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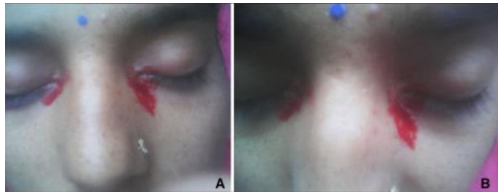
Woman cries blood tears during menstruation in 'rare and unusual clinical case'

A young woman's menstrual cycle brought tears to her eyes. But unlike most period-related tears, hers were bright-red tears of blood.

By Mindy Weisberger - Senior Writer 3 days ago

When the 25-year-old visited an emergency room with bloody tears oozing from both eyes, it was her second such episode in the past two months, doctors recently reported. Blood tears are a rare condition known as haemolacria, which can have different causes.

In the woman's case, her eyes were otherwise normal and she wasn't ill or injured. However, both instances of bloody tears coincided with the onset of her period, the physicians wrote in a case report.



***Both of the woman's eyes produced blood tears.* (Image credit: BMJ Case Reports)**

Normal menstruation can sometimes trigger cyclical bleeding outside the uterus, known as vicarious menstruation. The woman's crimson teardrops likely represented a highly unusual convergence of two conditions — vicarious menstruation and haemolacria — leading to period-triggered tears of blood, according to the report.

Though the woman's crimson tears looked alarming, when the doctors examined her they found that her eyes were undamaged and the blood tears weren't accompanied by headaches, dizziness or other symptoms of a health problem. Nor were there any signs of abnormality in her sinuses, tear ducts or in the bloody tears themselves, the researchers wrote in the March issue of the journal BMJ Case Reports.

Common causes of haemolacria include inflammation, trauma, lesions, tumors, hypertension, diseases such as jaundice and anemia, and vascular disorders, according to a report published on Feb. 14 by the National Center for Biotechnology Information. But after ruling out these possible causes of the woman's blood tears, the doctors identified the source as vicarious menstruation, which can cause bleeding from the nose, ears, lungs, nipples, intestines "and even skin," as well as from the eyes, the doctors wrote.

Indeed, the woman said that she had also experienced a nosebleed the first time she cried blood.

Certain types of eye tissue are known to be affected by hormonal changes; for example, the cornea's curve and thickness can vary "during different phases of menstrual period, pregnancy and lactation," which could explain why the woman's menstruation triggered bleeding from her eyes, according to the report. The doctors treated her with oral contraceptives, and after three months of hormonal therapy, the woman experienced no additional bleeding incidents.

"This is a rare and unusual clinical case," the doctors wrote, adding that there was nothing like it described in any recent scientific literature. However, more research would be required in order to understand exactly what caused the woman's bloody tears, and to determine how such a condition could be effectively managed long-term, the researchers concluded.

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Deluge of DNA changes drives progression of fatal melanomas

Melbourne researchers have revealed how melanoma cells are flooded with DNA changes as this skin cancer progresses from early, treatable stages through to fatal end-stage disease.

Using genomics, the team tracked DNA changes occurring in melanoma samples donated by patients as their disease progressed, right through to the time the patient died. This revealed dramatic

and chaotic genetic changes that accumulated in the melanoma cells as the cancers progressed, providing clues to potential new approaches to treating this disease.

The research, published in *Nature Communications*, was led by Professor Mark Shackleton, Professor Director of Oncology at Alfred Health and Monash University; Professor Tony Papenfuss, who leads WEHI's Computational Biology Theme and co-heads the Computational Cancer Biology Program at Peter MacCallum Cancer Centre; and Dr Ismael Vergara, a computational biologist at WEHI, Peter Mac and the Melanoma Institute Australia.

At a glance

- Genomics has been used to track DNA changes in melanoma samples donated by patients whose disease recurred and progressed after treatment.
- The research revealed that end-stage melanomas acquired dramatic and chaotic genetic changes that are associated with aggressive disease growth and treatment resistance.
- Understanding the genetic changes that drive melanoma growth and treatment resistance could lead to new approaches to treating this cancer.

Tracking a devastating cancer

Melanoma - the third most commonly diagnosed cancer in Australia - is caused by damaging changes occurring in the DNA of skin cells called melanocytes, usually as a result of exposure to ultraviolet (UV) radiation from sunlight. These genetic changes enable uncontrolled growth of the cells, forming a melanoma. As the melanoma cells keep dividing, some accumulate even more DNA changes, helping them to grow even faster and spread, said Professor Shackleton.

"At early stages, melanomas can be cured with surgery. However, they sometimes recur and progress to more aggressive forms. While there are excellent new therapies in these contexts, for some patients this progressing disease is difficult to treat," he said.

"We used DNA sequencing to document genetic changes that occurred as melanomas recurred and progressed in patients."

The team obtained genome sequencing data from tumours that had been donated by these patients and fed it into a mathematical model. This revealed that, as melanomas progress, they acquire increasingly dramatic genetic changes that add substantially to the initial DNA damage from UV radiation that caused the melanoma in the first place, said Professor Papenfuss.

"Early-stage primary melanomas showed changes in their DNA from UV damage - akin to mis-spelt words in a book. These changes were enough to allow the melanoma cells to grow uncontrollably in the skin," he said.

"In contrast, end-stage, highly aggressive melanomas, in addition to maintaining most of the original DNA damage, accumulated even more dramatic genetic changes. Every patient had melanoma cells in which the total amount of DNA had doubled - a very unusual phenomenon not seen in normal cells - but on top of that, large segments of DNA were rearranged or lost - like jumbled or missing pages in a book. We think this deluge of DNA changes 'supercharged' the genes that were driving the cancer, making the disease more aggressive.

"The genomes in the late-stage melanomas were completely chaotic. We think these mutations occur in a sudden, huge wave, distinct from to the gradual DNA changes that accumulate from UV exposure in form earlier-stage melanomas. The melanoma cells that acquire these chaotic changes seem to overwhelm the earlier, less-abnormal, slower growing cells," Professor Papenfuss said.

New insights into melanoma

Professor Shackleton said the research provided an in-depth explanation of how melanomas change as they grow and may also provide clues about how melanoma could be treated.

"We mapped sequential DNA changes to track the spread of the disease in individual cases, creating 'family trees' of melanoma cells that grew, spread and changed over time in each patient. In early-stage melanomas in the skin, the DNA changes were consistent with UV-damage, while the changes we saw in later-stage melanoma were totally wild, and associated with increased growth and spread of the disease, and evasion of the body's immune defences. We could also link some DNA changes to the development of treatment resistance," he said.

The research also revealed key cancer genes that may contribute to the growth and spread of the melanoma.

"Many patients' late-stage melanomas had damage to genes known to control cell growth and to protect the structure of DNA during cell growth and division. When these genes don't work properly, cell growth becomes uncontrolled and the DNA inside cells becomes even more abnormal - it's a snowball effect. The findings also suggest that therapies which exploit these damaging changes might be useful for treating late-stage melanoma," Professor Shackleton said.

The study included tumour samples from Peter Mac's Cancer tissue Collection After Death (CASCADE) program - in which patients volunteer to undergo a rapid autopsy following their death.

"Our whole team would like to extend our sincere gratitude to the patients and their families whose participation in CASCADE made this research possible. We hope that the insights we have gained will lead to better treatments for people with melanoma," Professor Shackleton said.

The research was supported by the Lorenzo and Pamela Galli Charitable Trust, the Australian NHMRC, Pfizer Australia, veski, the Victorian Cancer Agency, a European Commission Horizon 2020 grant, the Victorian Institute of Forensic Medicine, Tobin Brothers Funerals, the Peter MacCallum Cancer Foundation, Bioplatforms Australia, the Melanoma Institute of Australia, Cancer Council of Victoria, the Victorian Cancer Biobank, the Melbourne Melanoma Project and the Victorian Government.

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Worth one's salt

Researchers at LSU uncover more on the ancient Maya commodity

The first documented record of salt as an ancient Maya commodity at a marketplace is depicted in a mural painted more than 2,500 years ago at Calakmul, a UNESCO World Heritage site in the Yucatan Peninsula in Mexico. In the mural that portrays daily life, a salt vendor shows what appears to be a salt cake wrapped in leaves to another person, who holds a large spoon over a basket, presumably of loose, granular salt.

This is the earliest known record of salt being sold at a marketplace in the Maya region. Salt is a basic biological necessity and is also useful for preserving food. Salt also was valued in the Maya area because of its restricted distribution.

The first documented record of salt as an ancient Maya commodity at a marketplace is depicted in a mural painted more than 2,500 years ago at Calakmul, a UNESCO World Heritage site in the Yucatan Peninsula in Mexico. **Rogelio Valencia, Proyecto Arqueológico Calakmul**

Salt cakes could have been easily transported in canoes along the coast and up rivers in southern Belize, writes LSU archaeologist Heather McKillop in a new paper published in the *Journal of Anthropological Archaeology*. She discovered in 2004 the first remnants of ancient Maya salt kitchen buildings made of pole and thatch that had been submerged and preserved in a saltwater lagoon in a mangrove forest in Belize. Since then, she and her team of LSU graduate and undergraduate students and colleagues have mapped 70 sites that comprise an extensive network of rooms and buildings of the Paynes Creek Salt Works.

"It's like a blueprint for what happened in the past," McKillop said.

"They were boiling brine in pots over fires to make salt."

Her research team has discovered at the Paynes Creek Salt Works, 4,042 submerged architectural wooden posts, a canoe, an oar, a high-quality jadeite tool, stone tools used to salt fish and meat and hundreds of pieces of pottery.

"I think the ancient Maya who worked here were producer-vendors and they would take the salt by canoe up the river. They were making large quantities of salt, much more than they needed for their immediate families. This was their living," said McKillop, who is the Thomas & Lillian Landrum Alumni Professor in the LSU Department of Geography & Anthropology.

She investigated hundreds of pieces of pottery including 449 rims of ceramic vessels used to make salt. Two of her graduate students were able to replicate the pottery on a 3D printer in McKillop's Digital Imaging Visualization in Archaeology lab at LSU based on scans taken in Belize at the study site. She discovered that the ceramic jars used to boil the brine were standardized in volume; thus, the salt producers were making standardized units of salt.

"Produced as homogeneous units, salt may have been used as money in exchanges," McKillop said.

