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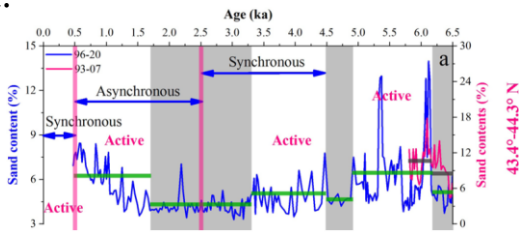
# Abrupt Climate Shifts Change the Latitudes of Storm Activity

***A new 6500-year construction of storms combined with other paleo-storm records finds abrupt changes in the Atlantic Ocean circulation impact the latitudinal preference of storm activity.***

**By Janet Sprintall 2 November 2020**

Storm activity, including hurricanes, in the Atlantic Ocean has an outsized influence on the economic production and societal well-being of the hundreds of millions of people who live along the north American shorelines that are vulnerable to storm damage. Major storm events are expected to become stronger and occur more often in a warming climate.

Yang et al. [2020] show that we might also expect shifts in the preferential pathways of the storm activity between low- and mid-latitudes.




***The time series of the sand content (%) determined from two paleo sediment cores in Eastern Canada provide an indicator of storminess over the past 6500 years. Gray bars show periods of decreased storm activity at the site, and the green and gray bars indicate the average sand content corresponding to the active and inactive periods. Pink lines mark abrupt shifts in the storm frequency pattern in the North Atlantic and separate periods when storm activity between low and mid-latitudes was synchronous or asynchronous.***

**Credit: Yang et al. [2020], Figure 4a**

A new 6500-year record on storm activity in the mid-latitude is reconstructed from two sediment cores collected in eastern Canada. This record, combined with other paleo-storm records from low and mid latitudes along the eastern American seaboard, shows that peaks in storminess can be similar across all latitudes for thousands of years before abrupt climate shifts cause the peaks in storm activity to be out of phase between the low- and mid-latitudes. The latitudinal response shows a strong correspondence to changes in the strength of the Atlantic Meridional Overturning Circulation (AMOC) which is known to influence sea surface temperature patterns and hence storm activity. A sustained increase in AMOC is associated with a synchronous storm pattern in the Atlantic, and vice-versa.

The study may encourage development of better strategies for management risk in vulnerable coastal areas at different latitudes, as well as provides food for thought about how other climate phenomena might vary geographically in a warming world.

*Citation: Yang, Y., Maselli, V., Normandeau, A., Piper, D. J. W., Li, M. Z., Campbell, D. C., et al. [2020]. Latitudinal response of storm activity to abrupt climate change during the last 6,500 years.* Geophysical Research Letters, *47, e2020GL089859.* https://doi.org/10.1029/2020GL089859

https://bbc.in/2TZwCfJ

# Algorithm spots 'Covid cough' inaudible to humans

***An algorithm developed in the US has correctly identified people with Covid-19 only by the sound of their coughs.***

**By Zoe Kleinman Technology reporter**

In tests, it achieved a 98.5% success rate among people who had received an official positive coronavirus test result, rising to 100% in those who had no other symptoms. The researchers would need regulatory approval to develop it into an app.

They said the crucial difference in the sound of an asymptomatic-Covid-patient cough could not be heard by human ears.

**'Pool testing'**

The artificial-intelligence (AI) algorithm was built at the Massachusetts Institute of Technology (MIT) lab.

MIT scientist Brian Subirana, who co-authored the paper, published in the IEEE Journal of Engineering in Medicine and Biology, said: "The way you produce sound changes when you have Covid, even if you're asymptomatic."

"Practical use cases could be for daily screening of students, workers and public, as schools, jobs, and transport reopen, or for pool testing to quickly alert of outbreaks in groups," the report says. Several organisations, including Cambridge University, Carnegie Mellon University and UK health start-up Novoic, have been working on similar projects.

**Sample sounds**

In July, Cambridge's Covid-19 Sounds project reported an 80% success rate in identifying positive coronavirus cases based on a combination of breath and cough sounds.

By May, it had a dataset of 459 cough and breath sample sounds submitted by 378 members of the public, and it says it now has around 30,000 recordings. But the MIT lab has collected about 70,000 audio samples each containing a number of coughs. Of those, 2,500 are from people with confirmed cases of coronavirus.

**'Detect cancer'**

Artificial-intelligence expert Calum Chace described the algorithm as "a classic piece of AI". "It's the same principle as feeding a machine a lot of X-rays so it learns to detect cancer," he said.

"It's an example of AI being helpful. "And, for once, I don't see a lot of downside in this."

***https://wb.md/38epzbv***

# Do Leisure Activities Really Mitigate Dementia Risk?

***Contrary to some previous research, new findings question whether leisure activities in middle age really do help mitigate subsequent dementia risk.***

**Megan Brooks**

The study showed no association between taking part in more leisure activities at age 56 and the risk of dementia over the next 18 years. There was some benefit when leisure activity participation was assessed later in life.

"Of course there are many reasons to participate in leisure activities and this finding does not question the importance of keeping active for general health and well-being, but it does suggest that simply increasing leisure activity may not be a strategy for preventing dementia," study investigator Andrew Sommerlad, PhD, from University College London, United Kingdom, said in a news release.

The study also showed that some people who were later diagnosed with dementia stopped participating in leisure activities years before they were diagnosed, suggesting that changes in the amount of leisure activity may be an early sign of dementia.

"Dementia appeared to be the cause, rather than consequence, of low levels of leisure activities," Sommerlad told *Medscape Medical News*. The study was published online October 28 in the journal *Neurology*.

**Still Beneficial**

The study included 8280 adults (mean age, 56 years) who were followed for an average of 18 years as part of the Whitehall II study. Participants reported their leisure activities at the beginning of the study, 5 years later, and again 10 years later.

They were placed in low, medium, and high groups based on their levels of participation in leisure activities such as reading, listening to music, taking classes, participating in clubs, visiting friends/ relatives, playing cards or games, taking part in religious activities, and gardening.

During the study, 360 people developed dementia at a mean age of 76.2 years. The overall dementia incidence rate was 2.4 cases for 1000 person-years.

In fully adjusted Cox regression analyses, taking part in more leisure activities at an average age of 56 was not associated with a lower risk of dementia 18 years later (hazard ratio [HR] 0.92, 95% CI, 0.79 - 1.06).

However, those with higher participation in leisure activities later in life, at a mean age of 66, were less likely to develop dementia over the next 8 years than those with lower participation (HR, 0.82; 95% CI, 0.69 - 0.98). In addition, a decline in leisure activity during the study was associated with an increased risk of dementia (HR, 1.38; 95% CI, 1.20 - 1.59).

Of the 1159 people whose activity decreased during the study, 53 (5%) developed dementia, compared with 17 (2%) of 820 people who maintained their leisure activity level.

"More research is needed to confirm these results, but we know that early changes in the brain can start decades before any symptoms emerge," Sommerlad said in the news release.

"It's plausible that people may slow down their activity level up to 10 years before dementia is actually diagnosed, due to subtle changes and symptoms that are not yet recognized," he added.

"There is no question of the wider benefits of taking part in leisure activities, for promoting enjoyment, quality of life and general physical and mental health," Sommerlad said in an interview.

"But other measures have better evidence specifically for dementia prevention. These are treating health problems like diabetes and hypertension, reducing smoking and alcohol intake, physical activity, treating hearing problems, and having social contact with others," he added.

**Experts Weigh In**

Commenting on the findings for *Medscape Medical News*, Ronald C. Petersen, MD, PhD, from the Mayo Clinic in Rochester, Minnesota, urged caution in drawing any firm conclusions from this study. "It's hard to do these kinds of studies accurately and actually demonstrate that something, in this case leisure activities, can prevent dementia. That's a tall order," he said.

It's possible, he noted, that people who may be experiencing "very early features of a cognitive decline would be less likely to engage in these activities, so it's a little bit of a selection bias from the get-go. On the other hand, we certainly don't want to send the message, 'Don't do these things.' " "Staying involved in your social network, eating a heart-healthy diet, engaging in some physical activity are things I tell my patients in the office," Petersen said.

The authors of an editorial note that the role of leisure activity in dementia prevention is "far from settled and additional research is needed."

"Midlife and late-life leisure activity certainly does no harm, but its role in dementia prevention is not yet clear. There is more work to be done," write Victor Henderson, MD, with Stanford University in California, and Merrill Elias, PhD, University of Maine in Orono.

They note that long-term, population-based or representative cohort studies, although tough to do, will provide "increasingly precise estimates of the role that lifestyle choices in adulthood — leisure activity, aerobic activity, social engagement, adult education, nutrition, and others — might play in reducing dementia risk."

In addition, large, long-term, randomized controlled trials "could provide even stronger evidence of any causal relationship," they point out.

Several such trials that focus on lifestyle interventions are planned or underway in the US and other countries. They include the FINGER study, which incorporates diet, exercise, cognitive training, and the amelioration of vascular comorbidity.

Another is the US POINTER study, a multisite randomized clinical trial evaluating whether lifestyle interventions — including exercise, cognitively stimulating activities, and the MIND diet — may protect cognitive function in older adults who are at increased risk for cognitive decline.

*The Whitehall II study is supported by grants from the US National Institutes of Health, the UK Medical Research Council, and the British Heart Foundation. The authors, editorial writers, and Petersen have disclosed no relevant financial relationships.*

*Neurology*. Published October 28, 2020. Abstract

https://wb.md/3k4OoZE

# Medicare Fines Half of Hospitals for Readmitting Too Many Patients

***Nearly half the nation's hospitals will get lower payments for all Medicare patients because of their history of readmitting patients***

**Jordan Rau**

Nearly half the nation's hospitals, many of which are still wrestling with the financial fallout of the unexpected coronavirus, will get lower payments for all Medicare patients because of their history of readmitting patients, federal records show.

The penalties are the ninth annual round of the Hospital Readmissions Reduction Program created as part of the Affordable Care Act's broader effort to improve quality and lower costs. The latest penalties are calculated using each hospital case history between July 2016 and June 2019, so the flood of coronavirus patients that have swamped hospitals this year were not included.

The Centers for Medicare & Medicaid Services announced in September it may suspend the penalty program in the future if the chaos surrounding the pandemic, including the spring's moratorium on elective surgeries, makes it too difficult to assess hospital performance.

For this year, the penalties remain in effect. Retroactive to the federal fiscal year that began Oct. 1, Medicare will lower a year's worth of payments to 2,545 hospitals, the data show. The average reduction is 0.69%, with 613 hospitals receiving a penalty of 1% or more.

Out of 5,267 hospitals in the country, Congress has exempted 2,176 from the threat of penalties, either because they are critical access hospitals — defined as the only inpatient facility in an area — or hospitals that specialize in psychiatric patients, children, veterans, rehabilitation or long-term care. Of the 3,080 hospitals CMS evaluated, 83% received a penalty.

The number and severity of penalties were comparable to those of recent years, although the number of hospitals receiving the maximum penalty of 3% dropped from 56 to 39. Because the penalties are applied to new admission payments, the total dollar amount each hospital will lose will not be known until after the fiscal year ends on July 30.

"It's unfortunate that hospitals will face readmission penalties in fiscal year 2021," said Akin Demehin, director of policy at the American Hospital Association. "Given the financial strain that hospitals are under, every dollar counts, and the impact of any penalty is significant."

The penalties are based on readmissions of Medicare patients who initially came to the hospital with diagnoses of congestive heart failure, heart attack, pneumonia, chronic obstructive pulmonary disease, hip or knee replacement or coronary artery bypass graft surgery. Medicare counts as a readmission any of those patients who ended up back in any hospital within 30 days of discharge, except for planned returns like a second phase of surgery.

A hospital will be penalized if its readmission rate is higher than expected given the national trends in any one of those categories.

The industry has disapproved of the program since its inception, complaining the measures aren't precise and it unfairly punishes hospitals that treat low-income patients, who often don't have the resources to ensure their recoveries are successful.

Michael Millenson, a health quality consultant who focuses on patient safety, said the penalties are a useful but imperfect mechanism to push hospitals to improve their care. The designers of the penalty system envisioned it as a way to neutralize the economic benefit hospitals get from readmitted patients under Medicare's fee-for-service payment model, as they are otherwise paid for two stays instead of just one.

"Every industry complains the penalties are too harsh," he said. "If you're going to tell me we don't need any economic incentives to do the right thing because we're always doing the right thing — that's not true."

