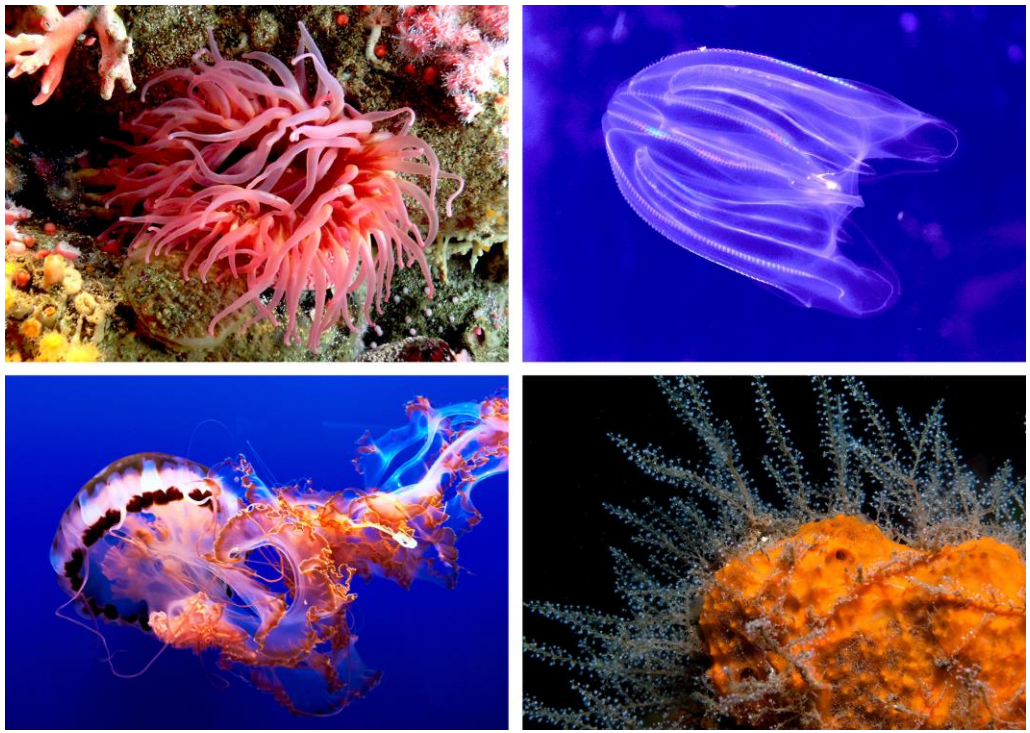
From his doctoral work, he had already created a large list of animal neuropeptides, and as he began looking for them farther down the animal tree, he stumbled on the realization that choanoflagellates made protein precursors of two mature neuropeptides, phoenixin and nesfatin.

Their presence in choanoflagellates was a surprise because neuropeptides typically appear in the context of sender and receiver neurons. "In a unicellular organism, it's more difficult to make sense of," Yañez-Guerra said. "This shows that these neuronal molecules started evolving even before the need for this extensive communication between cell and cell. That's why it was kind of shocking."

The precursors of phoenixin and nesfatin are not used directly as neuropeptides by nervous systems; instead, these long peptides are chemical precursors that get chopped up and processed into smaller molecules that become the functional, mature neuropeptides. Their hidden identity may be why they were not identified as promising leads earlier.

A further search of the gene expression data confirmed Yañez-Guerra's hunch that phoenixin and nesfatin might be the keys to

understanding neuropeptide evolution. Not only were the precursor peptides present in the choanoflagellates, but they were also present in all the early animal groups — even the sponges, where they had been overlooked.



Neuropeptides have now been found in all the major early branches of animal life, including (clockwise from top right) the ctenophores or comb jellies, the sponges, and the cnidarians, such as jellyfish and sea anemones. **(clockwise from top right) Maritime Museum at Norwalk; Klaus Stiefel; Pedro Szekely; Bernard Spragg**

Given that the precursor molecules in the choanoflagellates are so directly connected to these neuropeptides found in all animals, Burkhardt explained, "The last common ancestor of all animals likely had at least two neuropeptides."