An ethnographic interview with a modern day salt producer in Sacapulas, Guatemala collected in 1981 supports the idea that the ancient Maya also may have viewed salt as a valuable commodity:

"The kitchen is a bank with money for us...So when we need money at any time during the year we come to the kitchen and make money, salt."

http://bit.ly/3rnFzhd

Distinct chemical 'signatures' for concussion identified in spit of elite rugby players

Potentially paves way for non-invasive diagnostic test at all levels of participation

Distinct chemical 'signatures' for concussion have been identified in the spit of elite male rugby players, reveals research published online in the *British Journal of Sports Medicine*.

This potentially paves the way for a non-invasive and rapid diagnostic test for the condition that could be used pitch side and after the game at all levels of participation, suggest the researchers.

This is especially important because concussion can be hard to diagnose, particularly at grass-roots level, where most of it occurs, but where gold standard medical assessment by trained clinicians during and after a game isn't readily available, they add.

As a result, a high percentage of concussions are missed, and concerns have emerged about the long-term brain health of athletes exposed to repeated concussions.

The short term consequences of a missed diagnosis range from a prolonged recovery period, often with protracted and pervasive symptoms, to a heightened risk of further injuries, including catastrophic brain swelling, although this is rare, emphasise the researchers.

In the absence of objective diagnostic tests for concussion, diagnosis currently relies on a clinician's interpretation of the observed signs and symptoms, and the results of formal clinical assessments.

But recent technological advancements in gene sequencing have allowed scientists to look into the diagnostic potential of molecules called small non-coding RNAs, or sncRNAs for short. sncRNAs regulate the expression of different cellular proteins that are linked to various diseases, such as cancer and Alzheimer's disease.

So the researchers obtained saliva samples from more than 1000 male professional players in the top two tiers of England's elite rugby union across two seasons (2017-19) of competition.

Samples were collected before the season began from 1028 players, and during standardised 'gold standard' head injury assessments at three time points--during the game, immediately afterwards, and

36-48 hours later in 156 of these players.

Saliva samples were also collected from a comparison group of 102 uninjured players and 66 who had sustained muscle or joint injuries, and so had not been assessed for head injury.

A combined panel of 14 sncRNAs differentiated concussed players from those with suspected traumatic brain injury, but whose head injury assessments had ruled out concussion, and from the comparison group, both immediately after the game and 36-48 hours later.

This is an observational study, and the study design makes it clear that the sncRNA biomarkers can't outperform the gold standard clinical assessment, caution the researchers.

But it is thought that saliva can receive cellular signals directly from cranial nerves in the mouth and throat, and so can rapidly register traumatic brain injury, making a saliva test particularly suitable for a pitch side diagnosis, they suggest.

"Concussion can be hard to diagnose and is often missed, especially where a structured evaluation by an expert clinician is not possible--for example, at grass-root level," they write. "Small non-coding RNAs can provide a diagnostic tool that might reduce the risk of missing this type of injury at all levels of participation," they suggest.

"In community sport, [sncRNAs] may provide a non-invasive diagnostic test that is comparable in accuracy to the level of assessment available in a professional sport setting," while the test could be added to current head injury evaluation protocols at the elite level," they add.

And as the biology of concussion is still not fully understood, sncRNAs might help to shed light on the response to injury as this evolves over time, they suggest.

"The detection of signatures of concussion at early time points in saliva (a non-invasively sampled biofluid) presents both at the pitch side, and in primary care and emergency medicine departments, an opportunity to develop a new and objective diagnostic tool for this common clinical presentation," they conclude.

*As an addendum to their findings, they add: "A patented salivary concussion test is in the process of being commercialised as an over-the-counter test for elite male athletes.

"Meanwhile our research team aims to collect further samples from players in two elite men's rugby competitions to provide additional data to expand the test and develop its use. This will guide the prognosis and safe return to play after concussion and further establish how the test will work alongside the head injury assessment process.

We are also currently carrying out several additional studies to further validate and expand the test for use in different groups that were not included in the present SCRUM study, including female athletes, young athletes, and community sports players."

Externally peer reviewed? Yes Evidence type: Observational Subjects: Male athletes

http://bit.ly/31jtpv5

The same sea level for everyone

The Earth's gravity field as the basis for an International Height Reference System

Maps generally indicate elevation in meters above sea level. But sea level is not the same everywhere. A group of experts headed by the Technical University of Munich (TUM), has developed an International Height Reference System (IHRS) that will unify geodetic measurements worldwide.

How high is Mount Everest? 8848 meters? 8844 meters? Or 8850 meters? For years, China and Nepal could not agree. In 2019, Nepal sent a team of geodesists to measure the world's highest mountain. A year later a team from China climbed the peak. Last December the two governments jointly announced the outcome of the new measurement: 8848.86 meters.

The fact that both China and Nepal recognize this result must be seen as a diplomatic success. It was made possible by the new International Height Reference System (IHRS), used for the first time by the geodetic specialists conducting the new measurement. Scientists from TUM played a leading role in developing the new system. It establishes a generally agreed zero level as a basis for all future measurements. It thus replaces the mean sea level, which has traditionally served as the zero level for surveyors and thus for all topographical maps. A paper in the *Journal of Geodesy*, jointly authored by TUM scientists and international research groups, outlines the scientific background and theoretical concept of the IHRS as well as the strategy for implementing it.

When zero is not always zero

The standard used until now - the mean sea level - was flawed from the outset: There was never a fixed definition. Every country could use arbitrary tide gauges to define its own zero level. As a result, Germany's official sea level is 31 centimeters higher than Italy's, 50 cm higher than that used in Spain and actually 2.33 m higher than in Belgium, where the zero height is based on low water in Ostend.

When topographical maps are only used for hiking, no one is bothered by such differences. But for geodetics specialists trying to arrive at a universally agreed height - for Mount Everest, for example, half in Nepal and half in China - the inconsistent zero levels are a bigger problem. And it can be very costly when planners of cross-border structures such as bridges and tunnels forget to check the different coordinates used by the teams and convert them as needed. On the Hochrheinbrücke, a bridge connecting Germany and Switzerland, a discrepancy of this kind was noticed just in time.

Surveys from orbit

"The introduction of an internationally valid height reference system was long overdue," says TUM researcher Dr. Laura Sánchez of the Deutsches Geodätisches Forschungsinstitut (DGFI-TUM), who has headed working groups studying theoretical aspects and implementing the new global height reference system at the International Association of Geodesy for several years.

What is needed is obvious: a universally accepted zero level. The new International Height Reference System (IHRS) defines how it can be calculated: It takes into account the shape of the Earth - which is close to spherical, but flattened at the poles and bulging slightly at the equator due to its rotation - and the uneven distribution of masses in the interior and on the surface. The resulting irregularities in the gravity field are the basis for calculating the height system because the strength and direction of the force determine the distribution of water in the oceans. If we assume that the Earth's surface is completely covered with water, the height of a hypothetical sea level and thus the zero level for the entire globe can be calculated precisely.

In construction projects, even the smallest deviations can be crucial

"It became possible to realize the IHRS only with the availability of global data from satellite missions such as the ESA earth observation satellite GOCE (Gravity field and steady-state Ocean Circulation Explorer)," says Prof. Roland Pail of the TUM Chair of Astronomical and Physical Geodesy (APG). His team played an integral role in analyzing the GOCE measurements and using them to calculate global models of the Earth's gravity field. "The information gained in this way provides the basis to calculate the mean sea level for every point on Earth with the new International Height Reference System, regardless of whether it is on a continent or in an ocean, and thus to compute the internationally accepted zero level," explains Sánchez.

Does every map have to be redrawn? "It won't be that dramatic," says Sánchez. "In the industrial countries, where they have been

making gravity measurements for decades, the deviations are quite small - only in the decimeter range." But with construction projects, for example, even small deviations can cause serious troubles. Consequently, the scientist is confident that the new reference system will gain acceptance quickly.

Publications: *Sánchez L., J. Ågren, J. Huang, Y. Ming Wang, J. Mäkinen, R. Pail, R. Barzaghi, G. Vergos, K. Ahlgren, Q. Liu: Strategy for the realisation of the International Height Reference System (IHRS). Journal of Geodesy, 95(33), doi: 10.1007/s00190-021-01481-0, 2021.*

https://bit.ly/3d71unP

Vast Fragments of an Alien World Could Be Buried Deep Within Earth Itself

They are among the largest and strangest of all structures on Earth: huge, mysterious blobs of dense rock lurking deep within the lowermost parts of our planet's mantle.

Peter Dockrill

There are two of these gigantic masses – called the large low-shear-velocity provinces (LLSVPs) – with one buried under Africa, the other below the Pacific Ocean. These anomalies are so massive, they in turn breed their own disturbances, such as the large phenomenon currently evolving within and weakening Earth's magnetic field, known as the South Atlantic Anomaly.

As for how and why the LLSVPs came to exist like this within the mantle, scientists have lots of ideas, but little in the way of hard proof.

The African LLSVP. **(Ward et al., Geochemistry, Geophysics, Geosystems, 2020)**

What is known, however, is that these giant blobs have been around for a very long time, with many thinking they could have been a part of Earth since before the giant impact that birthed the Moon – ancient traces of the collision between Earth and the hypothetical planet Theia.

According to that widely held argument, the Mars-sized Theia struck the very early Earth around 4.5 billion years ago, with a huge chunk of Theia and/or possibly Earth fragmenting off, and becoming the Moon we know today in orbit around Earth.

As for what happened to the rest of Theia, it's uncertain. Was it destroyed, or did it simply ricochet off into the eternity of space? We don't know.

Some researchers have suggested the cores of these two primordial planets may have fused into one, and that chemical exchanges wrought by this epic merger are what enabled life itself to thrive on the world that resulted.

Now, scientists have returned to these monumental questions with a new proposal, and it's an idea that reconciles the mysterious LLSVP blobs too, weaving them into the Earth/Theia hybrid hypothesis.

According to new modeling by researchers from Arizona State University (ASU), the LLSVPs may represent ancient fragments of Theia's iron-rich and highly dense mantle, which sank deep into Earth's own mantle when the two developing worlds came together, and has been buried there for billions of years.

"The Giant Impact hypothesis is one of the most examined models for the formation of Moon, but direct evidence indicating the existence of the impactor Theia remains elusive," the researchers, led by first author Qian Yuan, a PhD candidate studying mantle dynamics at ASU, explain in a summary of their findings presented last week at the Lunar and Planetary Science Conference.

"We demonstrate that Theia's mantle may be several percent intrinsically denser than Earth's mantle, which enables the Theia mantle materials to sink to the Earth's lowermost mantle and accumulate into thermochemical piles that may cause the seismically-observed LLSVPs."

