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Researchers unveil oldest evidence of human activity in African desert cave

Potentially the earliest cave occupation in the world and the site of some of the earliest indications of fire use

Few sites in the world preserve a continuous archaeological record spanning millions of years. Wonderwerk Cave, located in South Africa's Kalahari Desert, is one of those rare sites. Meaning "miracle" in Afrikaans, Wonderwerk Cave has been identified as potentially the earliest cave occupation in the world and the site of some of the earliest indications of fire use and tool making among prehistoric humans.

***The Kalahari desert Wonderwerk Cave.* / Michael Chazan / Hebrew University of Jerusalem**

New research published in *Quaternary Science Reviews*, led by a team of geologists and archaeologists from the Hebrew University of Jerusalem (HU) and the University of Toronto, confirms the record-breaking date of this spectacular site. "We can now say with confidence that our human ancestors were making simple Oldowan stone tools inside the Wonderwerk Cave 1.8 million years ago. Wonderwerk is unique among ancient Oldowan sites, a tool-type first found 2.6 million years ago in East Africa, precisely because it is a cave and not an open-air occurrence," explained lead author Professor Ron Shaar at HU's Institute of Earth Sciences.

The team were able to successfully establish the shift from Oldowan tools (mainly sharp flakes and chopping tools) to early handaxes over 1 million years ago, and to date the deliberate use of fire by our prehistoric ancestors to 1 million years ago, in a layer deep inside the cave. The latter is a particularly significant because other examples of early fire use come from open-air sites where the possible role of wildfires cannot be excluded. Moreover, Wonderwerk contained a full array of fire remnants: burnt bone, sediment and tools as well as the presence of ash.

Dating cave deposits is one of the greatest challenges in paleo-anthropology, aka the study of human evolution. To overcome this challenge, the team analyzed a 2.5-meter thick sedimentary layer that contained stone tools, animal remains and fire remnants using two methods: paleomagnetism and burial dating. "We carefully removed hundreds of tiny sediment samples from the cave walls and measured their magnetic signal," described Shaar.

Magnetization occurred when clay particles, that entered the cave from outside, settled on the prehistoric cave floor, thereby preserving the direction of the earth's magnetic field at that time. "Our lab analysis showed that some of the samples were magnetized to the south instead of the north, which is the direction of today's magnetic field. Since the exact timing of these magnetic "reversals" is globally recognized, it gave us clues to the antiquity of the entire sequence of layers in the cave," added Shaar.

Prof. Ari Matmon, Director of HU's the Institute of Earth Sciences, relied on a secondary dating method to further confirm when the earliest human ancestors may have occupied the site. "Quartz particles in sand have a built-in geological clock that starts ticking when they enter a cave. In our lab, we are able to measure the concentrations of specific isotopes in those particles and deduce how much time had passed since those grains of sand entered the cave," he explained.

The dating of prehistoric human activity at Wonderwerk Cave has far-reaching implications. The co-directors of the Wonderwerk Cave project, Prof. Michael Chazan at the University of Toronto and Liora Kolska Horwitz at HU's National Natural History

Collections, explained that the findings at Wonderwerk "are an important step towards understanding the tempo of human evolution across the African continent. With a timescale firmly established for Wonderwerk Cave, we can continue studying the connection between human evolution and climate change, and the evolution of our early human ancestors' way of life."

More information: *Ron Shaar et al. Magnetostratigraphy and cosmogenic dating of Wonderwerk Cave: New constraints for the chronology of the South African Earlier Stone Age, Quaternary Science Reviews (2021).* *DOI: 10.1016/j.quascirev.2021.106907*

https://bit.ly/3e5wNB7

Drug derived from Kentucky-grown plant shows promise for ovarian cancer treatment

A new study from University of Kentucky Markey Cancer researchers shows that Artemisia annua, a plant that has been traditionally used for its anti-malaria components, shows promise in treating ovarian cancer.

Lexington, Ky. - The study, recently published in *Diagnostics*, demonstrates that artesunate, a drug synthesized from Artemisia annua, kills ovarian cancer cells in multiple preclinical model systems. Despite accounting for only 1.3% of all new cancer cases, 2.3% of cancer deaths in 2021 are predicted to be caused by ovarian cancer. The current standard of care for advanced ovarian cancer, which hasn't changed since 2003, is the use of two chemotherapy agents: carboplatin and paclitaxel.

In this study, the researchers determined that artesunate, both alone and in combination with carboplatin and paclitaxel, has anticancer activity at concentrations that are achievable in the clinic, which support the further clinical development of this strategy.

"Artesunate is historically used as an anti-malarial but with emerging evidence, it demonstrates its anti-cancer activity," said Jill Kolesar, PharmD, professor in the UK College of Pharmacy and administrative director of Markey's Precision Medicine Clinic. "This supports bringing it into the clinic and we hope to have positive outcomes for these patients, based on our preclinical data."

Kentucky is the only state currently growing substantial quantities of Artemisia annua, meaning the Commonwealth could become a new epicenter for growing the plant worldwide. The plant's growth process is similar to that of tobacco, potentially giving Kentucky's tobacco farmers a new cash crop to supplement their incomes.

Artemisia annua is also grown at UK's Spindletop Farm, where it is harvested primarily for research purposes within the College of Agriculture, Food and Environment and the College of Pharmacy.

"We're growing Artemisia on Kentucky farms, studying it in our Kentucky lab, and now moving it into Kentucky clinics," Kolesar said. "Potentially improving the economy of the state and developing a cancer treatment for your patients - that's truly a dream."

https://bit.ly/3339IsA

Lactic acid bacteria can extend the shelf life of foods

Researchers at the National Food Institute have come up with a solution that can help combat both food loss and food waste:

They have generated a natural lactic acid bacterium, which secretes the antimicrobial peptide nisin, when grown on dairy waste.

Nisin is a food-grade preservative, which can extend the shelf life of foods, and thus can be used to reduce food waste. The discovery also makes it possible to better utilize the large quantities of whey generated when cheese is made.

Nisin is approved for use in a number of foods, where it can prevent the growth of certain spoilage microorganisms as well as microorganisms that make consumers sick. It can for instance inhibit spore germination in canned soups and prevent late blowing in cheeses—without affecting its flavour.

In theory, nisin could be added to fresh milk to extend its shelf life. However, different countries have different rules stating what types

of products nisin may be added to and in which amounts.

Extra step towards better utilization of whey

Many dairies are already turning a profit by extracting protein and lactose from the many tons of whey they generate, which they use in e.g. infant formula and sports nutrition. What is left behind can still be used to produce nisin. In addition to ensuring better resource utilization, there may be a financial gain from producing nisin: Most commercially available nisin products contain 2.5% nisin and cost approximately 40 euro per kilogram.