***https://bit.ly/2U2cQ37***

## A Huge Fusion Experiment in The UK Just Achieved The Much Anticipated 'First Plasma'

***After a seven-year development, a fusion reactor has been powered on for the time, confirming all its components can heat hydrogen gas into the plasma phase of matter.***

**Peter Dockrill**

After a long, seven-year development, an experimental fusion reactor in the UK has been successfully powered on for the time, achieving 'first plasma': confirmation that all its components can work together to heat hydrogen gas into the plasma phase of matter.

This transition – achieved last week by a machine called MAST Upgrade in Culham, Oxfordshire – is the fundamental ingredient of a working nuclear fusion reactor, a dream scientists have been trying to realise for decades.

In nuclear fusion, the nuclei of two or more lighter elements fuse into a heavier nucleus, and release energy. This phenomenon is what goes on in the heart of the Sun, and if we can recreate and maintain the same reactions on Earth at sufficient scale, we stand to reap the rewards of clean, virtually limitless, low-carbon energy.

Artist's impression of the MAST Upgrade tokamak. (CCFE/UKAEA)

Not that we're there quite yet, but the successful completion and first test run of MAST Upgrade is a significant milestone in the journey. The original MAST (Mega Amp Spherical Tokamak) facility ran from 1999 to 2013, and its successor has been in the works ever since, so it's an important proof of concept.

"We want the UK to be a world leader in fusion energy and to capitalise on its amazing potential as a clean energy source that could last for hundreds of years," UK Science Minister Amanda Solloway said in a statement.

"Powering up the MAST Upgrade device is a landmark moment for this national fusion experiment and takes us another step closer towards our goal of building the UK's first fusion power plant by 2040."

A fusion reactor requires some sort of device to harness the reactions occurring in the plasma. Tokamaks - circular devices that use magnetic fields to contain the plasma created by the fusion reaction - are one of the leading designs for such a device.

For a long time, tokamaks employed a doughnut-shaped configuration, but newer devices like MAST Upgrade are examples of a more advanced spherical tokamak design, expected to provide numerous benefits in terms of efficiency and performance.

MAST Upgrade, which is operated by the Culham Centre for Fusion Energy (CCFE), which is part of the UK Atomic Energy Authority (UKAEA), will need all those advantages, too. Now that it's operational, the fusion experiment has some pretty big challenges to solve over the next several years.

First and foremost among these is heat exhaust. Fusion reactors create incredible amounts of heat that can damage the reactor's components. To fix this problem, MAST Upgrade will be trialling a new kind of exhaust system called the 'Super-X divertor', designed to reduce heat and power loads from particles leaving the plasma.

If the divertor is successful, it could offer a 10-fold heat reduction compared to what's been possible before now, which might be sufficient to make fusion reactors a cost-effective technology in future power plants.

That's a big if, but everything about fusion reactors is big, and MAST Upgrade – despite being a huge project that took seven years to build – is only a small part of the whole puzzle.

The device is actually a trial run for an even bigger project, the Spherical Tokamak for Energy Production (STEP), which will be the UK's first prototype fusion power plant, expected to be finished by 2040.

In the meantime, what researchers can learn from MAST Upgrade will also inform another massive venture: the world's largest nuclear fusion experiment, called the International Thermonuclear Experimental Reactor (ITER).

ITER is currently being assembled in southern France, involving thousands of scientists from over 30 countries. It's been in planning for years, and is about five years behind schedule, but when the project is complete (estimated to cost in the vicinity of US$65 billion), ITER will be our best chance yet of showing that the energy produced by nuclear fusion can be harnessed by human hands.

We may be years away from the discovery, but MAST Upgrade is a big step forward to getting us there. "ITER is the next generation of fusion device," explains CCFE physicist Andrew Thornton. "MAST Upgrade will support it by providing data from experiments we do here to direct how to run that machine in the future."

***https://nyti.ms/2IaJ89X***

## We've Rarely Seen a Dinosaur Brain Like This Before

***While later dinosaurs in this lineage were giant herbivores with tiny brains, this small species packed a lot more power in its skull.***

**By Veronique Greenwood**

Some 230 million years ago, in the forests of what humans would eventually call Brazil, a small bipedal dinosaur zipped after its prey. It had a slender head, a long tail and sharp teeth, and it was about the size of a basset hound.

Buriolestes schultzi, as paleontologists have named the creature, is one of the earliest known relatives of more famous dinosaurs that emerged 100 million years later: the lumbering brachiosaurus, up to 80 feet long and weighing up to 80 metric tons, the likewise massive diplodocus, as well as other sauropod dinosaurs. By the time the Jurassic period rolled around and the time of Buriolestes had passed, these quadrupedal cousins had reached tremendous size. They also had tiny brains around the size of a tennis ball.

***An artist's concept of the skull and brain of the sauropodomorph Buriolestes, a small, late Triassic dinosaur.*** **Márcio L. Castro and Rodrigo Temp Müller**

Buriolestes*'s* brain was markedly different, scientists who built a 3-D reconstruction of the inside of its skull report in a paper published Tuesday in the Journal of Anatomy. The brain was larger relative to its body size, and it had structures that were much more like those of predatory animals. The findings suggest that the enormous herbivores of later eras, whose ancestors probably looked a lot like Buriolestes, lost these features as they transitioned to their ponderous new lifestyle. It's also a rare glimpse into dinosaurs' neural anatomy at a very early moment in their evolution.

In 2009, Rodrigo Müller of the Universidade Federal de Santa Maria and colleagues discovered the first partial Buriolestes fossil in southern Brazil. In 2015, they uncovered another Buriolestes nearby — and this time, to their excitement, the dinosaur's skull was nearly all there. They used computed tomography scanning to get a peek inside, drawing inferences about the brain from the contours of the cavity left behind. They found that one portion of the cerebellum, the floccular lobe, was particularly large in Buriolestes.

"This structure is related with the capability to track prey with the eyes," Dr. Müller said.

***A Buriolestes fossil was discovered in southern Brazil.*** **Márcio L. Castro**

It's tiny in the enormous brachiosauruses, diplodocuses and other sauropods that lived later, which suggests that the structure grew less important as they transitioned to eating only plants.

Buriolestes also had small olfactory bulbs, suggesting that smell wasn't of crucial importance to the little hunter. In later sauropods, these bulbs grew in relative size, which might have helped them smell each other or detect predators.

Most striking, however, was the brain's large size relative to the rest of the body, Dr. Müller said. In many lineages, relative brain size increases over time, he said — but not, apparently, in this case.

"Probably this change is related with the feeding habits changing," he said. "Carnivorous animals generally need more cognitive capabilities."

These details about Buriolestes's brain are intriguing because it is such an early dinosaur, said Lawrence Witmer, a paleontologist and professor of anatomy at Ohio University who studies sauropods.

"It gives us a window into the earliest evolution of the brain and sensory systems of the largest animals ever to walk on land, the sauropod dinosaurs," he said, noting that Buriolestes*'s* inner ear canal and floccular lobe suggest it used quick, coordinated movements of the head, neck and eyes.

"For the slow-moving sauropods, there was no premium on retaining such capabilities, and we now know that they must have lost these capabilities," he said, "since ancestral species like Buriolestes had them."

Our knowledge of early dinosaur brains is very slight, said Fabien Knoll, a paleontologist at the Dinopolis Foundation in Teruel, Spain. Buriolestes, which is one of the oldest known dinosaurs, and its contemporaries are mainly found in Brazil and Argentina. When fossil remains do turn up, the skulls may be crushed or missing, making this study a rarity.

It helps illuminate a shadowy but fascinating evolutionary story — the slow transformation of small, quick, two-legged hunters into immense, unhurried quadrupeds who ate only plants.

"The study of the brain of dinosaurs is booming as it is now easier than ever to reconstruct the brain morphology thanks to digital technology," Dr. Knoll said. "However, information about the brain in early dinosaurs is hampered by a lack of quality fossils. So I'd say that it is important to keep digging in those sites in Brazil, Argentina and elsewhere that are likely to provide well-preserved very early dinosaurs."

***https://bit.ly/38ikvTu***

## Scientists Find Tissue in The Human Eye That Appears Resistant to SARS-CoV-2

***Evidence suggests at least some of the eye may in fact be resistant to SARS-CoV-2***

**Peter Dockrill**

As the coronavirus pandemic spread across the world this year to such devastating effect, many of us were asking the same questions. How does the virus spread? How do I protect myself from the infection?

The truth is, we're still learning how SARS-CoV-2 works. Official guidance from the CDC suggests the main way the virus spreads is through respiratory droplets or small particles, ejected from the mouth or nose of infected people, and then inhaled by others.

But that's not the only way the virus circulates. The same infectious droplets and particles can land on surfaces and be transferred by touch – meaning infection could result if you touch something with

virus particles on it, and then touch your mouth, nose, or eyes, the CDC says.

While this general advice is repeated by health authorities the world over, there's still a lot we don't know about how the coronavirus might enter the body through the eyes, although scientists suggest it's "biologically plausible". However, new evidence suggests at least some of the eye may in fact be resistant to SARS-CoV-2 – even while it's susceptible to other kinds of viruses.

In a new study, researchers at Washington University in St. Louis found that the cornea – the transparent dome at the front of the eye, which covers the iris and pupil – appeared to be resistant to coronavirus infection in experiments, although they're eager to emphasise the findings are only preliminary. "Our findings do not prove that all corneas are resistant," says molecular microbiologist Jonathan J. Miner, the first author of the study.

"But every donor cornea we tested was resistant to the novel coronavirus. It's still possible a subset of people may have corneas that support growth of the virus, but none of the corneas we studied supported growth of SARS-CoV-2."

In experiments using corneal tissue from 25 human donors and also mice corneas, the researchers exposed the eye tissue to three separate viruses: SARS-CoV-2, Zika virus, and herpes simplex virus 1 (HSV-1, which produces cold sores).

In the human cornea explants tested (which also contained some conjunctiva tissue, the membrane that covers the rest of the front of the eye), the experiment showed that herpes and Zika virus were able to replicate in the tissue – but tests showed no sign of SARS-CoV-2 replication.

"The cornea and conjunctiva are known to have receptors for the novel coronavirus, but in our studies, we found that the virus did not replicate in the cornea," says senior author and ophthalmologist Rajendra S. Apte. "Our data suggest that the novel coronavirus does not seem to be able to penetrate the cornea."

As for how the human cornea and conjunctiva might be capable of resisting SARS-CoV-2, the team isn't entirely sure. A potential molecular inhibitor of viruses in the eye – called interferon lambda – was able to limit virus growth in the human cornea for HSV-1 and Zika virus, but blocking the protein didn't seem to boost SARS-CoV-2's ability to replicate.

Without more to go on, the researchers' best guess for now is that the human cornea's resistance to coronavirus is "likely regulated by a distinct antiviral pathway". Quite what that pathway is we still don't know, and the team says further study is needed to confirm these findings.

In other words, health professionals shouldn't ditch their protective eyewear yet, and until we know otherwise, nobody should assume coronavirus can't get into the body via the eyes, despite the cornea's seeming resistance.

"It's important to respect what this virus is capable of and take appropriate precautions," Miner says. "We may learn that eye coverings are not necessary to protect against infection in the general community, but our studies really are just the beginning."

The findings are reported in *Cell Reports*.

***https://bit.ly/2GyEPV2***

## An Asteroid Trailing After Mars Could Actually Be The Stolen Twin of Our Moon

***Surprising resemblance raises interesting questions about the object's ancient origins***

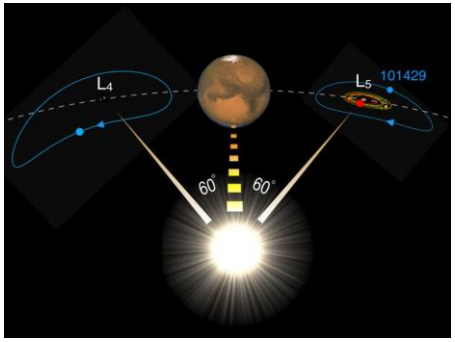
**Peter Dockrill**

A distant asteroid trailing in the gravitational wake of Mars has been observed in greater detail than ever before, and the close-up reveals a surprising resemblance – one that raises some interesting questions about the object's ancient origins.

The asteroid in question, called (101429) 1998 VF31, is part of a group of trojan asteroids sharing the orbit of Mars.