While speculation has existed for years that the LLSVPs may be an

alien souvenir implanted by Theia, the new research appears to be the most comprehensive formulation yet. The findings are currently under review, ahead of future publication in *Geophysical Research Letters*. Beyond the mantle modeling, the results are also consistent with previous research suggesting that certain chemical signatures tied to the LLSVPs are at least as primitive as the Theia impact.

"Therefore, the primitive materials may [originate] from the LLSVPs, which is well explained if the LLSVPs preserve Theia mantle materials that are older than the Giant Impact," Yuan and his co-authors write.

We'll have to see how the rest of the scientific community respond to the team's findings, but for now at least, we've got another lead on just what these mysterious anomalies might be – and it's literally the most far-out explanation yet.

"This crazy idea is at least possible," Yuan told *Science*.

The findings were presented at the 52nd Lunar and Planetary Science Conference, conducted as a virtual event last week.

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Our Brains Could Be Directly Involved in Processing Alcohol, Mouse Study Hints

Despite alcohol being a common recreational substance we've been drinking for at least 12,000 years, it seems we still don't fully understand just what it does inside our bodies... or brains, for that matter.

Jacinta Bowler

A new study in mice and human brain samples has looked at the enzyme called aldehyde dehydrogenase and discovered that it might break down a particular byproduct of alcohol digestion in the brain rather than just in the liver.

We do know that when you drink alcohol, your body jumps into action to begin breaking it down into other compounds. Alcohol breaks down into acetaldehyde, which then breaks down to acetate, which eventually becomes carbon dioxide and water.

It's this acetaldehyde-to-acetate relationship that the team looked at more closely; the enzyme that controls this process, called aldehyde dehydrogenase, is encoded by a gene called ALDH2.

You may have heard of this gene before. Many people from Asian populations have a genetic variation that causes a flushed face and elevated levels of acetaldehyde when they drink alcohol - due to the molecule being broken down less efficiently.

Acetaldehyde and acetate are both well-known products of alcohol production, and it was thought that the process occurred entirely in the liver before acetate passed through the blood-brain barrier into the nervous system to cause some of the drunken behavior.

"At the behavioral level, much of the research on alcohol intermediate metabolites has focused on acetaldehyde, whose pattern of effects is similar to that of ethanol," the team writes in their new paper. "Until recently, acetate had been considered a harmless alcohol by-product, and brain acetate is thought to derive largely from liver alcohol metabolism."

Using three human brain samples and eleven mice, the team looked at where the gene ALDH2 was being expressed – and turns out it wasn't just in the liver. Instead, ALDH2 was also being expressed in brain cells in the cerebellum known as astrocytes in two of the four human brain samples the team looked at.

We already knew that the cerebellum is a primary brain region involved in alcohol motor impairment, but it was thought that all the acetate was being trucked into the brain from the liver after acetaldehyde had been broken down there.

But when the researchers bred mice that were ALDH2 deficient in the brain and couldn't produce aldehyde dehydrogenase in the cerebellum astrocytes, they found something fascinating – alcohol didn't affect the animals' motor function as expected, and the levels of acetate in their brains stayed at pre-alcohol levels.

Plus, when the researchers removed ALDH2 from the liver, the levels of acetate in the mouse brains weren't affected.

Taken together, the researchers think this means some of the acetaldehyde produced by drinking becomes acetate directly in the brain, rather that all being transported from the liver. The brain itself in this case is metabolizing the alcoholic product.

"Thus, astrocytic ALDH2 controls the production, cellular and behavioral effects of alcohol metabolites in a brain-region-specific manner," the team writes.

"Our data indicate that astrocytic ALDH2 is an important, but previously under-recognized, target in the brain to alter alcohol pharmacokinetics and potentially treat alcohol use disorder."

There's a lot more work to do in this space, including confirming that this is also the case in humans, but it's still an exciting finding. It's fascinating to think we're still learning new things all the time – even with a drink that's arguably older than science itself.

The research has been published in *Nature Metabolism*.

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Scientists discover how humans develop larger brains than other apes

A new study is the first to identify how human brains grow much larger, with three times as many neurons, compared with chimpanzee and gorilla brains.

The study, led by researchers at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, UK, identified a key molecular switch that can make ape brain organoids grow more like human organoids, and vice versa.

The study, published in the journal *Cell*, compared 'brain organoids' - 3D tissues grown from stem cells which model early brain development - that were grown from human, gorilla and chimpanzee stem cells. Similar to actual brains, the human brain organoids grew a lot larger than the organoids from other apes.

Dr Madeline Lancaster, from the MRC Laboratory of Molecular Biology, who led the study, said: "This provides some of the first insight into what is different about the developing human brain that sets us apart from our closest living relatives, the other great apes. The most striking difference between us and other apes is just how incredibly big our brains are."

During the early stages of brain development, neurons are made by stem cells called neural progenitors. These progenitor cells initially have a cylindrical shape that makes it easy for them to split into identical daughter cells with the same shape. The more times the neural progenitor cells multiply at this stage, the more neurons there will be later. As the cells mature and slow their multiplication, they elongate, forming a shape like a stretched ice-cream cone.

Previously, research in mice had shown that their neural progenitor cells mature into a conical shape and slow their multiplication within hours. Now, brain organoids have allowed researchers to uncover how this development happens in humans, gorillas and chimpanzees. They found that in gorillas and chimpanzees this transition takes a long time, occurring over approximately five days. Human progenitors were even more delayed in this transition, taking around seven days. The human progenitor cells maintained their cylinder-like shape for longer than other apes and during this time they split more frequently, producing more cells.

This difference in the speed of transition from neural progenitors to neurons means that the human cells have more time to multiply. This could be largely responsible for the approximately three-fold greater number of neurons in human brains compared with gorilla or chimpanzee brains.

Dr Lancaster said: "We have found that a delayed change in the shape of cells in the early brain is enough to change the course of development, helping determine the numbers of neurons that are made.

"It's remarkable that a relatively simple evolutionary change in cell shape could have major consequences in brain evolution. I feel like we've really learnt something fundamental about the questions I've been interested in for as long as I can remember - what makes us human."

To uncover the genetic mechanism driving these differences, the researchers compared gene expression - which genes are turned on and off - in the human brain organoids versus the other apes. They identified differences in a gene called 'ZEB2', which was turned on sooner in gorilla brain organoids than in the human organoids.

To test the effects of the gene in gorilla progenitor cells, they delayed the effects of ZEB2. This slowed the maturation of the progenitor cells, making the gorilla brain organoids develop more similarly to human - slower and larger.

Conversely, turning on the ZEB2 gene sooner in human progenitor cells promoted premature transition in human organoids, so that they developed more like ape organoids.

The researchers note that organoids are a model and, like all models, do not to fully replicate real brains, especially mature brain function. But for fundamental questions about our evolution, these brain tissues in a dish provide an unprecedented view into key stages of brain development that would be impossible to study otherwise.

Dr Lancaster was part of the team that created the first brain organoids in 2013.

This study was funded by the Medical Research Council, European Research Council and Cancer Research UK.

https://bit.ly/3dfCMBJ

Deadly viral outbreak ravages European horses

Scientists are examining why a familiar virus that typically produces milder symptoms, appears to have hit these animals unusually hard

By Christa Lesté-Lasserre

Late last month, an international horse jumping competition in Spain that usually offers a sunny getaway for elite riders took a grim turn. A disease outbreak sickened scores of horses, leaving many so weak they couldn't stand and others exhibiting unusually aggressive behavior. At least 17 animals have since died; others have had abortions or needed surgery to repair organ damage.

The equestrian world is bracing for worse to come. Before researchers were able to identify the outbreak's cause—a known pathogen named equine herpesvirus type 1 (EHV-1)—some 600 of the 750 horses participating in the event were already heading home, threatening to spread what officials already call the most serious EHV-1 outbreak in Europe in decades. In a bid to contain the damage, the International Federation for Equestrian Sports (FEI), which oversees international equestrian competitions, has canceled all European events—including its World Cup—through at least mid-April. Horse owners, meanwhile, are frantically trying to vaccinate and isolate their horses.

For scientists, the outbreak has raised a host of questions. They are examining why EHV-1, a familiar virus that typically produces milder symptoms, appears to have hit these animals, particularly mares, unusually hard. Some are wondering whether drugs or the vaccine against EHV-1 itself may have played a role. "Our top priority must be to deal with the immediate impact of this terrible virus," says Göran Åkerström, veterinary director of FEI. But, "It is also crucial that we … expand our epidemiological data." A special FEI working group to study the outbreak had its first meeting on 18 March.

Researchers say conditions at the monthlong competition, held in Valencia, Spain, were ripe for an outbreak of EHV-1, which is primarily spread by exhaled droplets. The horses were housed in tightly packed stalls, and "All it takes is for one horse carrying a latent virus to have some sort of stress, and his virus gets activated

and starts shedding," says equine disease specialist Lutz Goehring of Ludwig Maximilian University of Munich.

Sick animals soon overwhelmed an equine hospital at the nearby CEU Cardenal Herrera University, says Ana Velloso Álvarez, a veterinarian there. Exhausted medics were treating up to 20 animals simultaneously, with many horses hoisted in slings, literally hanging between life and death. "I think I understand more what it's been like for [COVID-19] doctors," Álvarez says.

Studies have found that nearly all horses have been exposed to at least one of EHV-1's five major strains, and animals can carry inactive virus for years. Active infections usually cause fever and mild respiratory disease, sometimes abortion. One especially worrying variant, known as type 1, can cause serious neurological damage, rendering horses wobbly or unable to stand. Occasionally, it kills them.

Most outbreaks affect just a handful of horses before a farm is quarantined and disinfected. And less than 15% of infected animals typically exhibit neurological symptoms. But in Valencia up to 40% of sick horses have shown signs of neurological damage, Álvarez says. And, in an unusual twist for EHV-1, each horse had its own cocktail of problems. Some had intestinal blood clots and needed surgery. Others had swollen legs, walked like they were drunk, or exhibited unusual behavior. "This is completely different from what we're used to [with EHV-1]," Álvarez says.

Genetic sequencing suggests the outbreak wasn't caused by a new strain of EHV-1. That has researchers looking at other factors that might have worsened outcomes. One is travel. Some horses spent up to 3 days journeying to the event, and such long trips can be "a huge stressor," says Barbara Padalino, an equine scientist at the University of Bologna. Recent studies by her team have shown that after just a 12-hour trip, a horse's immune defenses against EHV-1 drop, increasing the chance of infection.