The work related to isolating the nisin secreting lactic acid bacteria has been described in further detail in a scientific article in the Journal of Agricultural and Food Chemistry: Efficient Production of Nisin A from Low-Value Dairy Side Streams Using a Nonengineered Dairy Lactococcus lactis Strain with Low Lactate Dehydrogenase Activity.

https://bit.ly/3qSreI6

A Revolution Is Sweeping the Science of Ancient Diseases

The study of DNA from millennia-old bacteria and viruses is revealing new secrets about the plague and other epidemics.

Sarah Zhang

When Johannes Krause was a graduate student working on the Neanderthal genome in the 2000s, so much of the DNA recovered from the ancient bone fragments came from everything else: the skin cells of excavators and scientists, the bacteria on those humans, the microbes in the soil. To get to Neanderthal DNA, you had to junk the rest. Once scientists figured out how, they rushed to sequence not just Neanderthal DNA but also ancient human DNA, which together have been rewriting the early history of our species. Only later did scientists realize that there is gold in the "junk" too.

If you know exactly how and where to look, you can also find DNA from ancient pathogens in old bones. The "junk" might actually contain clues about long-ago pandemics. Over the past decade, scientists have used ancient DNA to study diseases including the plague, syphilis, hepatitis B, and a mysterious "cocoliztli" epidemic—all using techniques honed through decoding the Neanderthal genome. A boom in ancient pathogen DNA is uncovering hints of forgotten and even extinct diseases.

Krause, now the director of the archaeogenetics department at the Max Planck Institute for Evolutionary Anthropology, is a co-author of the recent book *A Short History of Humanity*, with the German journalist Thomas Trappe. I've written about Krause's studies as they've come out over the years, but the book synthesizes two decades of work with ancient DNA, human and pathogen. This kind of research is difficult; it relies on a very small number of samples and requires the expertise of historians and archaeologists to interpret. And even then, some things about the past are unknowable. Amid our current pandemic, I spoke with Krause about some of the most intriguing yet puzzling genetic clues we now have about very old pandemics.

This interview has been condensed and edited for clarity.

Sarah Zhang: A lot of your work on ancient pathogens has relied on old teeth. Why are teeth so good for this?

Johannes Krause: Blood is what we're actually looking for, because most of the pathogens we're looking at—hepatitis B or *Yersinia pestis*—they are actually blood-borne. But how do you get a blood sample from 600 years ago? The tooth is the best place for blood samples because teeth are vascularized, so you have blood flow inside the teeth. And the teeth are protected by the enamel. They're like a little time capsule.

Zhang: How much of the tooth do you need?

Krause: Usually really tiny samples. We take an average of about 50 milligrams. It's like a bread crumb. Usually what you do is you cut off the crown of the tooth, and then you drill inside the crown, which is where the pulp chamber is. That's where the dried blood vessels of the tooth would be.

Zhang: Did you ever think that you would accidentally become a

dentist for ancient teeth?

Krause: It was kind of strange. When you're doing the sampling, it often smells like the dentist's. I started to realize I was doing something very similar. [Laughs.] I hated the dentist when I was young. Who likes them? But I kind of know quite a bit about all the names of teeth, like the P1, P2, the M1, M3, and things like that. When I go to the dentist, the dentist is always amazed.

Zhang: In 2011, you and your colleagues published the first genome of plague bacteria, *Yersinia pestis*, from the teeth of medieval Black Death victims. But for a long time, *Yersinia pestis* and the plague had been suspected but not confirmed as the cause of the Black Death. What did you find in the DNA?

Krause: When we started, many historians were discussing whether the Black Death was caused by the plague. People said it was a virus. People said it was a hemorrhagic fever. Some people were saying it's anthrax; other people were saying it's an unknown disease. And we just said, Yeah, let's look. We had access to this cemetery that was only used in the Black Death, which is perfect. When they had thousands and thousands of dead people in London, they just turned part of the city into graveyards. And the East Smithfield, which is close to the Tower of London today, was such a grave site.

We did the genome, and it worked surprisingly well. One of the first discoveries is that it didn't have what we would call a "derived mutation" or a gene or even a position in its genome that is specific to the Black Death. Today, plague is still found in nearly every continent. We found that the Black Death is literally the common ancestor, the mother of 80 percent of the strains that circulate in the world today. And that's pretty important, because it tells us that, biologically, the Black Death strain was not special. It's not that it was more infectious, more virulent. It's actually more or less what you have circulating today in the Grand Canyon in squirrels or in groundhogs or what you find in Madagascar.

Zhang: This is what I find so fascinating. If the bacteria are largely the same, why don't we have Black Death anymore or big outbreaks of bubonic plague?

Krause: First of all, we changed our lifestyle quite a bit. We are just living in much more hygienic conditions. Plague is actually not usually transmitted between people, but between animals and people, and usually the vector is a flea. We don't live with mice and rats in the house as much.

Also, the type of rodents changed. In the medieval time, when the Black Death happened, we had a very large population of black rats—much, much bigger than today. And in fact, they were largely replaced by brown rats, *Rattus norvegicus*. Now, brown rats are very different in their behavior. They live in the sewage, and they live in the ground. They don't live under the roof. The black rat was called the roof rat. They were living where people stored their grain, and when people still had the grain storage in the house, that's where the rats were.

But people that do have exposure to animals, like people that live in the countryside, people that go hunting, they are usually the people that contract plague these days. There's several cases in the U.S. every year. And there are warning signs if you go to the Grand Canyon: Don't feed the squirrels, because you could get plague. It's actually moving in the U.S. from the West Coast to the East Coast with rodent populations.

Zhang: I live in New York, so I guess we have that to look forward to at some point.

Krause: And you have a lot of rats in New York.

Zhang: Yes, but they're brown rats!

Krause: Fortunately, yes.

Zhang: The spread of brown rats through global shipping routes is one of the big ecological stories of the past several centuries.

Environmentally, it's been devastating, especially for a lot of island ecosystems, so it's really interesting to think about the role they might have played in spreading disease—or not spreading it.

Krause: Some people speculate that the brown rat saved us from the plague. One of the mysteries is that the plague disappeared in the beginning of the 18th century, when you still have rats, when you still have hygienic conditions which are not great. What happens in Europe is that the new rat gets introduced. The brown rat arrives—there's some historical documentation around the 1720s—and then it starts spreading. Actually, wherever the brown rat moves, the black rat is getting replaced, because they are really aggressive toward black rats. The black rats disappear. It's ironic, almost, that people, when they see rats today, they think about the plague and How horrible. But maybe that rat that you see today, like in New York in the subway, is actually the one that saved us from the plague.

Zhang: I think this really speaks to how disease is contingent on human behavior. We might think of diseases as things that just exist in nature—they're out there and they're trying to kill us. But what's happening is that these pathogens are only successful if they find and exploit the seams in human behavior. We created the conditions for the plague because we started living in cities, because we started living with rats, because we have fleas.