Trojans are celestial bodies that fall into gravitationally balanced regions of space in the vicinity of other planets, located 60 degrees in front of and behind the planet.

Most of the trojan asteroids we know about share Jupiter's orbit, but other planets have them too, including Mars and Earth too.




What makes (101429) 1998 VF31 (hereafter '101429') interesting is that among the Red Planet's trailing trojans (the ones that follow behind Mars as it orbits the Sun), 101429 appears to be unique.

***Depiction of Mars and trojans; 101429 is the blue point circling L5.*** **(AOP)**

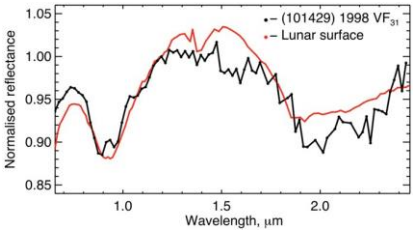
The rest of the group, called the L5 Martian Trojans, all belong to what's known as the Eureka family, consisting of 5261 Eureka – the first Mars trojan discovered – and a bunch of small fragments believed to have come loose from their parent space rock.

101429 is different, though, and in a new study led by astronomers from the Armagh Observatory and Planetarium (AOP) in Northern Ireland, researchers wanted to examine why.

Using a spectrograph called X-SHOOTER on the European Southern Observatory's 8-m Very Large Telescope (VLT) in Chile, the team examined how sunlight reflects off 101429 and its L5 kin in the Eureka family. Only, it looks like 101429 and the Eureka clan aren't kin after all, with the analysis revealing 101429 shows a spectral match for a satellite much closer to home.

"The spectrum of this particular asteroid seems to be almost a dead-ringer for parts of the Moon where there is exposed bedrock such as crater interiors and mountains," explains AOP astrochemist Galin Borisov.

While we can't be sure yet why that is, the researchers say it's plausible that this Martian trojan's origins began somewhere far removed from the Red Planet, with 101429 representing a "relic fragment of the Moon's original solid crust".




***Spectral comparison of 101429 and the Moon's surface.*** **(AOP)**

If that's true, how did the Moon's long-lost twin end up as a trojan bound together with Mars?

"The early Solar System was very different from the place we see today," explains lead author of the study, AOP astronomer Apostolos Christou.

"The space between the newly-formed planets was full of debris and collisions were commonplace. Large asteroids [planetesimals] were constantly hitting the Moon and the other planets. A shard from such a collision could have reached the orbit of Mars when the planet was still forming and was trapped in its Trojan clouds."

It's a captivating idea, but the researchers say it's not the only explanation for 101429's past. It's also possible, and perhaps more likely, that the trojan instead represents a fragment of Mars chipped off by a similar kind of incident impacting the Red Planet; or it might just be a commonplace asteroid that, through the weathering processes of solar radiation, ended up looking just like the Moon.

Further observations with even more powerful spectrographs might be able to shed more light on this question of space parentage, as could a future spacecraft visit, the team says, "which could, en route to the Trojans, obtain spectra at Mars or the Moon for direct comparison with the asteroid data".

The findings are reported in *Icarus*.

https://bit.ly/2U5Sarb

# Startling Case Study Finds Asymptomatic COVID-19 Carrier Who Shed Virus For 70 Days

***70 days after her first positive test, she was still shedding infectious SARS-CoV-2 particles.***

**Clare Watson**

If there's one thing we know about SARS-CoV-2, is that its effects on people vary. A lot. As the pandemic rolls on, this coronavirus continues to bring new surprises. A team of researchers and doctors has now reported the case of one woman with leukemia who had no symptoms of COVID-19 but 70 days after her first positive test, she was still shedding infectious SARS-CoV-2 particles.

This result is much longer than previous reports of hospitalised adults found shedding infectious SARS-CoV-2 virus up to 20 days after their COVID-19 diagnosis, plus other accounts of people shedding genetic material from the virus up to 63 days after their symptoms first appeared.

The new report should alert doctors and public health experts alike to the fact that people without symptoms and with weakened immune systems, such as cancer patients, can seemingly shed the SARS-CoV-2 virus for a really long time. In this case, even months. "Although it is difficult to extrapolate from a single patient, our data suggest that long-term shedding of infectious virus may be a concern in certain immunocompromised patients," the research team wrote in their paper describing the case.

An estimated 3 million people in the US have some kind of condition that compromises or weakens their immune system, making them vulnerable to infections. Cancer patients on chemotherapy and transplant recipients who take immunosuppressant drugs are some examples.

"As this virus continues to spread, more people with a range of immunosuppressing disorders will become infected, and it's important to understand how SARS-CoV-2 behaves in these populations," said virologist and co-author Vincent Munster from the US National Institute of Allergy and Infectious Diseases.

Virologists like Munster would have been on the lookout in this pandemic for prolonged viral shedding of SARS-CoV-2. It has been well established that immunocompromised people can shed common seasonal coronaviruses for weeks after infection.

Studies of Middle East respiratory syndrome (MERS) have likewise shown immunocompromised people shedding the virus that causes this illness for up to one month after infection.

But the proportion of asymptomatic COVID-19 cases still remains unclear. The danger is that these carriers of the virus could easily go about their days unaware of their capability of spreading the virus.

In this case, doctors detected, isolated and tracked one woman's SARS-CoV-2 infection using diagnostic PCR tests and throat swabs.

A decade ago, the 71-year-old woman was diagnosed with chronic lymphocytic leukemia (CCL), a cancer of white blood cells that most commonly affects older adults and progresses slowly.

She first tested positive for SARS-CoV-2 on 2 March 2020 after she was admitted to hospital for severe anaemia related to her cancer. She then tested positive for COVID-19 another 13 times and yet showed no symptoms of the disease.

Twice she received plasma from people who had recovered from COVID-19, and eventually cleared the virus from her system sometime in mid-June. Doctors don't know exactly when she acquired the coronavirus, but most likely it was at a rehabilitation facility which had a large COVID-19 outbreak in February, where the woman had stayed days earlier.

From the throat swabs collected over the course of her 15-week infection, the researchers showed that the woman was shedding infectious SARS-CoV-2 particles for 70 days. Some of its genetic

material was also detected up to 105 days after she first tested positive.

We have to be careful here to distinguish between infectious viral particles and the results of a diagnostic test, which just detects shreds of viral RNA. Importantly, in this study the researchers actually isolated SARS-CoV-2 from a few swab samples – day 70 included – to test whether the virus collected was able to replicate in lab-grown cells, which it was.

"This indicates that, most likely, the infectious virus shed by the patient would still be able to establish a productive infection in contacts upon transmission," the researchers wrote.

Additionally, once the doctors were alerted to the woman's case, they also quickly recognised it as an opportunity to study how SARS-CoV-2 might evolve over the course of such a long infection. The researchers sequenced the virus' genetic material from various samples to see how this particular SARS-CoV-2 virus changed while circulating through the woman's body. Different viral variants became more dominant at certain times, but the turnover was high and none stuck. Further experiments with the isolated virus in lab-grown cells also showed that these genetic changes didn't affect how fast the virus replicated.

While these are some valuable insights, more research still needs to be done. "Understanding the mechanism of virus persistence and eventual clearance will be essential to providing appropriate treatment and preventing transmission of SARS-CoV-2, as persistent infection and prolonged shedding of infectious SARS-CoV-2 occur more frequently," the study authors wrote in their paper.

And yes, this is a single case study, so we can't make any generalisations about persistent viral shedding in people with other immunocompromising conditions, or how effective convalescent plasma is as a treatment for COVID-19, the study authors warn.

It is, however, "the longest case of anyone being actively infected with SARS-CoV-2 while remaining asymptomatic," according to the medical research team. They think the woman remained infectious for so long because her compromised immune system never allowed her to mount a response.

"We've seen similar cases with influenza and with Middle East respiratory syndrome, which is also caused by a coronavirus," Munster said. "We expect to see more reports like ours coming out in the future." With each one, we'll surely learn more about this virus, how long it persists, and what we need to do to take care of the most vulnerable people in our communities.

The study was published in the journal *Cell*.

***https://bit.ly/3p5wrxN***

## Gene therapy for autism-linked condition weakened legs, robbing two people of ability to walk

***Small clinical trial of gene therapy for Angelman syndrome on hold after two participants temporarily lose ability to walk.***

**By Giorgia Guglielmi, Spectrum**

A small clinical trial of a gene therapy for Angelman syndrome—a rare genetic condition related to autism—is on hold after two participants temporarily lost the ability to walk. The safety issue is important to resolve, experts say, given that the therapy otherwise appears to be effective, and the trial could guide treatment strategies for similar brain conditions.

Biopharmaceutical company Ultragenyx in Novato, California, in collaboration with Florida-based biotech startup GeneTx, launched the trial in February to assess the safety of a therapy for Angelman syndrome, a neurodevelopmental condition characterized by intellectual disability, balance and motor problems, seizures, sleep problems and, in some cases, autism.

Angelman syndrome results from the mutation or absence of a gene called UBE3A. People inherit two copies of UBE3A. Typically,

only the maternal copy is active in neurons and the paternal copy is silent. But in people with Angelman syndrome, the maternal copy is mutated or missing, so their brain cells express no active UBE3A protein.

The drug developed by Ultragenyx and GeneTx, called GTX-102, is a short snippet of RNA called an antisense oligonucleotide that activates the paternal copy of UBE3A and aims to restore the protein to typical levels. Three other companies—Roche, Biogen, and Ionis—are pursuing similar therapies for the syndrome.

**Adverse effect**

On 26 October, Ultragenyx and GeneTx reported that the clinical trial had enrolled five individuals with Angelman syndrome, aged 5 to 15. The plan had been to administer to each participant a dose of GTX-102 once a month over four months. Researchers injected the drug directly into the nutrient-rich solution that envelops the brain and spinal cord through a site in the lower back.

The participants were to receive increasing doses, but all started with different amounts: Two began at the lowest dose, two started with the second-lowest dose, and one started at the second-highest dose. The final dose was about 10 times higher than the lowest dose. After a single dose at the second-highest level, one participant developed leg weakness. The other four participants experienced the same adverse effect after taking the highest dose. The symptoms emerged one to four weeks after the participants' last dose.

"Two of the patients were not able to support themselves to walk and three were, but they were weaker," says Elizabeth Berry-Kravis, professor of child neurology at Rush University Medical Center in Chicago, Illinois, where the five children were treated.

The side effects appear to be a result of inflamed nerves where the drug was injected, perhaps due to accumulation of the drug in that area. In animal studies, the drug didn't cause similar adverse effects, says Ultragenyx chief executive officer, Emil Kakkis. "We do know, though, that antisense oligonucleotides are known to have local toxic effects if given at high concentrations."

The participants all recovered after they received drugs that decrease inflammation, Berry-Kravis says. "Even those who couldn't support themselves on their legs are walking around fine—they actually are somewhat more coordinated now than they were before the study."

**Drug benefits**

When the researchers evaluated the participants at day 128, all five showed significant improvements in some traits, including communication, sleep, and motor skills, Berry-Kravis says. Within weeks of the initial doses, parents and caregivers reported that the participants had acquired new words and gestures.

"We're seeing things like using a fork independently for the first time ever, learning to swim on their own, using their augmentative communication device, being able to play an interactive game with the family," Berry-Kravis says. But, she adds, "you can't go on with an adverse event."

Going forward, the companies plan to limit the maximum dose to a range in which the drug appears to improve traits without causing leg weakness. They also intend to change how they administer the drug so it cannot accumulate at the site of injection. "The drug solution will be given to the patient with their head down to allow the drug to flow toward the brain more efficiently," Kakkis says.

Before resuming the study, the companies will seek approval from the U.S. Food and Drug Administration, says Scott Stromatt, chief medical officer of GeneTx. "We hope dosing will start in the next one to two months," he says. "Parents are pretty excited to resume because of the positive changes they've observed in their children."

**Leading the way**

All drugs have a side effect at some point, says Mark Zylka, professor of cell biology and physiology at the University of North

Carolina at Chapel Hill, who was not involved in the study. “It seems like they’re just going to need to dial in the dosage better.”

Zylka is working on a therapy for Angelman syndrome that uses the gene-editing technology CRISPR to unmute the paternal copy of UBE3A. The rapid improvement observed in the trial participants is encouraging, he says. “It suggests that this idea of turning on the dad’s copy of the gene really has the potential to help individuals with Angelman.”