Other scientists are examining the role of sex. About 80% of the most severe Valencia cases involved mares, Álvarez says. Some researchers wonder whether medications used to stop the mares' reproductive cycles—a treatment some riders think makes a horse easier to handle—might have contributed to illness. One popular drug, altrenogest, is based on progesterone, which has been shown to weaken immune function, notes Christine Aurich, an equine gynecologist at the Graf Lehndorff Institute in Germany.

Researchers are also scrutinizing the EHV-1 vaccine, which has a spotty record of preventing disease and requires booster shots every 6 months. Many of the sick horses had been vaccinated, Åkerström says—but past studies have hinted that horses may be at higher risk of neurological symptoms in the weeks after vaccination. FEI's working group is gathering vaccination records, as well as infection and symptom data, in hopes of clarifying such issues—and developing better ways to treat and prevent future outbreaks.

https://bit.ly/3csIpxi

New method could shine 'a healing light' on the brain for those with movement disorders

Scientists make pivotal discovery of method for wireless modulation of neurons with X-rays that could improve the lives of patients with brain disorders.

by Joseph E. Harmon, Argonne National Laboratory

The X-ray source only requires a machine like that found in a dentist's office.

Many people worldwide suffer from movement-related brain disorders. Epilepsy accounts for more than 50 million; essential tremor, 40 million; and Parkinson's disease, 10 million.

Relief for some brain disorder sufferers may one day be on the way in the form of a new treatment invented by researchers from the U.S. Department of Energy's (DOE) Argonne National Laboratory and four universities. The treatment is based on breakthroughs in both

optics and genetics. It would be applicable to not only movement-related brain disorders, but also chronic depression and pain.

This new treatment involves stimulation of neurons deep within the brain by means of injected nanoparticles that light up when exposed to X-rays (nanoscintillators) and would eliminate an invasive brain surgery currently in use.

"Our high-precision noninvasive approach could become routine with the use of a small X-ray machine, the kind commonly found in every dental office," said Elena Rozhkova, a lead author and a nanoscientist in Argonne's Center for Nanoscale Materials (CNM), a DOE Office of Science User Facility.

Traditional deep brain stimulation requires an invasive neurosurgical procedure for disorders when conventional drug therapy is not an option. In the traditional procedure, approved by the U.S. Food and Drug Administration, surgeons implant a calibrated pulse generator under the skin (similar to a pacemaker). They then connect it with an insulated extension cord to electrodes inserted into a specific area of the brain to stimulate the surrounding neurons and regulate abnormal impulses.

"The Spanish-American scientist José Manuel Rodríguez Delgado famously demonstrated deep brain stimulation in a bullring in the 1960s," said Vassiliy Tsytsarev, a neurobiologist from the University of Maryland and a co-author of the study. "He brought a raging bull charging at him to a standstill by sending a radio signal to an implanted electrode."

About 15 years ago, scientists introduced a revolutionary neuromodulation technology, "optogenetics," which relies on genetic modification of specific neurons in the brain. These neurons create a light-sensitive ion channel in the brain and, thereby, fire in response to external laser light.

This approach, however, requires very thin fiberoptic wires implanted in the brain and suffers from the limited penetration depth of the laser light through biological tissues.

The team's alternative optogenetics approach uses nanoscintillators injected in the brain, bypassing implantable electrodes or fiberoptic wires. Instead of lasers, they substitute X-rays because of their greater ability to pass through biological tissue barriers.

"The injected nanoparticles absorb the X-ray energy and convert it into red light, which has significantly greater penetration depth than blue light," said Zhaowei Chen, former CNM postdoctoral fellow.

"Thus, the nanoparticles serve as an internal light source that makes our method work without a wire or electrode," added Rozhkova.

Since the team's approach can both stimulate and quell targeted small areas, Rozhkova noted, it has other applications than brain disorders. For example, it could be applicable to heart problems and other damaged muscles.

One of the team's keys to success was the collaboration between two of the world-class facilities at Argonne: CNM and Argonne's Advanced Photon Source (APS), a DOE Office of Science User Facility. The work at these facilities began with the synthesis and multi-tool characterization of the nanoscintillators.

In particular, the X-ray excited optical luminescence of the nanoparticle samples was determined at an APS beamline (20-BM). The results showed that the particles were extremely stable over months and upon repeated exposure to the high-intensity X-rays.

According to Zou Finfrock, a staff scientist at the APS 20-BM beamline and Canadian Light Source, "They kept glowing a beautiful orange-red light."

Next, Argonne sent CNM-prepared nanoscintillators to the University of Maryland for tests in mice. The team at University of Maryland performed these tests over two months with a small portable X-ray machine. The results proved that the procedure worked as planned.

Mice whose brains had been genetically modified to react to red

light responded to the X-ray pulses with brain waves recorded on an electroencephalogram.

Finally, the University of Maryland team sent the animal brains for characterization using X-ray fluorescence microscopy performed by Argonne scientists. This analysis was performed by Olga Antipova on the Microprobe beamline (2-ID-E) at APS and by Zhonghou Cai on the Hard X-ray Nanoprobe (26-ID) jointly operated by CNM and APS.

This multi-instrument arrangement made it possible to see tiny particles residing in the complex environment of the brain tissue with a super-resolution of dozens of nanometers. It also allowed visualizing neurons near and far from the injection site on a microscale.

The results proved that the nanoscintillators are chemically and biologically stable. They do not wander from the injection site or degrade.

"Sample preparation is extremely important in these types of biological analysis," said Antipova, a physicist in the X-ray Science Division (XSD) at the APS. Antipova was assisted by Qiaoling Jin and Xueli Liu, who prepared brain sections only a few micrometers thick with jeweler-like accuracy.

"There is an intense level of commercial interest in optogenetics for medical applications," said Rozhkova. "Although still at the proof-of-concept stage, we predict our patent-pending wireless approach with small X-ray machines should have a bright future."

The related article "Wireless optogenetic modulation of cortical neurons enabled by radioluminescent nanoparticles" appeared in *ACS Nano*.

More information: *Zhaowei Chen et al, Wireless Optogenetic Modulation of Cortical Neurons Enabled by Radioluminescent Nanoparticles, ACS Nano (2021). DOI: 10.1021/acsnano.0c10436*

https://bit.ly/3w71wor

After more than 2 decades of searching, scientists finger cause of mass eagle deaths

Eagles may get exposed to a neurotoxin through their prey.

By Erik Stokstad

More than 25 years ago, biologists in Arkansas began to report dozens of bald eagles paralyzed, convulsing, or dead. Their brains were pocked with lesions never seen before in eagles. The disease was soon found in other birds across the southeastern United States. Eventually, researchers linked the deaths to a new species of cyanobacteria growing on an invasive aquatic weed that is spreading across the country. The problem persists, with the disease detected regularly in a few birds, yet the culprit's chemical weapon has remained unknown.

Today in *Science*, a team identifies a novel neurotoxin produced by the cyanobacteria and shows that it harms not just birds, but fish and invertebrates, too. "This research is a very, very impressive piece of scientific detective work," says microbiologist Susanna Wood of the Cawthron Institute. An unusual feature of the toxic molecule is the presence of bromine, which is scarce in lakes and rarely found in cyanobacteria. One possible explanation: the cyanobacteria produce the toxin from a bromide-containing herbicide that lake managers use to control the weed.

The discovery highlights the threat of toxic cyanobacteria that grow in sediment and on plants, Wood says, where routine water quality monitoring might miss them. The finding also equips researchers to survey lakes, wildlife, and other cyanobacteria for the new toxin. "It will be very useful," says Judy Westrick, a chemist who studies cyanobacterial toxins at Wayne State University and was not involved in the new research. "I started jumping because I got so excited."

Wildlife biologists with U.S. Geological Survey and local

institutions first detected the eagles' brain disease, now called vacuolar myelinopathy, at DeGray Lake in Arkansas in late 1994. They soon learned that coots and owls at the lake were dying with similar brain lesions. The researchers ruled out industrial pollutants and infectious disease, and they couldn't find any algal toxins in the water. Then funding ran out, and the scientists turned to other projects.

But Susan Wilde, an aquatic ecologist at the University of Georgia, Athens, persisted, with intermittent funding. "I just had a lot of colleagues and graduate students that were self-propelled to work on this." Birds were dying at lakes and reservoirs throughout the southeast, and at every lake her team visited, they found *Hydrilla verticillata*, a tough and fast-growing invasive plant.

In 2001, Wilde noticed dark spots on the underside of the leaves. Back in the lab, she put a sample under a microscope and shone light that makes cyanobacteria glow red. The whole leaf lit up. "I was running around the hallways," Wilde recalls. "It was kind of a eureka moment." The cyanobacterium was a new species, which Wilde named *Aetokthonos hydrillicola* in 2014. She suspected it was producing a neurotoxin.

To confirm that hunch, Wilde and colleagues fed hydrilla to mallards in the lab. Only those that ate leaves harboring the cyanobacteria developed brain lesions. Next, a group led by Timo Niedermeyer, a natural products chemist at Martin Luther University Halle-Wittenberg, figured out how to culture the cyanobacterium and initially found that the lab-grown strain did not cause lesions in chickens.

"Huge disappointment," he recalls. But when they added bromide salts to the culture medium, the cyanobacteria began to produce the neurotoxin. In further tests, Wilde and colleagues found that the toxin also kills fish, insects, and worms. "This is a really potent neurotoxin, even at fairly low levels," she says. Wilde suspects mammals are also vulnerable; her colleagues hope to test the compound on mice.

Niedermeyer's lab discovered the neurotoxin was fat-soluble, which is unusual for cyanobacterial toxins and suggests it can accumulate in tissues. Fish and birds are exposed when they eat hydrilla coated with the new species of cyanobacteria, and then the toxin may move through the food web as eagles and owls consume afflicted prey.

"If verified, bioaccumulation has important consequences to the whole ecosystem and human health" if people consume toxin-contaminated fish or waterfowl, says Kaarina Sivonen, a microbiologist at the University of Helsinki.

The cyanobacterium appears to get the bromide it needs to make the toxin from hydrilla, which can concentrate bromide from lake sediment in its leaves. Bromides are rare in freshwater, but they could be eroding from rocks, or they might originate from coal-fired power plants. Other sources could include brominated flame retardants, fracking fluids, and road salt. Wilde suspects one local source might be an herbicide, diquat dibromide, that is used to kill hydrilla.

Wilde points to recent success managing the weed without chemicals, by stocking lakes with fish that eat hydrilla. Although grass carp are not desirable for fishing, using sterile carp would ensure the population would die out once its work was done. The Army Corps of Engineers has already released the fish into a reservoir on the border of Georgia and South Carolina, where they removed the hydrilla. Since then, no more sick eagles have been found.