Krause: Absolutely, we are creating the niche for those pathogens. We ourselves only became an interesting host in the last 10,000 years, when we started agriculture and having large populations and a sedentary lifestyle where we live with a lot of people in the same place and dump our excrement behind our houses. Basically we are surrounded by garbage, and that attracts a lot of rodents and potential parasites of those rodents.

It's only from that point, where the population size is big enough, that infectious disease can spread and can be passed on between one population and another—only then it becomes a human pathogen. We've become even a better and more interesting host, like we've seen with coronavirus, right? It took three weeks, and it was in almost every country in the world.

In the book, we say humans have become like bats because we now have dense populations. Bats live in these really dense populations, like millions sometimes in one cave. But unlike bats, we have only had 5,000 years to adapt, and bats have done that for the last 40 million years. But we have our big brains and really powerful medicine.

Zhang: Yeah, the plague–or some form of it—seems to have existed in the Stone Age too. You and your colleagues and others have found evidence of bacteria that looks like *Yersinia pestis* in teeth going back nearly 5,000 years in Europe. But it also looks very different from modern plague, right?

Krause: It is different, and I am still not quite sure what it is and what kind of disease it's causing. I'm pretty certain it's lethal, because we find it in high concentrations in the teeth, and then it has caused some sort of sepsis, and it has somehow killed those people. But how it actually enters the blood, we don't know.

It basically cannot be transmitted by fleas. It lacks the genes that are necessary for flea transmission, which is a very nifty mechanism: Fleas get the bacteria, they clog the stomach of the flea, the flea starves, and then it keeps on biting. Every time it bites, it infects. ˜This whole nifty mechanism, we could show, only evolved about 4,000 years ago. This earlier form, which we call Stone Age plague, doesn't have that.

So how does it get transmitted? One explanation could be pneumonic, so it's droplet infection. People cough on each other and inhale and then get infected in their lungs. The most likely other possibility is some sort of enteric fever, like something that is maybe gastrointestinal. They ingest and then maybe pass it on like

typhoid fever.

What's most striking for me is that it was all over Eurasia at that time. We find it in Siberia. We find it in Iberia. And it was somehow related to this highly mobile lifestyle, probably related also to herding. It's not really what you would expect for plague later on, which occurs in settlements and cities.

Zhang: Have you thought about what kind of mark the coronavirus pandemic could leave in the archaeogenetics record—if any?

Krause: I mean, not that much, right? Much of it is a cultural response that wouldn't really preserve that well. But maybe people will also see a change in our behavior. You could have the drop in carbon-dioxide emissions over that year. Mortality is high, relatively, compared to other respiratory diseases, but it's not, of course, comparable to the Black Death. But last year, when people were doing mass graves in New York City, the image is really burned in my brain. It looks like East Smithfield. It looked the same. It was a long, long, long trench where they had put one grave after another.

https://bit.ly/3qUNctQ

Study reports links between blood types and disease risks

A scan of health data on more than five million people for links between blood type and more than 1,000 diseases reveals new connections and supports previously reported ones

People with certain blood types are more likely to have blood clots or bleeding conditions, kidney stones, or pregnancy-induced hypertension, suggests a study published today in *eLife*.

The study confirms previously identified connections between certain blood types and the risk of blood clots and bleeding, and makes a new connection between kidney stones and having type B blood as compared to O. The discoveries may lead to new insights on how a person's blood type may predispose them to developing a certain disease.

Previous studies have found that people with blood type A or B were more likely to have cardiovascular disease or experience a blood clot than people with type O blood, and that people with type O blood were more likely to have a bleeding condition. Others have suggested that people with certain blood types may be more susceptible to some infectious diseases.

"There is still very little information available about whether people with RhD-positive or RhD-negative blood groups may be at risk of certain diseases, or how many more diseases may be affected by blood type or group," says first author Torsten Dahlén, a PhD student in the Department of Medicine, Solna, at Karolinska Institutet in Stockholm, Sweden. "To help fill this gap, we used an unbiased approach to investigate the link between ABO blood types and RhD groups and more than 1,000 diseases."

Dahlén and colleagues scanned Swedish health registries with information on more than five million people for links between ABO blood type or RhD-positive or RhD-negative blood groups and more than 1,000 diseases. They found 49 diseases that were linked to ABO blood types, and one that was linked to the RhD group.

Their findings confirmed that people with type A blood were more likely to experience a blood clot and that those with type O blood were more likely to experience a bleeding disorder. They also verified that women with type O blood were more likely to experience pregnancy-induced hypertension.

Additionally, they found a new connection between having type B blood and a lower risk of developing kidney stones. And women who were RhD-positive were more likely to experience pregnancy-induced hypertension.

The authors say that more studies are needed to confirm the results and to determine how different blood types or groups may increase

the risk of certain diseases, or whether there are alternative explanations for these relationships.

"Our findings highlight new and interesting relationships between conditions such as kidney stones and pregnancy-induced hypertension and blood type or group," concludes senior author Gustaf Edgren, Associate Professor of Epidemiology at Karolinska Institutet, and a physician in the Department of Cardiology at Södersjukhuset Hospital, Stockholm, Sweden. "They lay the groundwork for future studies to identify the mechanisms behind disease development, or for investigating new ways to identify and treat individuals with certain conditions."

https://bit.ly/3qQzpo1

Hepatitis C drugs multiply effect of COVID-19 antiviral Remdesivir

Existing drugs increase efficacy 10-fold in cell studies

Troy, N.Y. -- When combined with drugs currently used to treat hepatitis C, the antiviral remdesivir is 10 times more effective in treating cells infected with SARS-CoV-2, the virus that causes COVID-19.

Published this week in *Cell Reports*, this finding -- from Gaetano Montelione, a professor of chemistry and chemical biology at Rensselaer Polytechnic Institute, and his collaborators at the Icahn School of Medicine at Mount Sinai and the University of Texas at Austin -- raises the potential for repurposing available drugs as COVID-19 antivirals in cases where a vaccine isn't practical or effective.

Remdesivir, which blocks viral replication by interfering with a viral polymerase, must be administered intravenously, limiting its use only to patients sick enough to be admitted to a hospital. However, the efficacy of the drug combination would extend to other polymerase inhibitors, of which at least one orally administered version is under development, making possible an oral drug combination that could be taken at home.

"Nearly 3 million people have died worldwide from COVID-19. There are situations where the vaccine isn't the best option and it would be helpful to have orally available antivirals," said Montelione, a member of the Rensselaer Center for Biotechnology and Interdisciplinary Studies (CBIS). "Here we see a promising synergy that, if confirmed through additional research and clinical trials, could provide a new antiviral to combat COVID-19."

Repurposed drugs, already approved for use as therapeutics for a different disease, could potentially be approved for clinical use more rapidly than newly developed, more specific, and potent drugs. Remdesivir itself is a repurposed antiviral drug, originally developed to treat hepatitis C, Ebola virus disease, and other viral infections.