Others are excited about what the trial results might mean for other brain conditions. “One of the biggest questions in the field is how long the therapeutic window remains open in neurodevelopmental disorders like Angelman syndrome,” says Timothy Yu, assistant professor of pediatrics at Harvard University. The preliminary findings from the Ultragenyx and GeneTx trial suggest that the therapy can work even in teenagers.

“It’s still early days, and we have to be careful,” Yu says. “But if this result continues to hold true, that’s going to be really game-changing.”

*Originally published on* Spectrum

***https://wb.md/3mVcO9I***

## Menstrual Cycle Irregularity and Premature Death: The Take-Home Message

***Having irregular menstrual cycles had increased risk for premature death before age 70, as well as an increased risk for cardiovascular and cancer death***

**JoAnn E. Manson, MD, DrPH**

Hello. This is Dr JoAnn Manson, professor of medicine at Harvard Medical School and Brigham and Women's Hospital.

I'd like to talk with you about a recent report in The BMJ on menstrual cycle regularity and length during the early and middle reproductive years, as well as the risk for premature death from cardiovascular disease, cancer, and all causes. I'd like to acknowledge that I'm a coauthor of this report.

We've known for a long time that irregular menstrual cycles can be a marker for polycystic ovarian syndrome, increased risk for type 2 diabetes, and even cardiovascular disease. This, however, is the most detailed and comprehensive report on the association with premature death (death before age 70) and cause-specific mortality.

The cohort was the Nurses Health Study II, about 80,000 US women who were age 25-42 at enrollment and who were followed for about 24 years. These women reported their menstrual cycle characteristics during adolescence, early adulthood, and the middle reproductive years.

Compared with women who reported regular menstrual cycles that averaged 26-31 days (varying by no more than 4 days), the women who reported always having irregular menstrual cycles or cycles that tended to last 40 days or longer had an increased risk for premature death before age 70, as well as an increased risk for cardiovascular and cancer death. These women averaged a 30%-40% increased risk for all-cause mortality, with the greatest increase seen in cardiovascular death. Women with irregular cycles during the middle reproductive years had up to a 60% increase in risk for cardiovascular death.

Women taking oral contraceptives were analyzed separately, so that was not a confounder of these associations. We also adjusted for body mass index, physical activity, and other lifestyle factors so that it appeared that irregular or long menstrual cycles were an independent marker of increased risk for premature mortality.

Why would this be the case? We know that regular menstrual cycles indicate a generally healthy hypothalamic-pituitary-ovarian access. We also know that hormonal and metabolic perturbations or disruptions can lead to irregular menstrual cycles.

All of this suggests the value of asking women about the regularity of their menstrual cycles and the average length, which might be markers for general health. Try to determine the underlying cause

for those women who report irregular or excessively long menstrual cycles. These questions may also help to identify women who can be targeted for more diligent control of their risk factors, such as hypertension and dyslipidemia, with a focus on lifestyle modification, including increased physical activity and a heart-healthy diet.

Thank you so much for your attention. This is JoAnn Manson.

*Dr JoAnn Manson is a professor of medicine at Harvard Medical School and chief of the Division of Preventive Medicine at Brigham and Women's Hospital in Boston, Massachusetts.*

***https://bit.ly/36baZic***

## An Amazonian tea stimulates the formation of new neurons

***DMT – one component of ayahuasca tea - promotes neurogenesis***

One of the main natural components of ayahuasca tea is dimethyltryptamine (DMT), which promotes neurogenesis --the formation of new neurons-- according to research led by the Complutense University of Madrid (UCM). In addition to neurons, the infusion used for shamanic purposes also induces the formation of other neural cells such as astrocytes and oligodendrocytes.

"This capacity to modulate brain plasticity suggests that it has great therapeutic potential for a wide range of psychiatric and neurological disorders, including neurodegenerative diseases", explained José Ángel Morales, a researcher in the UCM and CIBERNED Department of Cellular Biology.

The study, published in *Translational Psychiatry*, a Nature Research journal, reports the results of four years of in vitro and in vivo experimentation on mice, demonstrating that these exhibit "a greater cognitive capacity when treated with this substance", according to José Antonio López, a researcher in the Faculty of Psychology at the UCM and co-author of the study.

**Changing the receptor eliminates the hallucinogenic effect**

Ayahuasca is produced by mixing two plants from the Amazon: the ayahuasca vine (Banisteriopsis caapi) and the chacruna shrub (Psychotria viridis).

The DMT in ayahuasca tea binds to a type-2A serotonergic brain receptor, which enhances its hallucinogenic effect. In this study, the receptor was changed to a sigma type receptor that does not have this effect, thus "greatly facilitating its future administration to patients".

In neurodegenerative diseases, it is the death of certain types of neuron that causes the symptoms of pathologies such as Alzheimer's and Parkinson's. Although humans have the capacity to generate new neuronal cells, this depends on several factors and is not always possible.

"The challenge is to activate our dormant capacity to form neurons and thus replace the neurons that die as a result of the disease. This study shows that DMT is capable of activating neural stem cells and forming new neurons", concluded Morales.

***References:*** *Jose A. Morales-Garcia1, Javier Calleja-Conde, Jose A. Lopez-Moreno, Sandra Alonso-Gil1, Marina Sanz-SanCristobal, Jordi Riba y Ana Perez-Castillo. "N,N-dimethyltryptamine compound found in the hallucinogenic tea ayahuasca, regulates adult neurogenesis in vitro and in vivo" Translational Psychiatry (2020)10:331. DOI: 0.1038/s41398-020-01011-0.*

***https://bit.ly/32mpv5v***

## Horse mastery helped mysterious Mongolian warriors build a multiethnic empire

***Until now, the only accounts of the Xiongnu came from their enemies.***

**By Andrew Curry**

Chinese records from 2200 years ago describe how these fierce mounted archers from the wide-open steppes of today's Mongolia clashed with armies in what is now northwestern China.

Their onslaughts spurred the Chinese to build what would become known as the Great Wall of China on their northern border, as protection against the mounted nomads. They also started to raise cavalry armies of their own.

***The horse was the heart of the mysterious Iron Age Xiongnu empire in Mongolia, as suggested by a decorative bronze belt plate showing two horses grappling.*** **National Museum Of Mongolia**

The equestrian empire of the Xiongnu left no written records. But biology is now filling out their story, and those of other Central Asian cultures in antiquity. Two studies—a sweeping survey of ancient DNA from more than 200 individuals across 6000 years and an analysis of horse skeletons from just before the rise of the Xiongnu—trace population movements across Central Asia and the key role played by horsemanship. The results "show the horse was probably the driver of some of the ancestry shifts we see in the human population," says Ludovic Orlando of Paul Sabatier University, who was not involved in the paper. "The horse provided new range in patterns of human mobility and allowed people to travel long distance faster."

Horses were probably domesticated by the Botai culture around 3500 B.C.E. near what is modern Kazakhstan. Horses may have been mainly used for meat and milk at first, and later began to pull wheeled chariots.

To learn more about human migration across Central Asia, a team led by Choongwon Jeong of Seoul National University and Harvard University's Christina Warinner sampled and sequenced DNA from human remains found in Mongolia. The results, which they report today in *Cell*, span the period from 5000 B.C.E. all the way to the heyday of another horse-riding culture—that of Genghis Khan's Mongol Empire, around 1000 C.E.

Genetic studies of Western European populations have shown that around 3000 B.C.E., the Yamnaya—mobile herders of cattle, sheep, and goats—pushed west from the steppes of what is today Russia and Ukraine and triggered a dramatic genetic turnover in Europe. Skeletons from Bronze Age Mongolia had shown the Yamnaya also moved east and introduced their dairy-oriented pastoralist lifestyle there. But they left no lasting genetic traces in Mongolia, the oldest samples in the new study show.

The ancient DNA does show that 1000 years later, another group from the steppes, called the Sintashta, left a lasting imprint. They also brought fateful cultural changes to Mongolia's grasslands, as earlier archaeological studies had shown.

Starting in about 1200 B.C.E., equestrian innovations including selective breeding for size and endurance, plus bridle bits, riding pants, and even early saddles, appeared in the record, says archaeologist William Taylor of the University of Colorado, Boulder, a co-author on both papers.


**N. Desai/Science**

Mongolians of the time were obviously riding horses, as vividly confirmed by the second paper, in the *Proceedings of the National Academy of Sciences*. The authors, Chinese and U.S. archaeologists, report that horse skeletons buried around 350 B.C.E. in the Tian Shan mountains, now part of China's Xinjiang province, show bone abnormalities from riding, including spinal damage from the weight of a rider and changes to the bones of the mouth from bits and bridles. "Put the lower back pathologies together with evidence for a bridle, and it all suggests horses were being ridden," says Sandra

Olsen, an archaeologist at the University of Kansas, Lawrence, who was not part of either study.

Not long after, the Xiongnu emerged. They translated their skills on horseback into a sophisticated means of waging war and organizing an empire over vast distances. Starting in about 200 B.C.E., the Xiongnu marshaled nomadic tribes from across Eurasia into a formidable force, turning the steppes into a political center rivaling neighboring China. "The Xiongnu have been a source of constant worry and harm to China," one contemporary Chinese historian wrote. "They move about in search of water and pasture and have no walled cities or fixed dwellings, nor do they engage in any kind of agriculture."

Jeong's study of DNA from 60 human skeletons from the Xiongnu's 300-year-run shows how the region was transformed into a multiethnic empire. After more than 1000 years in which three distinct, stable human populations lived side by side on the Mongolian steppe, genetic diversity rose sharply around 200 B.C.E. Populations from western and eastern Mongolia mixed with each other and with people carrying genes from as far away as present-day Iran and Central Asia. Such wide-ranging mixing has "never been seen before at that scale," Jeong says. "You can see the entire Eurasian genetic profile in the Xiongnu people."

The results suggest mastery of the horse made possible stunning long-distance voyages on Central Asia's sea of grass. Archaeological finds in the graves of Xiongnu elites, such as Roman glass, Persian textiles, and Greek silver, had suggested distant connections. But the genetic evidence suggests something more than trade. Eleven Xiongnu-period skeletons showed genetic signatures similar to those of the Sarmatians, nomad warriors who dominated the region north of the Black Sea, 2000 kilometers across the open steppe from Mongolia.

"There's no written evidence of [Xiongnu] contact with Sarmatians, and it's not well-attested archaeologically. It's really surprising they're mixing over these long distances," says Tsagaan Turbat, an archaeologist at the Mongolian Academy of Sciences's Institute of Archaeology. "This kind of information is really a game changer."

In the future, researchers hope the genomes will help reveal how the mysterious nomad empire worked. The Xiongnu are "doing the things that empires do—forcing or enticing people to move," says University of Michigan, Ann Arbor, archaeologist Bryan Miller. "Are people sent out to rule, or are local elites allowed to continue?" he asks. "Only genetics could answer that."

***https://bit.ly/32mrhnb***

## Vaccine shows promise against herpes virus

***New study demonstrates candidate's potential to generate antibodies, limit viral shedding***

A genetically edited form of a herpes simplex virus -- rewired to keep it from taking refuge in the nervous system and eluding an immune response -- has outperformed a leading vaccine candidate in a new study from the University of Cincinnati, Northwestern University and the University of Nebraska-Lincoln.

Published Nov. 6 in the journal *Nature Vaccines*, the study found that vaccinating guinea pigs with the modified live virus significantly increased the production of virus-combating antibodies. When challenged with a virulent strain of herpes simplex virus, the vaccinated animals displayed fewer genital lesions, less viral replication and less of the viral shedding that most readily spreads infection to others.

The modified virus is actually a form of herpes simplex virus type 1, best known for causing cold sores around the lip. The fact that it demonstrated cross-protection against HSV type 2 -- the sexually transmitted type usually responsible for genital herpes -- suggests

that an HSV-2-specific edition of the vaccine could prove even more effective, the researchers said.

The World Health Organization estimates that more than 500 million people have HSV-2, which persists for a lifetime and often flares up in response to stress. In addition to causing blisters, HSV-2 increases the risk for HIV infection and may contribute to Alzheimer's disease or other forms of dementia.

Despite the prevalence of the viruses, more than four decades of research have yet to yield an approved vaccine for HSV-1 or HSV-2. Part of the difficulty: The alphaherpesviruses, which include HSV, have evolved an especially sophisticated way of evading the immune responses aimed at destroying them.