Saving the birds from the neurotoxin will be a long fight, however, because both hydrilla and the cyanobacteria are exceptionally hardy. The invasive plant is likely to continue to be spread by boats, researchers say, and perhaps also migrating birds. "We should

expect the cyanobacterium to follow," says George Bullerjahn, a microbiologist at Bowling Green State University, "and the threat of toxicity to become a broader issue."

https://bit.ly/2Pb3TG1

We Finally Know The Genetic Reason Why This Bunny Walks on Its Front Paws

Selective breeding by humans has led to some incredibly odd and unfortunate pets over the years, and the sauteur d'Alfort rabbit is among the strangest of the lot.

Carly Cassella

This rare breed of bunny does not hop or walk like any other rabbit or hare in existence. When the sauteur is ready to go, it kicks its hind legs into the air and bounces forward on its front paws, like a human acrobat walking on their hands. While this may seem like an amusing trait, it sadly comes with other debilitating problems too. Now, the one bunny that can't hop properly has helped us better understand the genetics of hopping in mammals.

Crossing a single male sauteur with a single female of the New Zealand white breed and then crossing the resulting offspring, researchers raised 52 bunnies, 23 percent of which carried two copies of the mutant gene similar to the original father. These numbers match the statistics expected when there is only one recessive gene involved in a mutation.

(R. Cavignaux)

Pooling the DNA of the sauteur and non-sauteur young, researchers used whole-genome sequencing to compare the two groups. In the end - as they anticipated - there was only one gene that stood out.

The cause of the sauteur's defective jumping appears to lie with a mutation in an evolutionary conserved site of a gene known as RORB, which provides instructions to mammalian cells so they can create certain proteins.

RORB proteins are generally found throughout the rabbit nervous system, where they help turn genetic code into a protein building template. This particular mutation, however, causes a sharp decrease in the number of spinal cord neurons that can actually produce this protein.

Two copies of the RORB mutation, in fact, resulted in no proteins in the spinal cord at all, and this was tied to an inability to hop. Other rabbits in the litter capable of jumping with their hind legs showed no such protein loss. The RORB gene, the authors conclude, must be what allows rabbits to bound around. It could also be the key to other mammal hopping, too.

Over the years, there's been a lot of scientific interest in the special physiology and biomechanics that allow mammals - like kangaroos, bunnies, hares and some mice - to hop, but the underlying genetics of this feat have rarely been considered.

One of the few studies out there recently found mice with the same RORB mutation as sauteur rabbits also cannot hop like normal. Instead, these rodents waddle around on their front paws like a duck, with their tails and hind legs sticking up in the air.

"I spent four years looking at these mice doing little handstands, and now I get to see a rabbit do the same handstand," neuroscientist Stephanie Koch from the University College London told Science News. "It's amazing."

Koch's study on rabbits is the first to describe a specific gene required for leaping or hopping, and it lines up extremely well with what she's been observing in mutant mice.

Similar to mutant rodents, sauteur rabbits also show other anatomical defects beyond their strange walk. Many are born blind and develop cataracts in their first year of life. RORB knock-out mice also show retinal degeneration.

In mice, the RORB gene appears to play an essential role in differentiating cells in both the brain's cortex and the retina. It might also do something similar in the spinal cord, which is involved in the regulation of sensory information and locomotion among mammals.

As such, this lack of proteins might be what is causing the hind legs of rabbits and mice to lift instead of leaping. In sauteur rabbits, for instance, the RORB mutation appears to cause defects in the differentiation of spinal cord interneurons, although whether this is actually causing the bizarre locomotion remains unclear.

"In addition to its expression in the spinal cord, RORB is also expressed in many regions in the brain such as the primary somatosensory, auditory, visual and motor cortex, in some thalamus and hypothalamus nuclei, in the pituitary gland and in the superior colliculus," the authors write.

"Thus, we cannot exclude the possibility that an alteration of RORB function in the brain contributes to the locomotion phenotype characteristic for the sauteur rabbits."

The effects of the RORB mutation will require more study, but it's obvious it's involved somehow. This was the only variant identified in the whole genome sequence of rabbits that had any impact on hopping. While there might well be more genes involved in bunny hopping, it seems that poor sauteur rabbits have certainly pointed us in the direction of one. The study was published in *PLOS Genetics*.

https://wb.md/3sqSMXQ

Encephalopathy Common, Often Lethal in Hospitalized COVID-19 Patients

Toxic metabolic encephalopathy (TME) is common and often lethal in hospitalized patients with COVID-19, new research shows.

Batya Swift Yasgur, MA, LSW

Results of a retrospective study show that of almost 4500 patients with COVID-19, 12% were diagnosed with TME. Of these, 78% of developed encephalopathy immediately prior to hospital admission. Septic encephalopathy, hypoxic-ischemic encephalopathy (HIE), and uremia were the most common causes, although multiple causes were present in close to 80% of patients. TME was also associated with a 24% higher risk of in-hospital death.

"We found that close to 1 in 8 patients who were hospitalized with COVID-19 had TME that was not attributed to the effects of sedatives, and that this is incredibly common among these patients who are critically ill" lead author Jennifer A. Frontera, MD, New York University Grossman School of Medicine, New York City, told *Medscape Medical News*.

"The general principle of our findings is to be more aggressive in TME; and from a neurologist perspective, the way to do this is to eliminate the effects of sedation, which is a confounder," she said.

The study was published online March 16 in *Neurocritical Care*.

Drilling Down

"Many neurological complications of COVID-19 are sequelae of severe illness or secondary effects of multisystem organ failure, but our previous work identified TME as the most common neurological complication," Frontera said.

Previous research investigating encephalopathy among patients with COVID-19 included patients who may have been sedated or have had a positive Confusion Assessment Method (CAM) result.

"A lot of the delirium literature is effectively heterogeneous because there are a number of patients who are on sedative medication that, if you could turn it off, these patients would return to normal. Some may have underlying neurological issues that can be addressed, but you can't get to the bottom of this unless you turn off the sedation," Frontera noted.

"We wanted to be specific and try to drill down to see what the underlying cause of the encephalopathy was," she said.

The researchers retrospectively analyzed data on 4491 patients (≥ 18 years old) with COVID-19 who were admitted to four New York City hospitals between March 1, 2020 and May 20, 2020. Of these, 559 (12%) with TME were compared with 3932 patients without TME.

The researchers looked at index admissions and included patients who had:

- ***New changes in mental status or significant worsening of mental status (in patients with baseline abnormal mental status)***
- ***Hyperglycemia or hypoglycemia with transient focal neurologic deficits that resolved with glucose correction***
- ***An adequate washout of sedating medications (when relevant) prior to mental status assessment***

Potential etiologies included electrolyte abnormalities, organ failure, hypertensive encephalopathy, sepsis or active infection, fever, nutritional deficiency, and environmental injury.

Foreign Environment

Most (78%) of the 559 patients diagnosed with TME had already developed encephalopathy immediately prior to hospital admission, the authors report. The most common etiologies of TME among hospitalized patients with COVID-19 are listed below.

Table. Common etiologies of TME in hospitalized patients with COVID-19.

Etiology	N (Prevalence)
Septic encephalopathy	347 (62%)
Hypoxic-ischemic encephalopathy	331 (59%)
Septic and hypoxic-ischemic encephalopathy	173 (31%)
Uremic encephalopathy	156 (28%)
Uremic and hypoxic-ischemic encephalopathy	83 (15%)
Uremic and septic encephalopathy	71 (13%)
Uremic and septic and hypoxic-ischemic encephalopathy	71 (13%)
Multiple etiologies	435 (78%)

Compared with patients without TME, those with TME — (all *P*s < .001):

- ***Were older (76 vs 62 years)***
- ***Had higher rates of dementia (27% vs 3%)***
- ***Had higher rates of psychiatric history (20% vs 10%)***
- ***Were more often intubated (37% vs. 20%)***
- ***Had a longer length of hospital stay (7.9 vs. 6.0 days)***
- ***Were less often discharged home (25% vs. 66%)***

"It's no surprise that older patients and people with dementia or psychiatric illness are predisposed to becoming encephalopathic," said Frontera. "Being in a foreign environment, such as a hospital, or being sleep-deprived in the ICU is likely to make them more confused during their hospital stay.'"

Delirium as a Symptom

In-hospital mortality or discharge to hospice was considerably higher in the TME vs non-TME patients (44% vs 18%, respectively).

When the researchers adjusted for confounders (age, sex, race, worse Sequential Organ Failure Assessment score during hospitalization, ventilator status, study week, hospital location, and ICU care level) and excluded patients receiving only comfort care, they found that TME was associated with a 24% increased risk of in-hospital death (30% in patients with TME vs 16% in those without TME).

The highest mortality risk was associated with hypoxemia, with 42% of patients with HIE dying during hospitalization, compared with 16% of patients without HIE (adjusted hazard ratio 1.56, 95% CI, 1.21 - 2.00; *P* = .001).

"Not all patients who are intubated require sedation, but there's generally a lot of hesitation in reducing or stopping sedation in some patients," Frontera observed.

She acknowledged there are "many extremely sick patients whom

you can't ventilate without sedation."

Nevertheless, "delirium in and of itself does not cause death. It's a symptom, not a disease, and we have to figure out what causes it. Delirium might not need to be sedated and it's more important to see what the causal problem is."

Independent Predictor of Death

Commenting on the study for *Medscape Medical News*, Panayiotis N. Varelas, MD, PhD, vice president of the Neurocritical Care Society, said the study "approached the TME issue better than previously, namely allowing time for sedatives to wear off to have a better sample of patients with this syndrome."

Varelas, who is chairman of the Department of Neurology and professor of neurology at Albany Medical College, Albany, New York, emphasized that TME "is not benign and, in patients with COVID-19, it is an independent predictor of in-hospital mortality."

"One should take all possible measures…to avoid desaturation and hypotensive episodes and also aggressively treat SAE and uremic encephalopathy in hopes of improving the outcomes," added Varelas, who was not involved with the study.

Also commenting on the study for *Medscape Medical News*, Mitchell Elkind, MD, professor of neurology and epidemiology at Columbia University in New York City, who was not associated with the research, said it "nicely distinguishes among the different causes of encephalopathy, including sepsis, hypoxia, and kidney failure…emphasizing just how sick these patients are."

The study received no direct funding. Individual investigators were supported by grants from the National Institute on Aging and the National Institute of Neurological Disorders and Stroke. The investigators, Varelas, and Elkind have disclosed no relevant financial relationships.