"Repurposed drugs have the potential to be tested and approved quickly for safe use, while more effective therapies are under development" said Robert Krug, virologist and professor emeritus at the University of Texas at Austin, who helped to initiate the collaboration, interpret the results, and write the paper.

The *Cell Reports* paper identifies four hepatitis C drugs, simeprevir, grazoprevir, paritaprevir, and vaniprevir, which exhibited a synergistic effect - an effect that is greater than the sum of its parts. For example, when administered at low doses to virus-infected cells in the presence of simeprevir, 10 times less remdesivir is needed to inhibit 90% of the virus than when remdesivir is used on its own. Increasing the efficacy of the polymerase inhibitor remdesivir reduces the dosage required, and therefore could be more effective, and also reduce unwanted side effects in treating COVID-19.

The researchers discovered the synergistic effect as part of an effort to identify existing drugs that could be used against COVID-19. Remdesivir and the hepatitis C drugs inhibit viral replication, but they target different aspects of the process. The RNA that the virus

injects into the cell causes it to make two polyproteins, which are then cut into more than two dozen smaller pieces that help to replicate the virus, and make excellent targets for antivirals that block their activity. Remdesivir targets a polymerase cluster, but many antivirals target viral proteases, enzymes that are required for the life cycle of the virus.

In earlier work, Montelione, Krug, and Khushboo Bafna, a postdoctoral fellow at Rensselaer, used a bioinformatics approach to identify existing proteins that resemble the coronavirus protease structures. The search identified a "striking similarity" with a protease from the hepatitis C virus, which is the target of several approved drugs. This similarity between the structures of key proteases of the two viruses raised the possibility that existing drugs that bind and block the hepatitis C protease would have the same effect on at least one of the proteases, called Mpro, in SARS-CoV-2. That possibility was borne out by multiple subsequent studies, including Bafna's docking simulations using supercomputer facilities at the Rensselaer Center for Computational Innovations, predicting the effect of various hepatitis C drugs on the SARS-CoV-2 Mpro.

In *Cell Reports*, the team performed protein binding and viral replication studies with the SARS-CoV-2 virus, remdesivir, and 10 hepatitis C drugs, some of which are already approved by the Food and Drug Administration. Seven of the drugs, tested in a secure biocontainment facility at Mount Sinai, inhibit Mpro and suppress the replication of SARS-CoV-2 virus. These studies were enabled by specialized expertise in the laboratories of research collaborators Adolfo García-Sastre and Kris White at Mount Sinai.

But a careful analysis of the data revealed that three hepatitis C drugs were acting not only on Mpro, but also on second viral protease, the papain-like protease, called PLpro. It is this activity that creates the synergy with the polymerase inhibitor remdesivir. These results indicate that PLpro is an important target for future antiviral drug development, especially for virus variants that are resistant to vaccine-generated antibodies.

"The identification of PLpro as an antiviral target that has a synergistic effect with remdesivir is a very important finding. We hope this work will encourage the development of specific SARS-CoV-2 PLpro inhibitors for inclusion in combination therapies with polymerase inhibitors to produce a highly effective antiviral cocktail that will also prevent the rise of resistance mutations," said Kris White, an assistant professor at Mount Sinai School of Medicine.

Adolfo García-Sastre, professor of virology at Mount Sinai emphasized, "Combined use of remdesivir with an inhibitor of the PLpro for the treatment of COVID-19 would also reduce the possibility of selecting SARS-CoV-2 resistant viruses."

The studies at CBIS were carried out by Gaetano Montelione and Catherine Royer, professor of biological studies, along with postdoctoral fellows Bafna and Balasubramanian Harish. "These techniques and approaches made it possible to pinpoint the similarity between target molecules and accelerate discovery during a time of pressing need. The research is an excellent example of the benefits that bioinformatics and interdisciplinary biotechnology more broadly can deliver to human health," said Deepak Vashishth, the director of CBIS.

"Hepatitis C Virus Drugs Which Inhibit the SARS-CoV-2 Papain-Like Protease 2 Synergize with Remdesivir to Suppress Viral Replication in Cell Culture" was published in Cell Reports with support from the National Institutes of Health. At Rensselaer, Montelione was joined by Professor Catherine Royer, as well as Bafna, Harish, Theresa A. Ramelot, and Thomas B. Acton. Adolfo García-Sastre and Kris White led the effort at Mount Sinai with Romel Rosales, Elena Moreno, Thomas Kehrer, and Lisa Miorin. Robert M. Krug contributed from the University of Texas at Austin.

https://wb.md/3ucofhm

Half of Patients in Hospital for COVID-19 Get Acute Kidney Injury

Acute kidney injury (AKI) is a frequent complication among patients hospitalized for COVID-19

Mitchel L. Zoler, PhD

Acute kidney injury (AKI) is a frequent complication among patients hospitalized for COVID-19, with incidence rates of 39% and 52% in two independent, European case series presented recently at the International Society of Nephrology (ISN): 2021 World Congress. Many of the cases progressed to more severe, stage 3 AKI. Factors linked with incident AKI in the two reports included use of mechanical ventilation, vasopressors, or diuretics, and elevations in inflammatory markers.

The new findings confirm several US reports published during the past year. In those reports, roughly a third of patients hospitalized for COVID-19 developed AKI during their hospital stay, said Jay L. Koyner, MD, during another renal conference, the National Kidney Foundation (NKF) 2021 Spring Clinical Meetings.

Experience has shown it's bad news when hospitalized COVID-19 patients develop AKI, which can prove fatal or can lead to the development or worsening of chronic kidney disease (CKD), which in some cases rapidly progresses to end-stage disease.

COVID-19 Giving Nephrologists an Opportunity to Improve AKI Care

"COVID is giving us an opportunity to do a better job of taking care of patients who develop AKI, which is something that nephrologists have not often excelled at doing," said Koyner, professor and director of the nephrology intensive care unit (ICU) at the University of Chicago.

"Many studies will look at how we can manage COVID-19 patients better after they develop AKI, because I suspect a large number of these patients will wind up with CKD," Koyner said during his talk.

He cited several lessons from reports of AKI that occurs in patients hospitalized for COVID-19:

- ***Preexisting CKD, obesity, and severe COVID-19 appear to be risk factors for developing COVID-related AKI.***
- ***Patients who develop AKI during acutely severe COVID-19 may have slightly worse outcomes than patients without COVID-19 who develop AKI.***
- ***Certain genetic susceptibilities may play a role in developing COVID-19-related AKI.***
- ***Routine follow-up of AKI is generally inadequate and is not standardized, whether AKI develops while ill with COVID-19 or in other settings.***

The most encouraging AKI take-away from COVID-19's first year is that its incidence among patients hospitalized with COVID-19 appears to have dropped from very high rates early on, possibly because of more routine use of steroids for critically ill patients with COVID-19 and a reduction in the use of ventilators, Koyner suggests.