After infecting mucosal tissues of the mouth or genitourinary tract, HSV works its way to the tips of sensory nerves that transmit signals responsible for the sensations of pain, touch and the like. With the help of a specialized molecular switch, the virus then breaks into the nerve cell, hitching a ride on the molecular equivalent of a trolley car that transports it along a nerve fiber and into the nucleus of a sensory neuron. Whereas the mucosal infection is soon cleared by the immune response, the infected neurons become a sanctuary from the body's immune system, with HSV leaving only when stirred by rises in steroids or other stress-elevated hormones in the host.

Nebraska's Gary Pickard and Patricia Sollars, alongside Northwestern's Gregory Smith and Tufts University's Ekaterina Heldwein, have spent years studying how to prevent HSV from reaching the safety of the nervous system. Heldwein advanced those efforts when she characterized the architecture of a certain alphaherpesvirus protein, pUL37, that the team suspected was integral to the virus moving along nerve fibers. Computer analyses based on that architecture suggested that three regions of the protein might prove important to the process.

Smith then carefully plucked out and replaced five codons, the fundamental coding information in the DNA, from the viral genome of each region. The researchers hoped that those mutations might help impede the virus from invading the nervous system.

Their hopes were rewarded when Pickard and Sollars injected mice with a virus modified in region 2, or R2, of the protein. Rather than advancing deeper into the nervous system, the virus was stuck at the nerve terminal. But the team also knew that modifying HSV could have unintended consequences.

"You can keep the virus from getting into the nervous system," said Pickard, professor of veterinary medicine and biomedical sciences at Nebraska. "That's not that hard to do by making broadly debilitating mutations. But when you knock down the virus so much that it doesn't replicate well, you are not rewarded with a robust immune response that can protect you from future exposures."

So the researchers were heartened when further studies showed that the R2-mutated virus performed well as a vaccine in mice. Moreover, it circumvented certain stubborn issues that have cropped up with other vaccine approaches. Some approaches have involved challenging the immune system with only a subset of HSV components, or antigens, priming the body to recognize them but potentially miss others. Some have modified the virus so that it can replicate just once, preventing long-term persistence in the nervous system but also reducing spread in mucosal tissues and, by extension, a stout immune response.

"So it's the same story over and over again: Either your subunit vaccine doesn't present enough antigens, or you make the live virus essentially so sick that it doesn't work really well to generate an immune response," Pickard said. "That's why we're so optimistic about our R2 platform, because it avoids all those problems."

David Bernstein, a researcher at Cincinnati Children's Hospital Medical Center who evaluates herpesvirus vaccine candidates through a program supported by the National Institutes of Health, took note of the team's success and reached out to Northwestern's Smith in 2018. Armed with an R2-modified form of HSV-1, Bernstein decided to test its effectiveness against HSV-2 infection in guinea pigs. As promising as their prior results had been, Pickard conceded that he wasn't sure an HSV-1 vaccine would be up to the task of generating immunity against HSV-2.

But just one of the dozen R2-inoculated guinea pigs developed acute lesions after being injected with HSV-2, compared with five of 12 animals receiving another promising vaccine candidate that recently failed a human clinical trial. Whereas that latter vaccine candidate had no discernible effect on the number of days that guinea pigs shed the virus, the team's R2 vaccine cut the shedding period from 29 days to about 13. And unlike the guinea pigs receiving no vaccine or the other candidate, those receiving the R2 vaccine showed no sign of HSV-2 in the cluster of brain cells that normally house it. Neutralizing antibodies, meanwhile, registered about three times higher in the R2-inoculated guinea pigs than in those inoculated with the other vaccine candidate.

"The fact that the viral shedding was knocked down so much with the R2 vaccine is really important, because it's the viral shedding -- even if it doesn't cause lesions -- that can then pass on the virus," Pickard said. "If you have genital herpes, you can pass that on to your significant other, not knowing that you're doing it. It's very problematic. So the fact that the shedding was knocked down so much is a really good sign."

With an HSV-1 version of the R2 vaccine showing such promising cross-protection against its sexually transmitted counterpart, the researchers' to-do list now includes making and testing an HSV-2 vaccine against the HSV-2 virus.

"If you're making antibodies against the proteins of that particular virus, it stands to reason (that) it would work better than if you're making an antibody against something that's slightly different," he said. "So that's our expectation."

**'It's Going To Have A Big Impact'**

Around the time that Bernstein and his NIH program were expressing interest in the R2 vaccine design, Pickard and Smith were launching a startup, Thyreos LLC, aimed at further developing and eventually licensing their R2 vaccine design.

Fittingly for a couple of researchers based in Nebraska and Illinois, the duo is working on vaccines for livestock -- cattle and hogs, specifically -- that contend with alphaherpesviruses of their own. In cattle, the bovine herpesvirus can cause respiratory disease, curb appetite and even contribute to aborted calves, all of which add up to billions of dollars in lost revenue annually. Though a modified live-virus vaccine for cattle does exist, it also gets into the bovine nervous system. And that, Pickard said, can spell trouble in cattle just as easily as in people.

"What happens, then, is that when those cows are loaded on a truck and shipped to a feedlot, it's a stressful environment," he said. "The virus hiding in the immune system reactivates. They start shedding the virus from excretions in their nose, and they can then pass that virus on to other animals in that feedlot, and the cattle can get respiratory disease.

"So the fact that our R2-modified viruses don't enter the nervous system is not just an academic thing. Actually, it has a real, practical application for the cattle industry."

As they prepare to embark on a new series of studies that they hope will show the R2 design's superiority to the current industrywide vaccine, Pickard and Smith are also kicking off an initial round of seed funding for the enterprise.

Given that the team initially developed its R2 design in the alphaherpesvirus that infects pigs -- the so-called pseudorabies virus -- Pickard also expressed confidence in the design's promise for protecting hogs. In the late 1990s and early 2000s, the United States waged a successful campaign to eradicate pseudorabies from the country, in large part through vaccination. As with cattle, though, the vaccine can enter the nervous system of hogs and has proven less successful in countries that are less vigilant about outbreaks.

"Again, we are pretty confident that our pseudorabies virus R2 vaccine is going to be more effective than what's been out there," Pickard said. "In terms of protecting pigs, it's going to have a big impact at some point.

"These pathogens can survive trans-Pacific transport in feed ingredients or feed products. When you talk to people who are concerned about biosecurity, they say that whatever is going on elsewhere in the world in terms of these viruses, eventually, they may show up here. It's just a matter of time."

***https://bit.ly/357FsP6***

## On the hunt for wild bananas in Papua New Guinea

***The banana has its earliest origins in Papua New Guinea, where it was domesticated by indigenous communities at least 7,000 years ago.***

This ancestor, *Musa acuminata*, subspecies *Banksii*, looks very different from the ubiquitous Cavendish banana: peeling back its skin reveals hundreds of large, hard seeds that enable easy reproduction in the wild.

Today, a colorful mix of wild bananas (including *Banksii*) still grow throughout the humid forests of New Guinea. However, as deforestation and fires decimate tropical and subtropical forests across the South Pacific, we risk losing both the ancestors and the possible future of the banana we know and love.

Against the backdrop of climate change, pests, and rampant diseases, researchers and crop breeders are scrutinizing diverse banana varieties for traits such as disease tolerance, pest resistance, and their ability to adapt to fluctuating temperatures.

Wild bananas represent a largely untapped wealth of genetic diversity. Sebastien Carpentier, a scientist at the Alliance of Bioversity International and CIAT, explains: "It's very important for breeders to have access to crop wild relatives of bananas to help them find the traits that they are looking for."

***Bananas originally contained hard seeds. This trait can still be seen in wild species in Papua New Guinea.*** **Credit: S.Carpentier**

### Mission: Search and collect

At the International Musa Germplasm Transit Center (ITC) in Leuven, Belgium, the Alliance manages the world's largest collection of banana germplasm. Yet despite currently holding 1,617 banana accessions, the genebank only scratches the surface of wild banana diversity. Bart Panis, a senior scientist based at the ITC, notes, "We don't know how much is out there."

In-situ conservation is becoming less likely with the loss of the wild bananas' habitat, therefore scientists like Panis are working against the odds to "fill in the gaps" by collecting samples in their native habitat, then transporting them to genebanks for further research and ex-situ conservation.

***A farmer carries a bunch of wild maclayi bananas in Papua New Guinea.*** **Credit: S.Carpentier**

Last year, a collecting expedition touched down in Papua New Guinea that included Panis, Carpentier, and several other researchers collaborating with the county's National Agricultural Institute, NARI. For nearly two weeks, the team scoured terrain high and low, gathering a total of 31 bunches of eight different species while observing their adaptations in diverse environments.

One particularly fortuitous find was the giant *Musa ingens.* Despite competing with neighboring trees to grow as high as 15 meters, this towering species is no match for extensive land clearing and currently faces extinction.

**Collection challenges**

Collection is not easy work: elusive crop wild relatives are called wild for a reason. While they might have favorable traits, some species remain uncultivated because they are not edible for humans. Even banana specialists cannot always identify wild species in the field, and once they are found, the plants might not be in the brief stage where seeds or genetic material are available (bananas do not follow a predictable schedule for fruiting and flowering).

Preservation of viable material also makes successful storage and transportation a major challenge (fruits had to survive 2-4 weeks of travel before their seeds were extracted in Belgium). Furthermore, researchers must adhere to many countries' strict restrictions on the collection and transportation of plant genetic material.

**Ensuring future generations of bananas**

Back in Belgium, the team carefully stored genebank samples (techniques include drying and cryopreserving seeds) and began conducting a series of experiments to better understand the newly collected material.

Following field observation of *Musa balbisiana* persevering in open land recovering from fires (indicating the growth of extensive root systems to facilitate water uptake), the researchers have gained insights on water use efficiency, which could help breeders adapt bananas to resist future drought scenarios— a serious priority as banana farmers currently suffer from up to 65% harvest losses related to drought.

Carpentier notes that there is also potential to fight pests and diseases, saying, "We need to continue to collect, store and screen for resistance in banana wild relatives." Other points of interest include health benefits (wild bananas have been used in traditional medicine, but this is not well-documented) and implications for increasing the yield of bananas per plant. The results are summarized in two articles, one in *Plants* evaluating methods to ensure the viability of collected seeds, and the other in *Crop Science* summarizing the characterization of diverse phenotypes.

The scientists conclude that this work is just part of the ongoing effort to fill in knowledge gaps and ensure the survival of diverse, resilient bananas. Panis and Carpentier agree that it doesn't matter who does it, but it is critical that these banana wild relatives continue to be collected and conserved before they disappear forever.

***More information:*** *Simon Kallow et al, Challenges for Ex Situ Conservation of Wild Bananas: Seeds Collected in Papua New Guinea Have Variable Levels of Desiccation Tolerance, Plants (2020). DOI: 10.3390/plants9091243*

*David Eyland et al. Filling the gaps in gene banks: Collecting, characterizing and phenotyping wild banana relatives of Papua new guinea, Crop Science (2020). DOI: 10.1002/csc2.20320*

***https://bit.ly/3mZboeq***

## First Case Study of Its Kind Documents Girl With Mirror Movement And Rare Disorder

***With a rare condition known as mirror movement, one hand's actions are echoed simultaneously by the other***

**Mike Mcrae**

If you sit down at a piano, hitting different notes with each hand would be the first step to mastering the instrument. But what if both hands are intent on doing the same thing? That's the experience of

people with a rare condition known as mirror movement, and doctors have now documented a unique case.

Several years ago, researchers in India identified a case of this extremely rare condition in a 13-year-old girl who also has a diagnosis of the chromosomal disorder Turner syndrome.

Finding the two conditions together is a first for the medical community, raising questions of how – or even whether – the two might potentially be connected.

Most tiny humans take a while to become dextrous, but by age 10 the communication between the two halves of our brain allows us to pinch, poke, wave and wiggle the fingers on each hand independently of one another.

For about one in every million children, this development is incomplete, meaning one hand's actions are echoed simultaneously by the other. Make a victory sign with your left hand, and your right will be forced to approximate a similar shape.

The fundamental cause of such copy-cat movement is still largely a matter of speculation, though there's reason to suspect key nerves in the brain are 'cross-talking' as a result of the formation of false synapses between neurons.

In about a third of all cases, mutations in a couple of genes appear to be responsible, impairing development of the nervous system in such a way that instructions from either side of the brain are accidentally transmitted to both sides of the body.