The question that naturally arises is: What were those neuropeptide precursors doing in choanoflagellates, since it couldn't have been neural signaling? There isn't a definitive answer yet. Choanoflagellates do appear to produce the mature phoenixin neuropeptide, but not the mature nesfatin neuropeptide. It's possible that choanoflagellates used their phoenixin neuropeptides to communicate with each other, for instance to coordinate the formation of choanoflagellate colonies.

But in their paper, Yañez-Guerra and his colleagues also suggest that the precursors may be multifunctional "moonlighting" molecules. They point out that, based on their peptide sequences, both precursors are likely to be secreted molecules. They also noted that while the phoenixin precursor can be processed to yield neuropeptides, a segment of it can also become a "chaperone" that ensures that proteins are folded correctly to form a critical complex of the energy-harvesting equipment of mitochondria.

During the evolution of the precursors, selection pressure for those "moonlighting" functions might have been a bigger factor than any need for intercellular signaling. Currently, Yañez-Guerra and Burkhardt are working together to study a mutant choanoflagellate that is missing the phoenixin precursor in an effort to better understand its function. They are also searching for receptor molecules in the choanoflagellates that would receive the neuropeptides.

Unfortunately, the fact that these two neuropeptide precursors are shared by all animals hardly simplifies the early evolution of nervous systems. Last December, Mariia Sachkova and her colleagues at the Sars Center, working with Burkhardt, reported that with the help of a machine learning tool, they had identified many peculiar neuropeptides encoded in ctenophore genomes, many of them unlike any others in the animal kingdom.

The neuropeptides aren't the only thing that's unique about ctenophore nervous systems: The structures of their neural networks are so unusual that researchers suspect they evolved independently of those seen in humans and other animals. Why

ctenophores do things differently is a mystery, but it's clear that nervous systems went through a period of tremendous experimentation and innovation early in their evolution — and that at least some of that experimentation began before animals even existed.

https://bit.ly/38XX0Ss

We Should Have Seen Monkeypox Coming

Five years ago, monkeypox made a leap—and most of the world ignored it.

By Sarah Zhang

Nearly five years before an unusual cluster of monkeypox cases in the U.K. alarmed the world, doctors were dealing with an unusual cluster of monkeypox in another unexpected country: Nigeria. The virus is endemic to Central Africa, but Nigeria, far to the west, had not recorded a case of monkeypox since 1978. When an 11-year-old boy showed up with skin lesions in September 2017, doctors first suspected chickenpox. But no, tests pointed to the much more unusual monkeypox. From 2017 to 2022, Nigeria then found more than 500 confirmed monkeypox cases. Quite suddenly, it seemed, the virus had begun spreading somewhere new.

In Nigeria, too, doctors first picked up hints of a new pattern that would be repeated around the world. Many of the patients were men, and many had genital lesions, suggesting transmission via sexual contact. Four years later, many of the cases in Europe and the Americas are also in men and also characterized by genital lesions. "It looks like déjà vu to me," says Dimie Ogoina, a doctor at Niger Delta University Teaching Hospital, which treated the first and many subsequent cases of monkeypox in Nigeria in 2017. The virus was known to spread through droplets and any kind of physical contact with infectious sores and scabs—but sex, specifically, had never been high on the list of transmission risks. (Past cases were usually linked to contact with wild animals or household contact.) The unusual pattern and unusual size of the Nigeria outbreak should have been a signal that something had changed for monkeypox. But the world ignored it until too late, and a global outbreak is now well under way.