In-Hospital Diuretic Treatment Links With AKI

One of the World Congress of Nephrology reports involved 1248 patients admitted with confirmed COVID-19 at two tertiary-care hospitals in London during March–May 2020. The average age of the patients was 69 years, 59% were men, and 17% had CKD at admission, as determined on the basis of estimated glomerular filtration rate <60 mL/min/1.73 m^2.

During hospitalization, 487 patients (39%) developed AKI, including 175 (14%) with stage 3 AKI and 109 (9%) who required renal replacement therapy (dialysis or kidney transplant). The incidence of AKI peaked 5 weeks after COVID-19 admission, reported Paul Jewell and his associates from King's College Hospital, London, United Kingdom, in a poster.

Multivariate analysis identified several demographic and clinical variables that were significantly linked with an increased risk of developing AKI: male sex (which boosted risk by 55%), Black race (79% higher risk), CKD at admission (triple the risk), being hypertensive on admission (73% higher risk), and being administered diuretics during hospitalization (69% higher risk).

The findings of a risk linked with diuretic use "supports the cautious use of diuretics in patients hospitalized with COVID-19, especially in the presence of background renal impairment," the authors said.

For patients with incident AKI, the 30-day mortality rate was significantly increased; mortality was 59% higher among patients who developed stage 1 AKI and was roughly triple among patients who developed stage 2 or 3 AKI.

Second Report Links Ventilation, Vasopressors With Worse AKI

A separate report from clinicians at Charité Hospital, Berlin, Germany, retrospectively reviewed 223 patients admitted with symptomatic COVID-19 to three Charité sites during March–June 2020. During hospitalization, 117 patients (52%) developed AKI, including 70 (31%) with stage 3 disease; 67 (30%) required renal replacement therapy. Half the patients with stage 3 AKI required ICU admission.

Compared with patients with less severe AKI, patients who developed stage 3 AKI were more often male, older, and had a higher body mass index.

In a multivariate model, compared with patients who developed less severe AKI, those who developed stage 3 disease also were significantly more likely to have received mechanical ventilation or vasopressor drugs and were more likely to have increased levels of leukocytes or procalcitonin, two inflammatory markers, reported Jan-Hendrink B. Hardenburg, MD, a Charité nephrologist, and his associates in a poster at the meeting.

Mechanical ventilation was linked with a sixfold higher rate of stage 3 AKI, and treatment with vasopressor drugs was linked with a threefold higher rate. Elevations in procalcitonin or leukocyte levels were linked with about 60% increases in rates of stage 3 AKI. For both of these risk factors, temporal relationships were tighter; increases in both values appeared just before onset of stage 3 disease.

Joyner has been a speaker on behalf of NXStage Medical, a consultant to Astute Medical, Baxter, Mallinckrodt, Pfizer, and Sphingotec, and he has received research funding from Astute, Bioporto, NxStage, and Satellite Healthcare. Jewell and Hardenburg have disclosed no relevant financial relationships.

https://nyti.ms/2QD8TUM

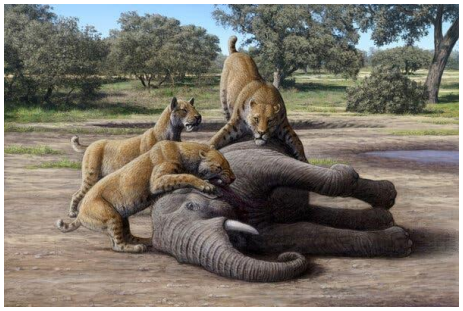
Baby Mammoths Were Meals for These Saber-Tooth Cats

Fossils from a Texas site suggest that the predatory felines not only snatched mammoths from their herds, but dragged the remains back to their cave.

By Jeanne Timmons

On a landscape that would one day become a suburb of San Antonio, paleontologists paint a picture that is as bloody as it is fascinating.

Mammoths were stalked by predatory cats with scimitar teeth protruding from their jaws. The cats would snatch a juvenile mammoth, blood staining the fur around their mouths and claws as it soaked into the grasses around them. Having eaten their fill, they would take the carcass back to their den. This was a meal that could be shared again later.



An artist's concept of Homotherium cats feasting on a juvenile mammoth. A study concludes that the cats had a diet unlike any other large cat, extinct or alive today. **Credit...Mauricio Antón**

Earlier this month, researchers published a paper in the journal Current Biology providing evidence that supported this scenario. What it also shows is that the cats had a diet unlike any other large cat, extinct or alive today.

When most people think of saber-tooth cats, they think of North

America's Smilodon. But they prowled the same terrain as another ferocious but less well-known feline, Homotherium serum, also known as a scimitar cat. While the authors compare Homotherium to a cheetah in some respects, this cat appears to have been built more for long-distance running than sprinting. Its teeth were sharp and coarsely serrated, and its fangs were shorter than Smilodon's iconic fangs. These shorter sabers may have been better at slashing as opposed to stabbing.

"Everything that we looked at basically told us that Smilodon and Homotherium are totally different cats," said Larisa DeSantis, the paper's lead author and a paleontologist at Vanderbilt University. She adds that although they were more closely related to each other than to any cat species living today, "They were able to coexist in these ecosystems likely due to having very different dietary niches."

The Friesenhahn Cave outside San Antonio has produced more Homotherium fossils than any other site in the world. It's a Pleistocene treasure trove, offering a diversity of fossil species, including a large number of juvenile mammoth bones. The abundance of Homotherium and mammoth suggests they may have been connected. But were they?

To answer this question, Dr. DeSantis and her colleagues had to establish the Homotherium diet.

They started with a three-dimensional analysis of the surface of Homotherium teeth, comparing them with similar predators during the Pleistocene as well as those that hunt today. They found that Homotherium ate soft and tough food, but not bones. If they were eating mammoths, this meant they could eat the animals' tough hides and soft flesh, but avoided crunching bone material.

The researchers also found chemical signatures that offered clear evidence that these cats were eating herbivores that grazed in open habitats. Homotherium's preference for such prey is unlike any other North American wild cat today or during the recent past.

This analysis, combined with the discovery of numerous detached mammoth limb bones in a cave populated by Homotherium led the researchers to conclude that mammoths were on the menu, and remains were dragged home after a successful hunt.

"I definitely think they would have hunted juvenile mammoths," said Aaron Woodruff, a paleontologist at the Florida Museum of Natural History who was not involved in this research. "But I don't think they would have done this often." He laughed.

"Like I don't think the crew got together every weekend and went looking for mammoths."

Mairin Balisi, paleoecologist at the La Brea Tar Pits and Museum who also was not involved in this research, praised the analysis in the paper, but added that it would be strengthened with "further evidence, like nitrogen isotopes from collagen, which might provide more insight about whether an animal is juvenile or not."

That the fossils were available to study at all required a bit of luck.