As for the rest of recorded cases, clearly there's still much to learn about the brain and its development.

One place we can look for more clues is in other symptoms and behaviours exhibited by those with the condition and ask if there is a deeper relationship.

For example, individuals who also have cerebral palsy will display degrees of mirror movements. Parkinson's disease is another condition that can come with this form of so-called synkinesia, especially if it affects more one side of the brain than the other.

Having breaks or an absence of connection between the hemispheres – a bridge of neurons called the corpus callosum – can also coincide with the behaviour. It's in many of these cases that a genetic link has been uncovered.

Kallmann syndrome is a condition caused by lack of certain hormones, giving rise to characteristics such as a lack of smell and delayed puberty. And, sometimes, mirror movements.

Turner syndrome is also a condition that impacts on a body's ability to coordinate hormonal responses.

Before this case, nobody had recorded a person who had the chromosomal abnormality and would experience mirror movements as well.

The syndrome is caused by an absence of a second X chromosome, leaving those with the disorder with just a single X to do the job. The consequences can be widespread across the body, ranging from heart defects to reduced height, and a failure in ovary development.

In the case of this particular young subject, there were some mild physical abnormalities, and an absence of secondary sexual characteristics. An echocardiogram of her heart revealed an aortic valve with two instead of the usual three flaps, but otherwise all appeared healthy.

Besides poor school work, her speech and other neurological signs were all as expected for a kid her age. Yet as you can see below, given a task of counting to five on her left hand, her right hand just couldn't help but join in.

An MRI scan didn't reveal any surprises, and without the resources to look closer at her brain's physiology, the medical staff at Sri Ramachandra Institute of Higher Education and Research were left to assume it's 'just one of those things'.

As mirror movements are incredibly rare, and Turner syndrome affects just one in 2,000 women, it's hard to say if it's a coincidence or if there's some kind of connection that might tell us more about both conditions. Medical science is often a matter of recording novel discoveries like these and waiting patiently to see if future findings add increments of evidence.

As for the young lady, who's now 19, we're happy to say the subject of this unusual case study appears to otherwise be doing well.

"Considering her age, she was started on gradually escalating doses of oestrogen followed by progesterone therapy," the endocrinologists write.

This case study was published in *BMJ Case Reports*.

***https://bit.ly/3paAEAo***

## Clay subsoil at Earth's driest place may signal life on Mars

***Earth's most arid desert may hold a key to finding life on Mars.***

Diverse microbes discovered in the clay-rich, shallow soil layers in Chile's dry Atacama Desert suggest that similar deposits below the Martian surface may contain microorganisms, which could be easily found by future rover missions or landing craft.

Led by Cornell University and Spain's Centro de Astrobiología, scientists now offer a planetary primer to identifying microbial markers on shallow rover digs in Martian clay, in their work published Nov. 5 in *Nature Scientific Reports*.

In that dry environment at Atacama, the scientists found layers of wet clay about a foot below the surface.

"The clays are inhabited by microorganisms," said corresponding author Alberto G. Fairén, a visiting scientist in the Department of Astronomy at Cornell University. "Our discovery suggests that something similar may have occurred billions of years ago—or it still may be occurring—on Mars."

If microbes existed on Mars in the past, their biomarkers likely would be preserved there, Fairén said. "If microbes still exist today," he said, "the latest possible Martian life still may be resting there."

The red planet will see rovers cruising across the surface there in the next few years. NASA's rover Perseverance will land on Mars in February 2021; Europe's Rosalind Franklin rover will arrive in 2023. Both of those missions will seek microbial biomarkers in the clay below the planet's surface.

"This paper helps guide the search," Fairén said, "to inform where we should look and which instruments to use on a search for life."

In the Yungay region of the Atacama desert, the scientists found the clay layer, a previously unreported habitat for microbial life, is inhabited by at least 30 salt-loving microbial species of metabolically active bacteria and archaea (single-cell organisms).

The researchers' Atacama discovery reinforces the notion that early Mars may have had a similar subsurface with protected habitable niches, particularly during the first billion years of its history.

"That's why clays are important," he said. "They preserve organic compounds and biomarkers extremely well and they are abundant on Mars."

***More information:*** *Armando Azua-Bustos et al, Inhabited subsurface wet smectites in the hyperarid core of the Atacama Desert as an analog for the search for life on Mars, Scientific Reports (2020). DOI: 10.1038/s41598-020-76302-z*

***https://bit.ly/3p5Rqk2***

## The weird genomes of domesticated fish

***Unlike most domestic animals, the goldfish is purely decorative.***

**John Timmer**

Humans have domesticated a large number of animals over their history, some for food, some as companions and protectors. A few species—think animals like rabbits and guinea pigs—have partly shifted between these two categories, currently serving as both food and pets. But one species has left its past as a food source behind

entirely. And, in another rarity, it ended up serving not so much as a companion but as a decoration.

We're talking goldfish here, and we've now gotten a look at their genome. And it's almost as weird as the fish themselves are.

**A fine kettle of fish**

It's worth stopping for a moment to consider just how weird they are within the realm of domestication. They started out just as slightly colored variants of a carp that is otherwise used entirely for aquaculture. We've completely removed them from the food chain and turned them into pets, but they're not the sort of pets that we interact with like a dog or cat, or even a guinea pig. Largely, they just sit there and look decorative. And in the process of making them even more decorative, we've bred a lot of varieties that are far less functional as fish.

(I invite you all to come up with an example of a species I'm not thinking of that has had an equally unusual trajectory and let me know in the comments.)

There's also a bit of odd history here, too. While we call them goldfish pretty generically, most of what we have are not the actual golden goldfish. After their domestication in China (and later move from garden ponds to indoor tanks), gold-colored fish ended up reserved for the emperor, so they're still fairly rare. In the meantime, we've bred strains with multiple tails, strains that lack dorsal fins, and more.

That's likely to do some weird stuff to the fish, genetically. But it turns out they were pretty weird to start with.

Even the process of reporting the genome turned out to be kind of odd. It was first reported back in May, when a group described the genome of a goldfish and compared it to its ancestor, the common carp. But the analysis was pretty minimalistic. Then, this week, a huge consortium dropped an analysis of not only a strain of goldfish but 185 different strains. Plus 16 different wild carp genomes for comparison. While the goldfish genome is only 1.8 billion base pairs long (1.8 Gibases), the raw sequence required to do all of this ran out to 4.3 trillion bases. It's an astonishing effort.

But because some other group published the data already, the researchers published it in PNAS using a route that only puts it through informal peer review. There doesn't seem to be anything problematic with the paper that would cause it to fail peer review, but publishers typically want novel results, and this apparently wasn't new enough.

**Fish fish fish fish**

Most animals have two sets of similar chromosomes, one each from their mother and father. In humans, there are 23 chromosomes, and we have two of each, meaning we each carry 46 of them. In both goldfish and the carp they were derived from, there are 25 chromosomes, but each fish carries 100 of them—instead of two copies, they have four, or rather two sets of two. Apparently, the lineage that produced the carp is a hybrid of two closely related lineages (possibly separate but closely related species).

Consequently, unless some copies of the genes have been deleted or disabled by mutation, the fish should have four copies of them. But there are some specific cases where they don't, such as DNA repair genes, where one set of copies has been eliminated. And in a lot of tissues, one or the other set of genes is more active, but there's no obvious and consistent pattern of which of the sets it is. So we're not at the point where we really understand what's happening with the fishes' four sets of genes, but the answer is not likely to be simple.

The fish were only isolated recently and have undergone pretty serious selection for unusual features—just check out the pictures in Wikipedia's list of goldfish strains. Many of the genetic variants underlying these physical traits are likely to be recent and have been selected as the only variant present in the strain. This creates

what's called a "selective sweep" in which the variant, and any others that happen to be near it when it arose, are the only ones present in a population.

So the researchers checked the fish for selective sweeps and unsurprisingly found quite a number of them. The top 1 percent of possible sweeps contained a total of almost 1,000 genes. In zebrafish, a species that's not too distantly related to carp, 173 of these genes had been deleted. Fish carrying these deletions had changes in features like pigmentation and body shape, which is exactly what you'd expect given the differences between goldfish and most other carp. There were also some changes related to behavior, but it's important not to think of them in terms of dog-like behaviors—in fish, it's more a matter of how they feed or their response to odorants.

***Enlarge** / An egg goldfish, which largely lacks a dorsal fin.* **Michelle Jo**

The researchers also looked carefully at the genomes of egg goldfish, which no longer make a dorsal fin. They identified a total of nearly 400 genes that were associated with the loss of the dorsal fin. Oddly, most of the variants were from one of the two ancestral genomes. And when the subset of those had been knocked out in zebrafish (57 of them), a quarter had an obvious change near the dorsal fin. Whether the remaining ones have a more subtle issue, contribute to the difference in some other way, or are simply spurious isn't clear.

While the current analysis is incomplete, the large number of strains and sequences means there's enough data here to keep researchers busy for a long time. With up to four copies of every gene, though, doing genetics on these animals is never going to be simple, so understanding what the sequence differences mean will take considerably more work.

To some extent, that idea justifies the decision of most geneticists to focus on zebrafish, which may not have as many strains as goldfish but do have simpler genetics. Still, the authors suggest those two species might be related. With an extra pair of copies of every gene, it may be that the goldfish tolerated far more mutations than the zebrafish could.

*PNAS*, 2020. DOI: 10.1073/pnas.2005545117 (About DOIs).

***https://bit.ly/3n8QOsd***

## Alcohol, Bowel Movements May Confound Microbiology Studies

***A review offers a glimpse of previously unconsidered variables that could hinder efforts to identify true correlations between disease and gut microbiome composition.***

**Max Kozlov**

Gut microbes represent a complex ecology of tens of trillions of bacterial cells that have far-reaching effects—from mental health disorders to cardiovascular health. While the composition of the microbiome has been correlated with certain diseases such as Parkinson's disease, it is hard to unpack whether such associations are just correlation, a consequence of the health condition, or a cause or contribution of the illness.

A review published in *Nature* on November 4 aims to search for potentially confounding variables by analyzing physiological and lifestyle differences between people with and without a particular disease and identifying differences that might be associated with the composition of the gut microbiota.

*The Scientist* spoke with National Institute of Allergy and Infectious Diseases immunologist Ivan Vujkovic-Cvijin, a postdoc and coauthor of the review, about its findings.

***The Scientist*: What motivated you to write this paper?**

Ivan Vujkovic-Cvijin: I've been involved in the field of examining how the gut microbiome may impact the health of people with HIV.

In that field, there was a fascinating discovery that men who have sex with men have a very different gut microbiome composition than men who have sex with women. The predominant population of people with HIV in the United States and a lot of Western Europe are men who have sex with men. It turned out that when we looked at some of the studies that that had been done in the field, we were comparing people with HIV that are men who have sex with men to uninfected subjects that were men who have sex with women. In those studies, we weren't only finding differences that were dependent on HIV, but also depending on sexual preference, when we were really intending only to identify those bacteria that differ as a result of HIV.

***https://bit.ly/3kaQq2X***

## Here's The Amazing Way The Sides of Our Brain Adapt if They Can't Talk to Each Other

***How the brains of people born without a corpus callosum adapt is truly extraordinary.***

**Clare Watson**

Between the two halves of our brains is a gap filled with fluid and spanned only by the corpus callosum: a bridge of neural fibres that ferries information to either side.

Some people, however, are born without a corpus callosum, meaning they lack the usual neural highway of approximately 190 million axons that would typically carry information between the left and right hemispheres. How their brains adapt is truly extraordinary.

Studies have shown that in individuals who never develop this major connection, the brain rewires itself and creates entirely new connective pathways that re-route signals through other brain regions, keeping communication flowing across the divide via the mid- and fore-brain.

The new fibres built to reconnect the brain's two hemispheres, called Probst bundles in some cases, aren't a perfect replacement for the corpus callosum, and yet "[r]emarkably, communication between the two hemispheres is maintained," explains neuroscientist Vanessa Siffredi from the University of Geneva in Switzerland.

Much about the process remains a mystery, but new research from Siffredi and colleagues has now revealed that the brain plasticity in children lacking a corpus callosum runs even deeper still.

Imaging results from a study of Australian children show that brains lacking a corpus callosum create a remarkable number of new connections inside each hemisphere as well, to help maintain overall brain function.

About one in every 4,000 people are born without a corpus callosum, which usually measures 10 centimetres (almost 4 inches). It first develops in the womb by around 20 weeks into gestation.