Neurocrit Care. Published online March 16, 2021. Full text

https://bit.ly/3w5pal8

Silent MRSA carriers have twice the mortality rate of adults without the bacteria

Unless MRSA carriers develop an infection or are tested for the bacteria, they may not even know they carry it, yet they are at significant risk for premature death

A University of Florida study of middle-aged and older adults finds those who unknowingly carry methicillin-resistant Staphylococcus aureus, or MRSA, on their skin are twice as likely to die within the next decade as people who do not have the bacteria.

"Very few people who carry MRSA know they have it, yet we have found a distinct link between people with undetected MRSA and premature death," said the study's lead author Arch G. Mainous III, Ph.D., a professor in the department of health services research, management and policy at the UF College of Public Health and Health Professions, part of UF Health, the university's academic health center.

The findings suggest that routine screening for undetected MRSA may be warranted in older people to prevent deaths from infection.

A third of Americans carry Staphylococcus aureus, or staph, on their skin or in nasal passages. About 1% of those people, or more than 3 million people, carry MRSA, the staph strain that is hard to treat and resistant to many antibiotics. Unless MRSA carriers develop an infection or are tested for the bacteria, they may not even know they carry it. Previous research has found that a quarter of people who carry MRSA without an active infection, known as colonized MRSA, for a year or more will eventually develop a MRSA infection.

"MRSA can be part of normal body flora, but it can lead to infection when immune systems are compromised, especially in people who are hospitalized, have underlying disease, or after antibiotic use," said Mainous, also vice chair for research in the UF

College of Medicine's department of community health and family medicine.

A Centers for Disease Control and Prevention report showed that in 2017, 119,000 Americans experienced a staph bloodstream infection and nearly 20,000 died. Hospitalized patients with colonized MRSA may be particularly vulnerable to developing an infection during a hospital stay or after discharge. Wounds, surgical incisions and use of medical devices, such as catheters, may also lead to MRSA infection among carriers.

For the study, which appears in the *Journal of the American Board of Family Medicine*, researchers analyzed data from the 2001-2004 National Health and Nutrition Examination Survey, a large, nationally representative study that combines survey questions with laboratory testing, including nasal swabs to test for the presence of MRSA. The researchers linked data on participants ages 40-85 with data from the National Death Index to track deaths over an 11-year period. Researchers adjusted for factors including gender, race and ethnicity, health insurance, poverty-income ratio, hospitalization in the previous 12 months, and doctor diagnosis of heart disease, diabetes and asthma.

They found the mortality rate among participants without MRSA was about 18%, but among those with colonized MRSA, the mortality rate was 36%. Participants who carried staph bacteria on their skin, but not MRSA, did not have an increased risk for premature death.

Some states and hospital systems require MRSA testing for patients before hospital admission, but policies for testing and treatment of colonized MRSA, which may include use of topical or oral antibiotics, are highly variable from hospital to hospital, Mainous said. "Without a uniform strategy, we are missing an opportunity to help prevent deaths caused by MRSA," Mainous said. "Maybe we should know who is carrying MRSA."

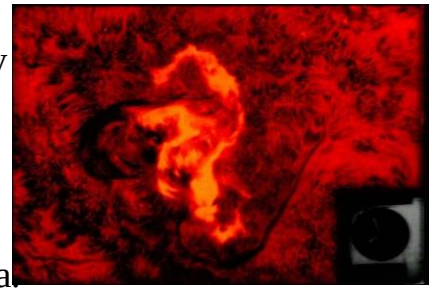
In addition to Mainous, the study team included Benjamin J. Rooks, M.S., a clinical research coordinator in the department of community health and family medicine at the UF College of Medicine; and Peter J. Carek, M.D., M.S., a professor and chair of the UF College of Medicine's department of community health and family medicine.

https://bit.ly/31rPtDS

A powerful solar storm hit Earth back in 1582

"A great fire appeared in the sky to the North, and lasted three nights," wrote a Portuguese scribe in early March, 1582.

by Scott Alan Johnston, Universe Today



***The 'Seahorse Flare', which caused a solar storm in August 1972.* Credit: NASA, Big Bear Solar Observatory**

Across the globe in feudal Japan, observers in Kyoto noted the same fiery red display in their skies, too. Similar accounts of strange nighttime lights were recorded in Leipzig, Germany; Yecheon, South Korea; and a dozen other cities across Europe and East Asia.

It was a stunning event. While people living at high latitudes were well aware of auroras in 1582, most people living closer to the equator were not. The solar storm that year was unlike anything in living memory, and it was so strong it brought the aurora to latitudes as low as 28 degrees (in line with Florida, Egypt, and southern Japan). People this close to the equator had no frame of reference for such dazzling nighttime displays, and many took it as a religious portent.

"All that part of the sky appeared burning in fiery flames; it seemed that the sky was burning," wrote Pero Ruiz Soares, an eyewitness in Lisbon, and the author of a 16th-century Portuguese chronicle. "Nobody remembered having seen something like that… At midnight, great fire rays arose above the castle which were dreadful and fearful. The following day, it happened the same at the same hour but it was not so great and terrifying. Everybody went to the

countryside to see this great sign."

These centuries-old accounts of the 1582 solar storm were recently uncovered by researchers hoping to learn more about the event. Just as early modern peoples sought meaning in the auroras, modern day scientists are also eager to understand the fiery skies of 1582. That massive solar storm, and other storms like it, are important indicators of historical solar weather patterns. Understanding them can help predict future solar activity.

The historical record seems to suggest that major storms like the one in 1582 are, at minimum, a once-in-a-century occurrence, and so we should expect one or more of them to hit Earth in the 21st century.

While pre-modern solar storms had little effect aside from their incredible auroras, a major solar storm today could do billions of dollars of damage and shut down power grids worldwide. A moderately large storm in 1989, for example, completely knocked out the power grid in Quebec, and a more powerful storm could do worse. The most severe solar storm in recorded history, the Carrington Event of 1859, were it to happen now, would be far more damaging, although at the time, it only affected early telegraph lines.

Solar storms are caused by disturbances in the sun's atmosphere. High energy explosions known as solar flares can be accompanied by an enormous rush of solar wind known as a coronal mass ejection. These fast-moving solar particles interact with Earth's magnetosphere, producing vibrant auroras and interfering with electronics.

Solar storms can also carry with them deadly doses of radiation. Earth's protective magnetosphere keeps us safe from their effects, but as NASA and its partners look to return to the moon and beyond in the coming decades, an accurate model of solar weather is going to be vital for mission planning. This lesson was learned during the Apollo era, when a solar storm blasted by Earth in August 1972. The storm would have been fatal to astronauts, had they been on the moon at the time. Luckily, Apollo 16 had returned to Earth in April that year, and Apollo 17 did not launch until December, so catastrophe was avoided. Careful planning, and a little luck, will be required to keep future lunar astronauts safe.

Should we be worried about future solar storms? Perhaps. At the very least, we ought to be prepared for them, just like any other natural disaster. Since the 1989 power outage, the power generation industry has begun working on mitigation techniques, and taken preventative measures to make power grids more resistant to solar weather, but it's hard to be fully prepared. When the next big solar storm comes, and it will come someday, we may not be fully ready for it. But one thing is for sure: it's going to put on one heck of a show.

More information: *Hattori, Hayakawa, and Ebihara, "Occurrence of Great Magnetic Storms on 6–8 March 1582." ArXiv Preprint, 2019. (see page 22 for an awesome 16th-century illustration of the Aurora). arxiv.org/abs/1905.08017*

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https://bit.ly/39nb1G3

Ancient oral biome points to overall health

Researchers looking at archaeological remains for an example of how Japanese oral biomes have changed

by A'ndrea Elyse Messer, Pennsylvania State University

When a baby puts something from the floor in their mouth, we panic, but the mouth already contains thousands of bacteria. Now a team of researchers is looking at archaeological remains for an example of how Japanese oral biomes have changed and what they say about the people who owned those mouths and teeth.

"We can now examine these communities by sequencing ancient DNA preserved within calcified dental plaque or dental calculus, providing insights into the origins of disease and their links to

human history," the researchers reported in a special edition of *Philosophical Transactions of the Royal Society B*.

Laura S. Weyrich, associate professor of anthropology, and her team looked at thousands of skeletons in collections and chose specimens that had the biggest calculus on their teeth. Calculus, sometimes called tartar, forms when dental plaque is not removed by brushing or flossing. It bonds strongly with the tooth surface and in modern times is removed during teeth cleaning at the dentist's office. Because dental plaque is a biofilm made up of mostly bacteria, sampling calculus, ancient or modern, can provide DNA identification of microbes in the mouth.

The researchers focused on two time periods. The oldest population lived 3,000 years ago during the Jomon period and were hunter-gatherers. The younger population lived 400 to 150 years ago during the Edo period and were agriculturalists.

Using these two populations, Weyrich and her team could investigate how the oral biome changed over time and how the introduction of agriculture affected the composition of bacteria and fungi. They also looked at the biome's association with oral diseases like periodontal disease and dental caries.

Images of skulls from Japanese museum collections. Top row shows two individual with blackened teeth. Bottom row shows individuals who did not have blackened teeth. **Credit: Ken-ichi Shinoda, National Museum of Nature and Science, Tsukuba, Japan**

The researchers did not find a significant difference between the early hunter-gatherers and the later agriculturalists, although "it looks like some microbes may have been brought to Japan with the introduction of rice growing," said Weyrich.

What the researchers found was a difference between the oral biomes found in male and female subjects. One possibility for this was the practice of Japanese women to blacken their teeth. This cultural practice may have migrated from other Asian countries and, in Japan, was a symbol of marriage among the aristocratic class. This practice, called ohaguru, was outlawed in Japan in 1870.

The compounds used to blacken teeth, which had to be routinely applied, may have affected the oral microbiome of women. These compounds often contained a mineral, such as iron, mixed with an acid, like vinegar, and then mixed with a colorant, like tea.

The researchers noted that "surprisingly, the practice of ohaguru was thought to protect teeth from dental decay, however, we find it associated with evidence of periodontal disease, raising questions about its health benefits."

The team looked at both alpha and beta diversity. Alpha diversity, in this case, is the diversity of species within a host, and beta diversity is the difference in diversity between different hosts.

"Alpha diversity is not different across men and women," Weyrich said. "Everyone has about the same number. There was also no significant difference in beta diversity."

While the number of species of bacteria were the same, the researchers did see a difference between the Jomon and Edo periods. "What becomes different is whether or not the strains are the same," said Weyrich. "New strains of the same species are brought in by agriculture and those are the ones that become dominant. Strains from the Jomon show evidence of extinction."