The Friesenhahn Cave, on private property, was discovered in the early 20th century, studied, excavated, then lost and rediscovered again. Ernest Lundelius, a co-author and emeritus geoscientist at the University of Texas, Austin, has been working at the cave since 1957.

The most recent property owners, after hearing of the cave's existence, rediscovered it and donated the site to Concordia University Texas in the 1990s. This donation, with the access afforded to paleontologists, and new scientific methods made the ideas in this recent paper possible.

"As paleontologists, we can only study fossils that are deposited in public collections," Dr. DeSantis said, "and we can only go back to fossil sites and expand excavations when those fossil sites exist and are not destroyed."

https://bit.ly/3u7BGze

Driving behaviors harbor early signals of dementia

Researchers develop highly accurate algorithms for early detection of mild cognitive impairment and dementia using naturalistic driving data

Using naturalistic driving data and machine learning techniques, researchers at Columbia University Mailman School of Public Health and Columbia's Fu Foundation School of Engineering and Applied Science have developed highly accurate algorithms for detecting mild cognitive impairment and dementia in older drivers. Naturalistic driving data refer to data captured through in-vehicle recording devices or other technologies in the real-world setting. These data could be processed to measure driving exposure, space and performance in great detail. The findings are published in the journal *Geriatrics*.

The researchers developed random forests models, a statistical technique widely used in AI for classifying disease status, that performed exceptionally well. "Based on variables derived from the naturalistic driving data and basic demographic characteristics, such as age, sex, race/ethnicity and education level, we could predict mild cognitive impairment and dementia with 88 percent accuracy, "said Sharon Di, associate professor of civil engineering and engineering mechanics at Columbia Engineering and the study's lead author.

The investigators constructed 29 variables using the naturalistic driving data captured by in-vehicle recording devices from 2977 participants of the Longitudinal Research on Aging Drivers (LongROAD) project, a multisite cohort study sponsored by the AAA Foundation for Traffic Safety. At the time of enrollment, the participants were active drivers aged 65-79 years and had no significant cognitive impairment and degenerative medical conditions. Data used in this study spanned the time period from August 2015 through March 2019.

Among the 2977 participants whose cars were instrumented with the in-vehicle recording devices, 33 were newly diagnosed with mild cognitive impairment and 31 with dementia by April 2019. The researchers trained a series of machine learning models for detecting mild cognitive impairment/dementia and found that the model based on driving variables and demographic characteristics was 88 percent accurate, much better than models based on demographic characteristics only (29 percent) and driving variables only (66 percent). Further analysis revealed that age was most predictive of mild cognitive impairment and dementia, followed by the percentage of trips traveled within 15 miles of home, race/ethnicity, minutes per trip chain (i.e., length of trips starting and ending at home), minutes per trip, and number of hard braking events with deceleration rates ≥ 0.35 g.

"Driving is a complex task involving dynamic cognitive processes and requiring essential cognitive functions and perceptual motor skills. Our study indicates that naturalistic driving behaviors can be used as comprehensive and reliable markers for mild cognitive impairment and dementia," said Guohua Li, MD, DrPH, professor of epidemiology and anesthesiology at Columbia Mailman School of Public Health and Vagelos College of Physicians and Surgeons, and senior author. "If validated, the algorithms developed in this study could provide a novel, unobtrusive screening tool for early detection and management of mild cognitive impairment and dementia in older drivers."

Co-authors are Carolyn DiGuiseppi, Colorado School of Public Health; David W. Eby and Lisa Molnar, University of Michigan Transportation Research Institute; Linda Hill, University of California San Diego School of Public Health; Thelma J. Mielenz, Columbia Mailman School of Public Health; David Strogatz, Bassett Research Institute; Howard Andrews, Terry Goldberg, Barbara Lang, and Minjae Kim, Columbia Vagelos College of Physicians and Surgeons.

The study was supported by the AAA Foundation for Traffic Safety.

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New duckbilled dinosaur discovered in Japan

An international team of paleontologists has identified a new genus and species of hadrosaur or duck-billed dinosaur, Yamatosaurus izanagii, on one of Japan's southern islands.

The fossilized discovery yields new information about hadrosaur migration, suggesting that the herbivors migrated from Asia to North America instead of vice versa. The discovery also illustrates an evolutionary step as the giant creatures evolved from walking upright to walking on all fours. Most of all, the discovery provides new information and asks new questions about dinosaurs in Japan.

The research, "A New Basal Hadrosaurid (Dinosauria: Ornithischia) From the latest Cretaceous Kita-ama Formation in Japan implies the origin of Hadrosaurids," was recently published in *Scientific Reports*.

Authors include Yoshitsugu Kobayashi of Hokkaido University Museum, Ryuji Takasaki of Okayama University of Science, Katsuhiro Kubota of Museum of Nature and Human Activities, Hyogo and Anthony R. Fiorillo of Southern Methodist University.

***Artist's illustration of Yamatosaurus izanagii (center) represents its ancestry to more advanced hadrosaurs (in the background).* Credit: Masato Hattori.**

Hadrosaurs, known for their broad, flattened snouts, are the most commonly found of all dinosaurs. The plant-eating dinosaurs lived in the Late Cretaceous period more than 65 million years ago and their fossilized remains have been found in North America, Europe, Africa and Asia.

Uniquely adapted to chewing, hadrosaurs had hundreds of closely spaced teeth in their cheeks. As their teeth wore down and fell out, new teeth in the dental battery, or rows of teeth below existing teeth, grew in as replacements. Hadrosaurs' efficient ability to chew vegetation is among the factors that led to its diversity, abundance and widespread population, researchers say.

The Yamatosaurus' dental structure distinguishes it from known hadrosaurs, says Fiorillo, senior fellow at SMU's Institute for the Study of Earth and Man. Unlike other hadrosaurs, he explains, the new hadrosaur has just one functional tooth in several battery positions and no branched ridges on the chewing surfaces, suggesting that it evolved to devour different types of vegetation than other hadrosaurs.

Yamatosaurus also is distinguished by the development of its shoulder and forelimbs, an evolutionary step in hadrosaurid's gait change from a bipedal to a quadrupedal dinosaur, he says.

"In the far north, where much of our work occurs, hadrosaurs are known as the caribou of the Cretaceous," says Fiorillo. They most likely used the Bering Land Bridge to cross from Asia to present-day Alaska and then spread across North America as far east as Appalachia, he says. When hadrosaurs roamed Japan, the island country was attached to the eastern coast of Asia. Tectonic activity separated the islands from the mainland about 15 million years ago, long after dinosaurs became extinct.

The partial specimen of the Yamatosaurus was discovered in 2004 by an amateur fossil hunter in an approximately 71- to 72-million-year-old layer of sediment in a cement quarry on Japan's Awaji Island. The preserved lower jaw, teeth, neck vertebrae, shoulder bone and tail vertebra were found by Mr. Shingo Kishimoto and given to Japan's Museum of Nature and Human Activities in the Hyogo Prefecture, where they were stored until studied by the team.