Around half of people born without a corpus callosum (called agenesis of the corpus callosum) have learning and memory difficulties. Some might also have poor attention and less cognitive flexibility than their peers. Others can be even more severely affected, and yet a quarter of people with the diagnosis show no visible signs of any impairment whatsoever.

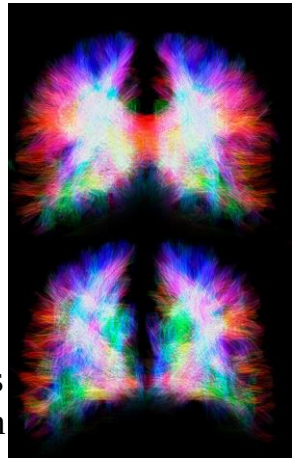
The researchers thought that looking at the connectivity of neural fibres within each hemisphere – aside from being another marker of the brain's malleability and brilliance – might also go some way to explaining this variability in effects.

In the study, 20 children (aged 8 to 17) who were born either without a corpus callosum or with an incomplete one had their brains scanned using an MRI machine so that the researchers could look at connections between different parts of their brain. These were compared with scans taken from 29 healthy children with an intact corpus callosum.

As well as having their brains scanned, the children also completed tasks to test their working memory, attention, and verbal learning abilities.

By analysing the structural connections in the whole-brain images from the children without a fully formed corpus callosum, the team found the brain responds by strengthening neural pathways inside each of its two hemispheres.

The children with corpus callosum agenesis showed greater connectivity within each brain hemisphere than the group of healthy children.



***In a healthy brain (top), the two hemispheres are connected by the corpus callosum fibres, shown in red. These fibres are absent in a brain with corpus callosum agenesis (bottom).*** **(Vanessa Siffredi/UNIGE)**

Incredibly, when analysing the functional links across the brain scans (in only 16 children with corpus callosum agenesis this time), there was no significant difference between the two groups.

Even without a corpus callosum, parts of the children's brains were still actively communicating with other areas, both within hemispheres and between them. This functional connectivity was comparable to their healthy peers with a normally developed corpus callosum.

This shows, again, how brain plasticity can triumph over what appears to be, on first impressions, gaping structural deficiencies in brain development.

"We think that plasticity mechanisms, such as the strengthening of structural bonds within each hemisphere, compensated for the lack of neuronal fibres between hemispheres," says Siffredi.

"New connections are created and the signals can be re-routed so that communication is preserved between the two hemispheres."

Focusing just on the kids with corpus callosum agenesis and their test results, the researchers also discovered that greater structural connectivity within hemispheres was associated with better learning outcomes, long-term and working memory, and attention.

Although the number of children involved in this study might seem small, it is sizeable for research examining this condition. There are also few studies to date that pair brain imaging with behavioural outcomes like this research does.

It's also worth noting that some of the children studied had other brain abnormalities in addition to their missing corpus callosum, though these kids showed similar levels of plasticity to their group mates.

All in all, this remains a spectacular example of brain plasticity at work, and the new findings could help explain why some children with this extraordinary condition fare better than others.

The research was published in *Cerebral Cortex*.

***https://bit.ly/3lbXC7Q***

## How a Coronavirus Mutation in Minks Could Wreak Havoc on Vaccine Development

***New strain is still transmissible from minks to humans, raising dire concerns about the efficacy of vaccines***

**By Matt Miller**

Officials in Denmark announced Wednesday that they would be euthanizing every last mink in the country's fur farms, some 17 million animals. The news came after a discovery by Danish scientists that SARS-CoV-2, the official name for the virus that causes COVID-19, had mutated in captive minks, producing a strain of the coronavirus that is not readily stopped by antibodies to the dominant strain of the virus. More troublingly, this new strain is still transmissible from minks to humans, raising dire concerns about the efficacy of vaccines currently in development worldwide.

There are currently five reported cases of the new strain in minks and 12 cases in humans, all workers at one of the roughly 1,100 mink farms in Denmark. Although the humans are being monitored, isolated, and treated in keeping with recommendations from public health officials, the minks are not so lucky—mass extermination is already underway. More than 400 mink farms have already culled the entirety of their mink populations, likely by gassing them. Police and military personnel are being deployed to destroy all minks on the remaining farms as soon as possible.

According to Finnish fur auctioneer Magnus Ljung, pelts from minks near infected farms are unfit for sale and will be destroyed, almost half the total count. The remaining pelts will be sold as less valuable summer pelts. All told, extermination of the minks will cost an estimated $785 million.

***Minks on a farm in Herning, Denmark.*** **Ole Jensen/Getty Images**

Since the beginning of the pandemic, more than 50 animal species have tested positive for the dominant strain of SARS-CoV-2. When news broke in April that several domestic dogs and cats had tested positive, there were no calls for mass euthanasia of house pets. Spread to wild animals—tigers, bats, and great apes to name a few—has also been documented, but at no point did epidemiologists recommend such dramatic intervention to stop the spread in those species, several of which are endangered. The case of the Danish minks, however, is different. Other animal species that have caught the coronavirus from people were infected with the dominant strain of the virus, the one that's been making headlines for the better part of the past year. Additionally, most of those species turned out to be dead-end hosts for the virus, meaning that although the virus could infect those animals, and even cause disease in those animals, the virus was unable to turn around and jump from animal to human, a phenomenon called zoonosis.

Minks are an exception to this rule. The European mink industry has been battling outbreaks of the dominant strain of COVID on farms since June, after a rash of COVID-19 cases in people in northern Denmark was ultimately traced back to those farms. Once it became clear that the animals themselves were the source of the infections, minks were slaughtered en masse on farms where these outbreaks had taken place. The Netherlands culled more than 10,000 after coronavirus outbreaks this summer. Officials in Spain slaughtered almost 10 times as many after an outbreak occurred at a farm in the Aragón province. Those minks were contracting and spreading the dominant strain of the coronavirus, the one we all know and dread.

The development this week is the discovery that minks in Denmark are now testing positive for a *mutant* strain of the virus that is not readily destroyed by COVID antibodies. Experts warn that if the outbreak of this mutant strain is not sufficiently contained, the world could be facing a second pandemic.

So how did the mutation happen? Every organism on the planet mutates. When the genetic code is getting copied, errors occur frequently. When a letter in the genome is inadvertently replaced with a different letter, that is called a mutation. The vast majority of mutations are either inconsequential or cause harm to the organism. Rarely, though, a mutation will actually empower the organism—in this case, the virus.

Coronaviruses as a general rule mutate slowly compared with other viruses. Take, for instance, the seasonal flu. Because influenza viruses can shuffle their genetic code like a deck of cards, battling the flu with seasonal vaccines is perpetually frustrating; some years the efficacy of the flu vaccine is as low as 10 percent. By the time researchers can develop a more effective vaccine, the flu has

mutated again, often rendering the previous year's vaccine useless. Because studies confirmed that SARS-CoV-2 was not undergoing significant mutations as it spread from person to person, researchers were optimistic in the early stages of the pandemic that a vaccine would confer long-lasting protection, unlike the flu vaccine.

However, SARS-CoV-2 has mutated before. Back in May, there was a small panic about a coronavirus mutation that seemed to increase the virus's transmissibility, or the ease with which it passes from one person to another, thanks to a modification in a spike protein on its surface. The fears later proved unfounded, spread by nonscientists over-interpreting the paper after it was discussed in publicly accessible online forums prior to peer review. Fortunately, researchers were later able to confirm that this mutation did not represent a paradigm shift in our response to the virus, nor would the mutation affect vaccine development; antibodies made against viral strains with the spike protein mutation were still able to destroy the previous, unmutated version of the virus.

"The worst-case scenario is a new pandemic, starting all over again out of Denmark." — Kåre Mølbak

The virus produced by the mink mutation, on the other hand, seems impervious to antibodies produced in response to the dominant strain of the virus. What makes this mutation so much more troubling than previous mutations is not that the mutation increases how quickly the virus will spread, nor that it increases the severity of resultant disease. It's the fact that the immune system cannot transfer knowledge about one form of the virus in fighting the other form. From the perspective of your immune system, they are two different viruses altogether.

In other words, if you have survived COVID-19, your immune system remains largely unequipped to battle the mink strain. Once pharmaceutical companies finish their monthslong race to devise an effective COVID vaccine, the vaccine would likely provide little protection against the emerging strain. The virus has mutated into what could eventually be thought of as COVID 2.0 if the Danes fail to contain its spread.

Kåre Mølbak, who directs the Danish government's public health and infectious disease arm, summed it up when he told Reuters on Wednesday, "The worst-case scenario is a new pandemic, starting all over again out of Denmark."

There is, fortunately, some cause for cautious optimism here. First, we don't know yet how the mutant strain will affect the human body clinically. The 12 people infected with the mink strain may all remain symptom-free if the mink mutation also happens to have lowered its ability to cause disease. For all we know, the mutation could just as easily result in a virus that is even better at killing people than the current virus. We simply don't have enough information.

The second silver lining is the low case count of this mutant coronavirus—currently 12 people and just five animals. Given the rapid, aggressive governmental response, there is a good chance that this mutation will be stamped out before it can spread significantly, at least in the mink population. What hangs in the balance is the fate of the 12 infected people whose current health status remains unknown. Were they asymptomatic for a time? Did they have contact with friends and family prior to diagnosis? Will they spread it to health care workers treating them? Barring the hope for an impotent strain of the virus, it's not hard to imagine a scenario in which cases of the mink strain explode exponentially, similar to the course of the original virus.

As our twin COVID-19 battles of public health and public resistance rage on in the U.S., the laudable response by officials in Europe stands in stark contrast to the response here. Wearing face covers, socially distancing, washing our hands frequently, and quarantining when appropriate are all we can do as individuals. But

the governmental response—contact tracing, free and speedy testing, a health care system that won't obliterate you with medical debt—is every bit as important. Fortunately for the world, the mink mutation didn't happen here.

*Update, Nov. 7, 2020: This article was updated to include information about what will happen to the pelts of the exterminated minks.*

***https://nyti.ms/2U88p7a***

# An Explanation for Some Covid-19 Deaths May Not Be Holding Up

***Recent studies have created doubts about an agent in cytokine storms, and suggest that treatments for it may not help.***

**By Gina Kolata**

Medical researchers are raising significant doubts about whether an agent of the human immune system causes some coronavirus patients to end up in the hospital with injured lungs and other organs, struggling to breathe. What remains is a continuing mystery about what causes certain people to die from Covid-19, and how best to prevent that.

A hypothesis that emerged early in the pandemic involves cytokine storms, an immune system response that is often invoked to explain severe viral infections, and to many doctors it seemed to make perfect sense: Patients who died from Covid were found to sometimes have little or no virus in their bodies. Their immune systems got rid of it. But in doing so, the hypothesis went, their body's defenses went rogue, spewing out powerful compounds — cytokines and other drivers of inflammation — that fatally damaged tissues and organs in a storm.

But in a number of recent studies, some researchers say, an agent suspected of causing the storms might not be the culprit or that such storms might not happen in the way doctors believed.

Not everyone agrees.

Dr. Randy Cron, a professor of pediatrics and medicine at the University of Alabama at Birmingham who has long studied cytokine storms, says some hospitalized Covid-19 patients do experience these immune overreactions. But he agrees they are not identical to the reactions seen in other disorders, and much remains

The storm idea has so far centered on one cytokine, interleukin-6, or il-6. The belief that it might be the culprit in certain Covid deaths began with reports from China early in the course of the pandemic. Doctors there said a patient who fared poorly had high levels of il-6. The doctors tried using drugs that block il-6, and the patient recovered. Similar reports followed there and in Italy.

A number of drugs that block il-6 are on the market to treat rheumatoid arthritis. They also can stop severe immune reactions in other situations, such as a cytokine release syndrome that can occur with some cancer treatments and with adult onset Still's disease, a rare form of inflammatory arthritis. But, said Dr. John Stone, a professor of medicine at Harvard, "these are not infections."

Nonetheless, anti-il-6 drugs quickly became a standard of care at many hospitals treating Covid patients. The idea that they were quelling cytokine storms became widely accepted.

"It is so easy to have your brain remember the cases that worked really well and ignore those that didn't work well," said Dr. Bruce Walker, an immunologist who is director of the Ragon Institute of Massachusetts General Hospital, M.I.T. and Harvard and was not involved in the new studies.