"What happened in 2017 in Nigeria was absolutely a warning sign," says Anne Rimoin, an epidemiologist at UCLA who has studied the virus. But as long as monkeypox stayed in Africa, the disease got little attention. The U.K., Singapore, and Israel did pick up the occasional case linked to travel to Nigeria in 2018 and 2019. "It's possible there were many importations that were missed," Rimoin says, which seeded local transmission that's finally being detected now. The exact path the virus took around the world is unknown, but the genomes of viruses sequenced so far from Europe and the U.S. are most closely related to those linked to the Nigeria outbreak. In fact, a preliminary genetic analysis from University of Edinburgh scientists suggests that the evolution of this monkeypox lineage suddenly accelerated sometime between 2017 and 2022. Poxviruses tend to accumulate mutations at a fairly slow rate of one or two a year, but the genomes from 2022 have a whopping 47 mutations. Intriguingly, almost all of the changes to the genetic code are TC to TT or GA to AA. This is unlikely to have happened through random copying error; instead it resembles the signature of an immune-system mechanism—found in both humans and animals—that introduces mutations in an attempt to disable the virus. This signature is seen in many common viruses, including SARS-CoV-2, notes Nicolas Gillet, a biologist at the University of Namur who has studied this defense mechanism. You can think of most of the mutations as "scars" from battling with the host immune system, says Richard Neher, a biologist at the University of Basel, though it's impossible to say whether any could also be adaptive. In any case, monkeypox seems to have found a new host since 2017: either humans directly or another animal that then spread the virus to

humans.

The lack of attention to monkeypox means basic questions—such as which animal or animals in fact spread the virus—remain unanswered. Despite the name, monkeypox is more commonly found in rodents, though it can infect a wide range of species, including primates and rabbits. When it comes to the virus's natural animal reservoir, "we don't know," says Boghuma Titanji, an infectious-disease doctor at Emory. In addition to the Nigeria outbreak that began in 2017, a separate outbreak of a more severe form of monkeypox has been intensifying around the Democratic Republic of Congo, where the virus has long circulated. The Congo has seen 1,200 cases and 58 deaths this year alone.

Only now, with a few hundred cases outside Africa, particularly in rich countries, do we "see a shift in attention," Titanji says. Earlier investments in research might have identified strategies to prevent spillovers from a reservoir before they happened. And now, scientists around the world are scrambling to understand the full range of monkeypox's transmission and symptoms in the middle of a global outbreak. "We could have been doing this much sooner and more preemptively," she says.

"Most of our information on the epidemiology and the clinical presentation [comes from] the early '80s," Rimoin says. Monkeypox was of particular interest then because doctors worried that it might sweep in following the eradication of its more severe relative, smallpox. Since then, however, monkeypox has been "neglected lamentably," says David Heymann, an epidemiologist at the London School of Hygiene and Tropical Medicine who has studied the virus in the Congo. He ticked off a list of basic questions he would like to see answered: "What does this virus do in immunocompromised people? Is there an asymptomatic form of infection? Does that asymptomatic form transmit to others? Is it transmitted by fomites when you sneeze or cough? Things like that are not known."

In particular, Heymann notes that the milder West Africa clade of the virus in Nigeria and now around the world may behave differently than the more severe and slightly better characterized one found in the Congo. Its relative mildness may have helped it spread, because people who are very sick are less likely to travel. Not everyone infected with the West Africa clade seems to get a generalized rash that is normally associated with the virus, Heymann adds. And the possibility of sexual transmission is not fully understood. Monkeypox sores can occur on many parts of the body, so their appearance in the genital area may have begun as a random event that then allowed it to spread through physical contact during sex. Whether the virus also spreads through semen or vaginal fluids, however, is unknown. Such studies hadn't been done, even though the 2017 Nigeria outbreak already hinted at the role of transmission during sex.

As monkeypox has gone global, patients in Europe and North America are getting antiviral drugs. Health-care workers and close contacts of patients are being offered vaccines. But at his hospital in Nigeria, Ogoina says, doctors never had any of the antiviral drugs or vaccines. All they had for monkeypox patients was supportive care. Furthermore, case numbers are likely being underestimated right now. "We need to step up surveillance," he says, pointing to the need for more labs that can diagnose the virus, antibody surveys to study its prevalence, and monitoring of potential animal carriers.

Countries in Europe and North Americas may be able to tame their monkeypox outbreaks. But "an infection anywhere is potentially an infection everywhere," Rimoin says. As long as monkeypox circulates in Africa, it will keep seeding cases elsewhere. And it will keep sickening and killing people in Africa. The early warning signs for monkeypox were there all along, and they should be by now unignorable.