"Japan is mostly covered with vegetation with few outcrops for fossil-hunting," says Yoshitsugu Kobayashi, professor at Hokkaido University Museum. "The help of amateur fossil-hunters has been

very important."

Kobayashi has worked with SMU paleontologist Tony Fiorillo since 1999 when he studied under Fiorillo as a Ph.D. student. They have collaborated to study hadrosaurs and other dinosaurs in Alaska, Mongolia and Japan. Together they created their latest discovery's name. Yamato is the ancient name for Japan and Izanagi is a god from Japanese mythology who created the Japanese islands, beginning with Awaji Island, where Yamatosaurus was found.

Yamatosaurus is the second new species of hadrosaurid that Kobayashi and Fiorillo have identified in Japan. In 2019 they reported the discovery of the largest dinosaur skeleton found in Japan, another hadrosaurid, Kamuysaurus, discovered on the northern Japanese island of Hokkaido.

"These are the first dinosaurs discovered in Japan from the late Cretaceous period," Kobayashi says. "Until now, we had no idea what dinosaurs lived in Japan at the end of the dinosaur age," he says. "The discovery of these Japanese dinosaurs will help us to fill a piece of our bigger vision of how dinosaurs migrated between these two continents," Kobayashi says.

More information: *Yoshitsugu Kobayashi et al. A New Basal Hadrosaurid (Dinosauria: Ornithischia) From the Latest Cretaceous Kita-ama Formation in Japan: the Rise of Hadrosaurs, Scientific Reports (2021).* *DOI: 10.21203/rs.3.rs-225217/v1*

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Using nanobodies to block a tick-borne bacterial infection

In cells and mice, tiny molecules stop bacteria from hijacking cells

Emily Caldwell

Columbus, Ohio - Tiny molecules called nanobodies, which can be designed to mimic antibody structures and functions, may be the key to blocking a tick-borne bacterial infection that remains out of reach of almost all antibiotics, new research suggests.

The infection is called human monocytic ehrlichiosis, and is one of the most prevalent and potentially life-threatening tick-borne diseases in the United States. The disease initially causes flu-like symptoms common to many illnesses, and in rare cases can be fatal if left untreated.

Most antibiotics can't build up in high enough concentrations to kill the infection-causing bacteria, Ehrlichia chaffeensis, because the microbes live in and multiply inside human immune cells. Commonly known bacterial pathogens like Streptococcus and E. coli do their infectious damage outside of hosts' cells.

Ohio State University researchers created nanobodies intended to target a protein that makes E. chaffeensis bacteria particularly infectious. A series of experiments in cell cultures and mice showed that one specific nanobody they created in the lab could inhibit infection by blocking three ways the protein enables the bacteria to hijack immune cells.

"If multiple mechanisms are blocked, that's better than just stopping one function, and it gives us more confidence that these nanobodies will really work," said study lead author Yasuko Rikihisa, professor of veterinary biosciences at Ohio State.

The study provided support for the feasibility of nanobody-based ehrlichiosis treatment, but much more research is needed before a treatment would be available for humans. There is a certain urgency to coming up with an alternative to the antibiotic doxycycline, the only treatment available. The broad-spectrum antibiotic is unsafe for pregnant women and children, and it can cause severe side effects. "With only a single antibiotic available as a treatment for this infection, if antibiotic resistance were to develop in these bacteria, there is no treatment left. It's very scary," Rikihisa said.

The research is published this week in *Proceedings of the National Academy of Sciences*.

The bacteria that cause ehrlichiosis are part of a family called

obligatory intracellular bacteria. E. chaffeensis not only requires internal access to a cell to live, but also blocks host cells' ability to program their own death with a function called apoptosis - which would kill the bacteria.

"Infected cells normally would commit suicide by apoptosis to kill the bacteria inside. But these bacteria block apoptosis and keep the cell alive so they can multiply hundreds of times very rapidly and then kill the host cell," Rikihisa said.

A longtime specialist in the Rickettsiales family of bacteria to which E. chaffeensis belongs, Rikihisa developed the precise culture conditions that enabled growing these bacteria in the lab in the 1980s, which led to her dozens of discoveries explaining how they work. Among those findings was identification of proteins that help E. chaffeensis block immune cells' programmed cell death.

The researchers synthesized one of those proteins, called Etf-1, to make a vaccine-style agent that they used to immunize a llama with the help of Jeffrey Lakritz, professor of veterinary preventive medicine at Ohio State. Camels, llamas and alpacas are known to produce single-chain antibodies that include a large antigen binding site on the tip.

The team snipped apart segments of that binding site to create a library of nanobodies with potential to function as antibodies that recognize and attach to the Etf-1 protein and stop E. chaffeensis infection. "They function similarly to our own antibodies, but they're tiny, tiny nano-antibodies," Rikihisa said. "Because they are small, they get into nooks and crannies and recognize antigens much more effectively.

"Big antibodies cannot fit inside a cell. And we don't need to rely on nanobodies to block extracellular bacteria because they are outside and accessible to ordinary antibodies binding to them."

After screening the candidates for their effectiveness, the researchers landed on a single nanobody that attached to Etf-1 in cell cultures and inhibited three of its functions. By making the nanobodies in the fluid inside E. coli cells, Rikihisa said her lab could produce them at an industrial scale if needed - packing millions of them into a small drop.

She collaborated with co-author Dehua Pei, professor of chemistry and biochemistry at Ohio State, to combine the tiny molecules with a cell-penetrating peptide that enabled the nanobodies to be safely delivered to mouse cells.

Mice with compromised immune systems were inoculated with a highly virulent strain of E. chaffeensis and given intracellular nanobody treatments one and two days after infection. Compared to mice that received control treatments, mice that received the most effective nanobody showed significantly lower levels of bacteria two weeks after infection.

With this study providing the proof of principle that nanobodies can inhibit E. chaffeensis infection by targeting a single protein, Rikihisa said there are multiple additional targets that could provide even more protection with nanobodies delivered alone or in combination. She also said the concept is broadly applicable to other intracellular diseases. "Cancers and neurodegenerative diseases work in our cells, so if we want to block an abnormal process or abnormal molecule, this approach may work," she said.

This study was supported by the National Institutes of Health.

Additional co-authors, all from Ohio State, include Wenqing Zhang, Mingqun Lin, Qi Yan, Khemraj Budachetri, Libo Hou, Ashweta Sahni, Hongyan Liu and Nien-Ching Han.

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Espresso, latte or decaf? Genetic code drives your desire for coffee

Whether you hanker for a hard hit of caffeine or favour the frothiness of a milky cappuccino, your regular coffee order could be telling you more about your cardio health than you think.

In a world first study of 390,435 people, University of South

Australia researchers found causal genetic evidence that cardio health - as reflected in blood pressure and heart rate - influences coffee consumption.