Now rigorous studies are failing to find that anti il-6 drugs are effective. Other studies are finding that il-6 levels are not even highly elevated in Covid patients compared to levels in other critically ill patients.

Three such studies, two published in JAMA Internal Medicine and one in the New England Journal of Medicine, found no evidence that a commonly used il-6 inhibitor, tocilizumab, a rheumatoid

arthritis treatment, reduced the death rates in severely ill coronavirus patients. Roche, which makes tocilizumab, did its own tests in Covid patients and reported that its drug was not helpful.


***Tocilizumab, a commonly used il-6 inhibitor, has not been shown to help fight Covid-19.*** **Credit...Pascal Rossignol/Reuters**

One issue is with the very term, cytokine storm.

"It has no definition," said Dr. Carolyn Calfee, an intensive care medicine specialist at the University of California in San Francisco. It is colorful and captured the imagination of doctors and much of the public, but with no definition there are no diagnostic criteria to show that such a thing is taking place.

And even if there is, il-6 might be a bystander rather than a driver. Hundreds of cytokines are released when the immune system goes into action. They drive and suppress one another in complex feedback loops. "You take this thing like spaghetti that is connected in so many different ways," Dr. Walker said. It is optimistic, he added, to think il-6 "will be the answer to everything."

Until recently, there were no systematic studies asking if il-6 levels really were unusually high in Covid patients.

It turns out that they often are not, recent research suggests.

Dr. Jonathan Parr, an infectious disease specialist at the University of North Carolina checked il-6 levels in his medical center's Covid patients early in the pandemic. They were difficult to interpret but generally were well below those seen in other inflammatory syndromes, like sepsis, where they are 27 times higher.

Dr. Calfee reviewed measurements reported in five studies with a total of more than 900 seriously ill coronavirus patients. Their il-6 levels ranged from normal to slightly higher.

And even when cytokine levels are sky high, as in sepsis, drugs that squelch immune reactions do not help, Dr. Stone said. Failed sepsis studies go back to the late 1980s, he said, when researchers tested etanercept, a drug used to treat autoimmune diseases. It blocks another cytokine, tumor necrosis factor, which, like il-6 is released by white blood cells in sepsis patients.

Etanercept turned out to increase the death rate in those patients.

Dr. William Fischer, a pulmonary and critical care physician at the University of North Carolina, said the idea of a cytokine storm "comes up in every severe viral infection." Examples include AIDS, Ebola, flu, Lassa fever, SARS and MERS, he said.

But, he said, "it can be difficult to tease apart what drives pathology — whether it's just the virus or both the virus and the very immune response that is needed to clear the virus."

"The next step should be a randomized clinical trial," in which patients are randomly assigned to receive the experimental treatment or not. Instead, Dr. Fischer said, trials, if they started at all, tended to begin after tens of thousands of patients had already gotten the drugs, which muddied the ability to prove safety and effectiveness.

So if not for this cytokine storm, what could be injuring the patients?

Inflammation from a variety of immune system overreactions may play a role, researchers said. One piece of evidence is that the steroid, dexamethasone, which broadly suppresses the immune system, can reduce the death rate.

But il-6 is not the only possible driver of a damaging immune response, Dr. Stone said. Other inflammatory chemicals such as ferritin appear and so does CRP, a protein that is a sign of inflammation.

Many Covid patients also suffer from blood clots, which themselves might be damaging lungs and other organs.

Dr. Walker cites another possibility. He was an author of a study that found that the virus can destroy germinal centers, places in

lymph nodes where antibodies are produced. The result can be fewer antibodies and less effective ones.

And it still remains possible that administering anti-il-6 drugs may help if done earlier or later during a patient's illness.

"We need randomized clinical trials to answer these hard questions," Dr. Stone said.

Dr. Calfee said the new findings should be teaching doctors a lesson. "We have to be really humble about biologic complexity," she said.

For now, Dr. Walker said, he and many others are sadder but wiser about using anti il-6 drugs to treat Covid patients.

"All of us were hopeful that this would work," he said. "It was definitely worth a try."

In that sense, we can say that those studies were confounded by sexual preference. It turns out that while HIV does have an impact on the gut microbiome, this other factor that we hadn't expected has a much stronger effect on the microbiome. That really led us to take a step back and ask what other confounding variables there might be out there that we are totally unaware of. There hadn't been an exhaustive examination of what variables might be confounding the comparisons of disease subjects to undiseased subjects, so that really spurred this this investigation.

***TS*: What other confounding variables did you find that were surprising?**

IVC: There were some things that had been relatively well described in the literature as having a major impact on the microbiome and had already been started to be incorporated in study designs, such as age and sex. But we were surprised to find that alcohol consumption and bowel movement quality—by that I mean whether the stool is typically loose, hard, or normal—were pretty strong sources of confounding effects for many diseases. This is something that I wouldn't say was appreciated by the field and it was certainly an unexpected result.

Both of those factors seemed to have a really strong impact on the microbiome and, importantly, those two variables often differ in people with a disease compared to people without a disease. Our alcohol consumption changes what when we learn of a diagnosis. [For example,] we're taking medications [that often] limit our alcohol use and sometimes the other way as well. And bowel movement quality is often affected by certain diseases. We hope that future studies incorporate consideration of those [two factors].

We are all very unique in terms of our immune systems, how we respond to infectious disease, and how susceptible we are to other chronic diseases. Biology, in a lot of ways, is an attempt to understand what causes these differences in how people respond. Certainly, we know that the microbiome is very different across populations. Some estimates say that I only share about ten percent of the bacteria that you might have at a certain taxonomic classification. We're excited that we may be expanding our understanding of the determinants of why my microbiome may be different from yours.

***TS*: Can you give me a breakdown of your findings with alcohol consumption?**

IVC: We did see a very dose-dependent effect. The more an individual consumed alcohol, the greater the impact on the microbiome. Even occasional drinking—one to two times per week—did have a measurable impact on the microbiome. One thing that we thought was interesting is that alcohol itself is used as a disinfectant in our microbiology labs, and one might expect for alcohol to kill some bacteria in the gut and reduce diversity of the gut microbiome, but we actually found the opposite effect, which we find fascinating. There was an increase in diversity that was also dose-dependent. We don't know the implications on health of this

increased diversity quite yet, but we are intrigued by the finding because it was a relative surprise.

***TS*: Tell me a bit about your methodology.**

IVC: Oh man, it's really beautiful. We were super stoked about the contribution of data science to our field of the microbiome. So what we did was we took advantage of an enormous study—the largest publicly available dataset examining gut microbiomes in human events across the world—and along with these samples, there were questionnaires given to every individual that were very detailed—over a hundred questions. We had a lot of information about each sample that we were able to use to identify the variables that had the greatest impact on the microbiome.

The methodology we chose to use was machine learning, and a really beautiful component of machine learning is the concept of cross-validation where you take a portion of your study participants that differ in one variable—let's say old individuals versus young—you take a subset of the total that you're comparing and you examine what patterns in the microbiome distinguish those two groups. With the subjects that the algorithm didn't see, you test whether the patterns that you found in the first subset are robust and are also observed in the unseen subjects.

This is a very powerful way to assess how strong and replicable the impact on the microbiome is of a given variable. We could quantify that discreetly, and we did so for all of the variables in the dataset and we ranked them by importance.

***TS*: What recommendations do you have for microbiologists or folks reading about microbiology?**

IVC: Based on these findings, we put forth the recommendation for human microbiome studies to capture information on these variables. These are two things that were not typically collected as part of clinical studies, whereas age, BMI, and sex more typically are. We recommend an expansion of the variables that are collected into terms of information and if possible to match these variables between the groups that are being compared, because they have an impact on the microbiome, and we want to mitigate how much studies are actually looking at these effects of these confounding variables and instead narrow down their results to what's really of interest in the disease that is that is being studied.

***I.V.C. et al., "Host variables confound gut microbiota studies of human disease" Nature, doi:10.1038/s41586-020-2881-9, 2020.***

***https://bit.ly/3naoZPZ***

## The mother's gut microbiome helps a child's brain develop its senses

***Without the maternal microbiome, a mouse's thalamus under-develops, resulting in reduced sensory processing***

**Simon Spichak**

Long before humans and other animals roamed the planet, microbes were alone. Humans co-evolved within the context of these microbes, so it is no surprise that a community of microbes now reside in our guts. They aid in stress responses, digestion, and even help establish our immune system. Incredibly, these microbes communicate and work with our bodies. These interactions are altered in many different disorders of the brain.

Gut microbes send signals to each other to communicate. Their language consists of chemical signals that are released into the gut. Like many languages with similar or identical words, our bodies recognize some of these words.

In September, researchers studying mice found microbial signals from the gut microbes of pregnant mice inside the fetus's growing brain. The study suggests that maternal microbes influence the development of brain cells in the thalamus, the part of the brain that receives touch, smell, visual, and auditory information. It builds upon decades of elegant research, impacting our understanding of brain development.

The simplest way to understand the function of something in biology is to remove it and see what breaks. Consequently, researchers developed sterile environments and techniques to ensure animals could be born without any microbes. In the 1940s, many researchers first identified the profound importance of gut microbes by generating these germ-free rodents. Mice born without these microbes had an elevated stress response as well as other alterations in the size and structure of different brain regions. Scientists began to wonder whether these microbes influence other behaviors or brain functions.

In this latest study, scientists assessed exactly how microbes influenced the developing mouse brain. They compared the fetal brains of developing mice that developed with normal and altered presence of gut bacteria in the mother. Some of the pregnant mice were germ-free, other mice had a normal gut community but received antibiotics, while the final group served as controls and had normal gut microbiomes. Removing the gut bacteria or just adding antibiotics (to kill off the gut microbiome) drastically changed gene expression in the fetal brains.

When compared to controls, a swath of gene expression involved in the development of individual nerve cells changed in the absence of maternal gut bacteria. These genes help neurons grow out long thin axons that allow them to communicate with their neighbors. Some of these genes play important roles in the thalamus, which accepts and relays sensory information to the rest of the brain. To confirm their findings, they used microscopy techniques to visualize this region of the brain to count the amount of these axons. The thalamus of mice whose mothers were germ-free or received antibiotics had less axon growth. Since nerve cells lacked these axons, the mice might experience deficits in processing sensory information.

To test out whether these mice had long-term deficits, they compared how quickly they were startled by sounds as adults. Mice with mothers without gut microbes as well as mice with mothers who received antibiotics showed a slower response. This indicated that maternal microbes were necessary for proper thalamus development. Without microbial signals from their mother present during development, mice would relay sensory information slower to the rest of their brain. Next, they found that giving germ-free mothers specific groups of gut bacteria could help these axons grow as normal, while also reversing the sensory deficit.

Pregnant mice without microbes showed a reduction of specific microbial signals in their bloodstream. Even though the signals impact the mice, they are only produced by bacteria. These findings suggest these microbial signals travelled from the bloodstream of the pregnant mouse to the fetal brain. Four of these signals were reduced in the fetal brains of mice whose mothers were germ-free or received antibiotics. Remarkably, if some brain cells were sampled, grown in a lab, and injected with these four metabolites, their growth was restored to normal.

These findings are incredible in part because of the challenges posed to researchers. Fetal mouse brains are incredibly tiny, difficult to work with and grow in a dish. Some limitations of this study stem from this difficulty. Researchers only looked at one point in time during pregnancy. While impaired offspring had altered brain development, it's unclear whether this sensory alteration is a substantial impairment. These findings don't rule out that microbes might simply speed up fetal development either.

Nonetheless, these differences may impact brain development or behavior later in life. These animal studies necessitate larger epidemiological studies in humans. Many people are administered antibiotics during pregnancy, but few studies assess the impacts on the baby. Could antibiotics at certain points of fetal development

increase the risk of poor outcomes in the brain? Answers to these questions will guide future clinicians when deciding whether or not antibiotics may harm a developing brain.

More broadly, this study contributes to the exciting area for deciphering microbial communication. Several signals generated by microbes in the pregnant mouse communicated with the fetal brain. Do these microbial signals send similar signals in humans? If they do, it might provide us with a specific marker of the developing brain.

Finally, this research further establishes that microbes during pregnancy are important. Once we learn which microbes produce the specific signals our bodies need for proper development. Ten or twenty years from now, we could assess the gut microbes from someone's feces to determine if they might be missing certain microbial signals or words. Then we could simply provide them with a microbe that will generate these signals, ensuring proper infant development.