These agriculturally related strains appear on a different branch of the evolutionary tree for the bacteria, indicating they came from somewhere else. "This is the first study to examine ancient microbiomes in an Asian population," said Weyrich.

Weyrich did note that there are many potential contamination

problems for the DNA analysis. The teeth had been buried in soil, so there were soil microbes. The researchers were also concerned with contamination from their own microbial DNA. To prevent this, they wore full body suits, gloves and masks.

More information: *Raphael Eisenhofer et al. Investigating the demographic history of Japan using ancient oral microbiota, Philosophical Transactions of the Royal Society B: Biological Sciences (2020). DOI: 10.1098/rstb.2019.0578*

https://bit.ly/3cveRyZ

The promise of super algae Galdiera: From volcanic springs to your plate

A microalga originally isolated from volcanic springs has all it takes to become the next 'superfood' on the market.

Compared to Spirulina—a similar organism that's been popular as a food and feed supplement for half a century—Galdieria is cheaper and easier to grow, and even more nutritious. In a closed-circuit reactor, it can convert organic waste into valuable proteins. Those are the conclusions of the Ph.D. research of Fabian Abiusi of the group Bioprocess Engineering at Wageningen University & Research. He will defend his thesis this Monday, March 29.

"Microalgae-based products have been around for a long time," says Fabian Abiusi, a biotechnologist originally from Italy, "but in general, they are costly to produce. When these algae are grown in the dark, they convert only half of their organic substrate into biomass, while when they are grown under illumination and use carbon dioxide, they generally yield only low biomass densities. Both strategies require a costly system for efficient gas exchange. In my Ph.D. research, I developed a new cultivation method for microalgae that doubles productivity while halving the production costs."

Oxygen balance

The trick, as Abiusi explains, is growing the microalgae in a so-called mixotrophic photobioreactor: a reactor that provides its algae with light as well as an organic substrate such as sugar. Microalgae, like all plants, use sunlight as an energy source to convert carbon dioxide into organic molecules and oxygen. This process is called photosynthesis. In the dark, however, the opposite happens: plants use oxygen and organic molecules and release carbon dioxide. Industrial fermentation uses this latter principle to produce various biomolecules, such as proteins, medicines or alcohol from an organic substrate.

"In those processes, usually only half of the organic carbon is converted into biomass, while the other half is lost as carbon dioxide," says Abiusi. "However, in a mixotrophic photobioreactor, you can couple the production of oxygen via photosynthesis to the consumption of oxygen in the cell's metabolism. Similarly, almost all of the carbon dioxide produced by the microalgae is used again by the photosynthesis, making this process almost carbon neutral, and very efficient. You have double productivity, without the need for electric energy for aeration or carbon dioxide."

On the market

As an added bonus, Galdieria turns out to be much richer in protein than Spirulina. Abiusi and colleagues discovered this by unraveling the full profile of the microalga's amino acids—its protein building blocks. "Two thirds of Galdieria's dry weight is amino acids," says Abiusi, "which is more than is the case for meat, milk, cheese and eggs." Specifically, the microalga contains much cysteine and methionine, two sulfur-containing amino acids, which it owes to its evolution in sulfur-rich volcanic springs. Abiusi: "These amino acids are limited in plants, which is one of the reasons that it is difficult for us to derive well-balanced nutrition from a plant-based diet."

In conclusion, Galdieria may be the next superfood, according to Abiusi. It has the potential to help feed the world, improve human health, transition to a more plant-based diet, reduce energy use, and

make good use of organic waste. "We now have a proof of principle," concludes the bio-engineer. "I'm working with a start up in Wageningen, called Algreen, to optimize and scale up the process, using food waste as a substrate. We expect approval by the European Food Safety Authority in the course of next year. In a few years' time, you'll find Galdieria products on the market, I have no doubt about that."

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We should study 'dead' alien worlds, and maybe (carefully) seed them with life

Life finds a way.

By Adam Mann - Live Science Contributor

The search for life in the universe tends to focus on habitable environments. But to answer questions about how life emerged and spread, as well as the limits of habitability, researchers may want to consider looking at dead worlds — and perhaps even (very carefully) seeding them with life.

"The biological study of lifelessness seems counterintuitive, because biology is the study of life," said astrobiologist Charles Cockell of the University of Edinburgh in the U.K.

But in a paper set to be published in April in the journal Astrobiology, Cockell makes the case that focusing entirely on living worlds leaves out an enormous and potentially informative percentage of the cosmos. The mind-bogglingly large spaces between planets, as well as places like the burning sun and frigid moon, are all presumably devoid of life.

Even Earth, which we consider to be teeming with life, is largely uninhabitable, with a thin biosphere situated on the surface but a largely dead interior, Cockell told Live Science.

Surveying lifeless worlds could help scientists learn exactly what percentage of the universe is uninhabitable, what proportion is potentially habitable but just lacking in life, and whether there are some worlds that are partially empty and partially covered in life.

After organisms emerged during the dawn of our planet, they are thought to have proliferated to fill every habitable environment they could find. Yet the details of this process are still only hazily understood, and Cockell thinks dead worlds could help provide scientific insight into fundamental questions such as the limits of where life can exist and how living things colonize uninhabited areas.

Dead worlds could also provide a clean slate, where scientists could start the experiment of life from scratch. If researchers were to release small quantities of microbes into lifeless environments, they could learn how quickly organisms spread, the sequence in which different species take over, and how living things alter the local chemistry and eventually start to co-evolve with a planet, he added.

Future astronauts in a base on Mars might discover the best bacteria to introduce into its surface in order to make it productive for crops.

Determining the right place to conduct such an experiment might prove tricky. It is not entirely clear which places in the solar system are totally dead. Many astrobiologists think the ice-covered oceans of the moons of Jupiter and Saturn are good bets to find life, but Cockell pointed out that some environments can be habitable yet are still uninhabited.

So, if the watery depths of Jupiter's Europa or Saturn's Enceladus were to prove lifeless, perhaps it could be informative to unleash bacteria into them and monitor them over an enormous timespan, such as 10,000 years. "It would be like the Star Trek Genesis experiment," he said, referring to a fictional device capable of generating an entire biosphere on a dead body.

Cockell acknowledged that such ideas carry significant ethical concerns, including whether we have the right to alter planets beyond ours for our own purposes. Other places in the solar system are legally protected from contamination under the 1967 Outer

Space Treaty—written largely by the United States and Russia and signed by every spacefaring nation in the world—and Cockell thinks it would be important to make sure that a world or environment is actually lifeless before rushing in and potentially changing it forever.

In 2019, the Israeli lunar lander Beresheet crashed into the surface of the moon carrying a secret bounty of tardigrades — hardy organisms capable of surviving in extreme conditions, Live Science previously reported. Though Cockell thinks the creatures are probably dead, their arbitrary introduction didn't sit well with him.

One final reason to study lifeless environments might be to accidentally stumble across life, Cockell said. Few thought that volcanic hydrothermal vents at the bottom of the ocean could be habitable until submarine exploration showed them to be bursting with organisms. Such places helped redefine our understanding of where living things can survive and show us life as we don't know it, he added. "The main point is to not get too obsessed with looking for life and habitable environments," Cockell said. "Lifeless worlds can tell us a lot."

https://bit.ly/2PA2AAq

What if humans didn't have an appendix?

That organ may not be a useless artifact of evolution after all.

By Charles Q. Choi - Live Science Contributor

The appendix is often thought of as a useless artifact of evolution, much like the remnants of hind leg bones seen in whales. In fact, about 1 in 100,000 people are born without an appendix, according to a report in the journal Case Reports in Surgery. What might life be like then if everyone lacked an appendix?

The appendix is a small worm-shaped dead-end sac that juts out from the cecum, the beginning of the large intestine. Slightly more than 1 in 20 people get appendicitis, the potentially deadly inflammation of the appendix, according to the National Institutes of Health.

Charles Darwin suggested the appendix was a vestigial organ from ancestors that ate leaves, potentially helping them digest food. As these ancestors evolved to rely on a fruit-based diet that was easier to digest, Darwin speculated the appendix no longer served a function, much like the small triangular coccyx bone at the base of the human spine, a remnant of tail bones found in our distant ancestors.

However, "if Darwin knew then what scientists know now about the appendix, he would have never suggested it was a worthless vestige of evolution," William Parker, an associate professor of surgery atDuke University School of Medicine in Durham, North Carolina, told Live Science.

In 2007, Parker and his colleagues found the appendix may serve as a reservoir of useful gut bacteria, the kind that help the body to digest food, they reported in the Journal of Theoretical Biology. When diseases flush both good and bad microbes from the gut, good bacteria can emerge from the safe harbor of the appendix to help restore the gut to a healthy state.

In addition, the appendix possesses a high concentration of lymphoid tissue. This tissue generates white blood cells known as lymphocytes that help mount immune system responses to invading germs, suggesting the appendix may help make, direct and train these immune cells, evolutionary biologist Heather F. Smith at Midwestern University in Glendale, Arizona, told Live Science.

When Smith, Parker and their colleagues investigated when the appendix evolved in the animal kingdom, they found the appendix has been around in mammalian evolution for at least 80 million years, much longer than expected if the appendix really was a vestige, they reported in 2009 in the Journal of Evolutionary Biology. Moreover, they also discovered the appendix evolved independently at least 32 times among mammals, in species as

diverse as orangutans, wombats, platypuses, beavers, koalas, porcupines and manatees, they wrote in 2013 in the journal Comptes Rendus Palevol.

"When we looked in species that have an appendix, we didn't find any commonalities in diet or how social they are or where they lived, but species that did have an appendix had a concentration of immune tissue there, so given this common theme, one might presume a common function," Smith said.

So what might happen "if you waved a magic wand and the appendix suddenly vanished?" Parker said. "That might depend on when in history it happened."

If the appendix disappeared in a hunter-gatherer society "and a scientist from a spaceship or something watched what happened, you'd see a lot more people dying of infectious diseases than they would otherwise," Parker said. "Then, over a long time, over millions of years, I think something would slowly evolve that worked the same as an appendix so that people wouldn't die so much."

If the appendix vanished in a society with agriculture after people started living in settlements, "I think more people would die," Parker said. "People would have started living in crowded areas, and with poor sanitation, disease would spread more."

If the appendix disappeared in a modern society after the Industrial Revolution, people would have antibiotics to help them survive, Parker said. However, without an appendix, people would not have the appendix's reservoir of helpful bacteria to help them recover from harmful infections. "When that happens, we may need to give people fecal transplants," Parker said.

Yes, that's right, fecal transplants. These increasingly common procedures transfer feces from healthy people into the guts of patients with intestinal problems, via a tube or capsule placed down one's throat or up one's bottom. The idea is that the transplant will bring healthy bacteria into guts overrun by harmful microbes. Bodies overrun with harmful microbes may become more common as antibiotics get overused and germs evolve resistance against these drugs. "Fecal transplants don't encourage antibiotic resistance," Parker said.

One potential upside of a world without appendixes is the disappearance of appendicitis. Globally, "there are more than 10 million cases of appendicitis every year, and up to 50,000 people a year die from it," Smith said. Appendectomies, or surgical removal of the appendix, "is one of the most frequently performed abdominal surgeries. If we didn't have the appendix in the first place, you wouldn't have people dying from appendicitis, and not costs from surgery and hospitalization."

However, prior work has suggested that appendicitis may be due to cultural shifts linked with industrialized society and improved sanitation, Parker said. The idea goes that these shifts left our immune systems with too little work, opening up the possibility that they could go haywire without the appendix.

All in all, a world without an appendix might leave humanity struggling with germs more often. The idea that the appendix is an organ whose time has passed may have itself become a notion whose time is over.

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A rare clotting disorder may cloud the world's hopes for AstraZeneca's COVID-19 vaccine

Symptoms resemble a rare side effect of the blood thinner heparin

By Kai Kupferschmidt, Gretchen Vogel

In the tumultuous rollout of AstraZeneca's COVID-19 vaccine, all eyes this week were on the United States, where the company had a highly public communication breakdown over the vaccine's efficacy with an expert panel overseeing a large study in the Americas. But on the other side of the Atlantic, the vaccine faces

new concerns about safety as an explanation gains ground for the unusual strokes and clotting disorders recorded in at least 30 recipients.

Many European countries suspended use of AstraZeneca's vaccine earlier this month following initial reports of the symptoms, which have led to at least 15 deaths. Most resumed vaccinations after the European Medicines Agency (EMA) recommended doing so on 18 March, saying the benefits of the vaccine outweigh any risks. EMA is continuing to investigate the matter and will convene a wide ranging committee of experts on 29 March.

Now, a group of researchers led by German clotting specialist Andreas Greinacher of the University of Greifswald says the highly unusual combination of symptoms—widespread blood clots and a low platelet count, sometimes with bleeding—resembles a rare side effect of the blood thinner heparin called heparin-induced thrombocytopenia (HIT).

The scientists, who first described their findings during a 19 March press conference, recommend a way to test for and treat the disorder and say this can help ease worries about the vaccine. "We know what to do: how to diagnose it, and how to treat it," says Greinacher, who calls the syndrome vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). Greinacher says he has submitted a manuscript to the preprint server Research Square.

Even if Greinacher's mechanism isn't the whole story, multiple researchers told *Science* they were convinced the vaccine was causing the rare set of symptoms. If that turns out to be true, it could have major consequences for the vaccine, which is one of the cornerstones of the World Health Organization's push to immunize the world. AstraZeneca is working with partners around the globe to make and distribute billions of doses in low- and middle-income countries, which might have a harder time identifying and treating rare side effects.

Europe is relying heavily on the vaccine as well; the European Union bought 400 million doses. The company's failure to deliver on time has delayed vaccine rollouts on the continent, and now dented confidence is exacerbating the delays. And even if the risk is very low, it may make sense to use the vaccine only in those who also stand to gain the most from it: elderly people at high risk of dying from COVID-19. Several European countries have started to do this. The situation has scientists walking a tightrope: They want to make the medical profession aware of their concerns without sowing panic.

But Greinacher's hypothesis is being taken seriously. Two German medical societies put out press releases lauding him for solving the issue. In the Netherlands, the Dutch Internal Medicine Society urged internists to be aware of the symptoms and the recommended course of action. The United Kingdom has officially reported only five cases—despite administering 11 million doses of the AstraZeneca vaccine—but the British Society for Haematology has urged its members to be aware of "an important and emerging area of haemostasis and thrombosis practice" and to report any possible cases. The Australian Technical Advisory Group on Immunisation has recommended against giving any COVID-19 vaccine to people with a history of HIT.

It is not yet clear how the vaccine could trigger VIPIT, and not everyone thinks the case is closed. "It's intriguing, but I am not entirely convinced," says Robert Brodsky, a hematologist at Johns Hopkins University. AstraZeneca, meanwhile, has not directly responded to the reports of the rare constellation of symptoms except to say that they did not appear in any of the company's clinical trials.

"People are absolutely working like crazy behind the scenes to provide more clarity," says Saskia Middeldorp, a vascular internist at Radboud University Medical Center in the Netherlands, who

disagreed with the temporary halt of the vaccine because she says the benefits clearly outweigh the risks.

A 'very striking' disorder

The VIPIT story began on 27 February, when Sabine Eichinger, a hematologist at the Medical University Vienna, was confronted with an unusual patient. A 49-year-old nurse had sought help at a local hospital the day before, suffering from nausea and stomach discomfort, and was transferred to Eichinger's hospital. She had a low platelet count and computed tomography scans found thromboses—blood clots—in the veins in her abdomen and later in arteries as well. "There was little we could do at this stage," Eichinger says. The patient died the next day.

The combination of low platelet count, or thrombocytopenia, and clots kept Eichinger thinking, however. "It's very striking," she says. Platelets, also known as thrombocytes, help to form blood clots, so low levels usually lead to bleeding, not clotting. "You would think that low platelets and thromboses are opposites really." One condition where they occur together is called disseminated intravascular coagulation, when severe infection, injury, or cancer trigger clotting so widespread it uses up all the platelets, "but she had none of these things," Eichinger says.

The unusual combination also appears in HIT, which can occur in patients given heparin as a drug. Heparin binds to a protein called platelet factor 4 (PF4), forming a complex. For reasons that aren't understood, some people produce antibodies against the complex, setting off an out-of-control clotting reaction. Eichinger's patient had not received heparin, but she had gotten a shot of the AstraZeneca vaccine 5 days before her symptoms began. "I thought maybe this is some kind of immune reaction," Eichinger says.

She reached out to Greinacher, who had studied HIT for decades. "Then things started happening thick and fast," she says, as multiple countries responded to reports of clotting by suspending use of the AstraZeneca vaccine.

Greinacher says he contacted other colleagues who had studied HIT in Canada and Germany and asked the Paul Ehrlich Institute (PEI), which oversees vaccine safety in Germany, if they had seen any cases. They had. PEI recommended Germany pause use of the vaccine as well and asked Greinacher to help investigate. He soon received blood samples from eight additional patients. All had both low platelets and unusual clotting, he says. In four samples, the researchers also found evidence for antibodies against PF4, a hallmark of HIT. He and his colleagues are now checking whether other vaccine recipients and former COVID-19 patients have similar antibodies.

Brodsky says it isn't clear whether VIPIT explains all of the cases. He agrees that the PF4 antibodies and the clotting seen in patients resemble HIT, but the link has not been proven, he says: "I'm convinced that these patients have platelet factor 4 antibodies, at least four of them. But I'm not convinced that those … antibodies are explaining the thrombocytopenia or the clotting."

Treatable condition

Greinacher agrees on the need for more data. But he says it's crucial to alert doctors to the potential complication. When recognized in time, HIT can be treated with immunoglobulins—nonspecific antibodies from blood donors—that help put the brakes on platelet activation. Nonheparin blood thinners can help dissolve the clots. VIPIT should be treated in a similar way, he says. In at least one case, Greinacher says, a doctor sought the group's advice and the patient recovered. The German Society for the Study of Thrombosis and Hemostasis, of which Greinacher is a member, has issued a set of recommendations for diagnosing and treating VIPIT. Greinacher says he has also been in touch with safety representatives at AstraZeneca.

Nigel Key, a hematologist at the University of North Carolina,

Chapel Hill, agrees on the need to alert doctors. “Maybe it is too much to expect at this point that there would be a very detailed molecular mechanism,” he says, but the advice to physicians who may encounter patients is crucial.

Brodsky and Key say the cases are striking enough that they probably represent a real side effect. “I think the vaccine is mostly safe. I think the benefits probably outweigh the risk for a general population,” Brodsky says. “But these cases raise concern that this vaccine is potentially life-threatening in a small subset of patients.”

Scientists are now scrambling to understand how big that subset is and who's in it. So far, most cases have been observed in women under 65. But that could be because of the vaccinated population: Many countries initially used AstraZeneca only in people under 65 because early clinical trials included few older recipients. That meant the vaccine was used in priority groups such as health care workers and teachers, a majority of whom are women. In Norway, for example, 78% of the AstraZeneca doses went to women, says Sara Viksmoen Watle, chief physician at the Norway Institute of Public Health. The United Kingdom, however, used the vaccine first in older people, which may explain why fewer unusual clotting events have been spotted there.

Data from Norway—whose extensive health registries make this type of research easier—suggest previous COVID-19 infection does not predispose vaccinees to a severe reaction, Watle says. Alerting clinicians will help ensure that fewer cases are missed for analysis, Key says. A global database of cases may be helpful too.

Many countries are, for now, accepting the risk that the AstraZeneca may carry, but several have restricted its use to people who are at the highest risk of dying from COVID-19: those aged 55 or older in France, 65 or older in Sweden and Finland, and 70 or older in Iceland. That approach makes sense, says Sandra Ciesek, a virologist at Goethe University, Frankfurt. “The argument I keep hearing is that the risk-benefit ratio is still positive. But we do not have just one vaccine, we have several. So, restricting the AstraZeneca vaccine to older people makes sense to me, and it does not waste any doses.”

Denmark and Norway are waiting for more data. Norway, which has administered the AstraZeneca vaccine to 130,000 people under 65, has reported five patients who had low platelets, hemorrhage, and widespread thromboses, three of whom died. That's about one case in 25,000 vaccinees, "a high number with a very critical outcome in previously healthy, young individuals,” Watle says. The country hopes to make a decision on the vaccine within 3 weeks. It can afford to hold off: COVID-19 cases are relatively low and AstraZeneca is delivering so few doses that the extended pause won't make a big difference in the short-term.

Middeldorp says she expects more clarity after Monday's meeting of EMA's expert group, which includes clotting experts, neurologists, virologists, immunologists, and epidemiologists. The agency says it will issue an update on the vaccine during the next meeting of its safety committee, being held from 6-9 April. Ideally, that meeting will help clarify how frequently the condition occurs and whether the risk varies by age or sex, Middeldorp says. The world needs AstraZeneca's vaccine, she says—but that means it is crucial to fully understand its benefits and its risks.