Conducted in partnership with the SAHMRI, the team found that people with high blood pressure, angina, and arrythmia were more likely to drink less coffee, decaffeinated coffee or avoid coffee altogether compared to those without such symptoms, and that this was based on genetics.

Lead researcher and Director of UniSA's Australian Centre for Precision Health, Professor Elina Hyppönen says it's a positive finding that shows our genetics actively regulate the amount of coffee we drink and protect us from consuming too much.

"People drink coffee for all sorts of reasons - as a pick me up when they're feeling tired, because it tastes good, or simply because it's part of their daily routine," Prof Hyppönen says.

"But what we don't recognise is that people subconsciously self-regulate safe levels of caffeine based on how high their blood pressure is, and this is likely a result of a protective genetic a mechanism. "What this means is that someone who drinks a lot of coffee is likely more genetically tolerant of caffeine, as compared to someone who drinks very little.

"Conversely, a non-coffee drinker, or someone who drinks decaffeinated coffee, is more likely prone to the adverse effects of caffeine, and more susceptible to high blood pressure."

In Australia, one in four men, and one in five women suffer from high blood pressure, with the condition being a risk factor for many chronic health conditions including stroke, heart failure and chronic kidney disease.

Using data from the UK Biobank, researchers examined the habitual coffee consumption of 390,435 people, comparing this with baseline levels of systolic and diastolic blood pressure, and baseline heart rate. Causal relationships were determined via Mendelian randomization.

Prof Hyppönen says how much coffee we drink is likely to be an indicator of our cardio health.

"Whether we drink a lot of coffee, a little, or avoid caffeine altogether, this study shows that genetics are guiding our decisions to protect our cardio health," Prof Hyppönen says.

"If your body is telling you not to drink that extra cup of coffee, there's likely a reason why. Listen to your body, it's more in tune with what your health than you may think."

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Avocado discovery may point to leukemia treatment

A compound in avocados may ultimately offer a route to better leukemia treatment, says a new University of Guelph study.

The compound targets an enzyme that scientists have identified for the first time as being critical to cancer cell growth, said Dr. Paul Spagnuolo, Department of Food Science.

Published recently in the journal *Blood*, the study focused on acute myeloid leukemia (AML), which is the most devastating form of leukemia. Most cases occur in people over age 65, and fewer than 10 per cent of patients survive five years after diagnosis.

Leukemia cells have higher amounts of an enzyme called VLCAD involved in their metabolism, said Spagnuolo.

"The cell relies on that pathway to survive," he said, explaining that the compound is a likely candidate for drug therapy. "This is the first time VLCAD has been identified as a target in any cancer."

His team screened nutraceutical compounds among numerous compounds, looking for any substance that might inhibit the enzyme. "Lo and behold, the best one was derived from avocado," said Spagnuolo.

Earlier, his lab looked at avocatin B, a fat molecule found only in avocados, for potential use in preventing diabetes and managing obesity. Now he's eager to see it used in leukemia patients.

"VLCAD can be a good marker to identify patients suitable for this type of therapy. It can also be a marker to measure the activity of the drug," said Spagnuolo. "That sets the stage for eventual use of this molecule in human clinical trials."

Currently, about half of patients over 65 diagnosed with AML enter palliative care. Others undergo chemotherapy, but drug treatments are toxic and can end up killing patients.

"There's been a drive to find less toxic drugs that can be used."

Referring to earlier work using avocatin B for diabetes, Spagnuolo said, "We completed a human study with this as an oral supplement and have been able to show that appreciable amounts are fairly well tolerated."

This study was funded partly by the Leukemia Research Foundation, the Cancer Research Society and the Ontario Institute for Cancer Research.

Spagnuolo co-authored the study with U of G PhD students Matthew Tcheng and Alessia Roma, former PhD student Nawaz Ahmed and technician Preethi Jayanth. Other co-authors are researchers at the University of Waterloo, Western University, McMaster University, the University of Colorado and the University of Pittsburgh.

The U of G team also worked with clinicians at Princess Margaret Hospital in Toronto.

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Alzheimer's disease is composed of four distinct subtypes

How tau spreads according to four distinct patterns that lead to different symptoms with different prognoses

Alzheimer's disease is characterized by the abnormal accumulation and spread of the tau protein in the brain. An international study can now show how tau spreads according to four distinct patterns that lead to different symptoms with different prognoses of the affected individuals. The study was published in *Nature Medicine*.

"In contrast to how we have so far interpreted the spread of tau in the brain, these findings indicate that tau pathology in the brain varies according to at least four distinct patterns. This would suggest that Alzheimer's is an even more heterogeneous disease than previously thought. We now have reason to reevaluate the concept of typical Alzheimer's, and in the long run also the methods we use to assess the progression of the disease", says Jacob Vogel from McGill University, and the lead author of the study.

The spread of tau in the cerebral cortex is a key marker for Alzheimer's. In recent years, it has become possible to monitor the accumulation of the toxic protein in the brain of Alzheimer's patients with the help of PET technology, an advanced medical imaging technique.

For the past thirty years, many researchers have described the development of tau pathology in Alzheimer's using a single model, despite recurring cases that do not fit that model. However, the current findings explain why different patients may develop different symptoms.

"Because different regions of the brain are affected differently in the four subtypes of Alzheimer's, patients develop different symptoms and also prognoses. This knowledge is important for doctors who assess patients with Alzheimer's, and it also makes us wonder whether the four subtypes might respond differently to different treatments. Right now, research on various drugs that reduce the amount of tau in the brain is very active, and it will be exciting to see if they vary in efficacy depending on the subtype of Alzheimer", says Oskar Hansson, professor of neurology at Lund University, who supervised the study.

The current study is a collaboration between sites in Sweden, Canada, USA and Korea. Together, the researchers have examined the largest and most diverse population in the world to date with tau-PET, which spans the entire clinical picture of Alzheimer's disease. The study included participants who had not yet developed any symptoms, so-called pre-symptomatic Alzheimer's, participants with mild memory difficulties and those with fully developed Alzheimer's dementia.

In a first sample, long-term data was compiled from 1,612 individuals within five independent multicenter studies. Among these, the researchers identified a total of 1,143 individuals who were either cognitively normal or individuals who had developed Alzheimer's in various stages.

An algorithm was applied to the data from the tau PET images from the 1,143 individuals, the so-called SuStaIn (Subtype and Staging Inference) algorithm. The material was processed with machine learning in an automated process, in order to be able to distinguish subtypes and patterns as impartially as possible.

As expected, many individuals did not show any abnormal tau PET signal, and these were therefore automatically assigned to a tau-negative group. By then cross-validating the tau PET images with a sixth independent cohort, and following up the individuals for about two years, the researchers were able to develop four patterns that best represented the data from the remaining individuals. Although the number of subgroups varied in relation to the individuals, all were represented in all cohorts.

"We identified four clear patterns of tau pathology that became distinct over time. The prevalence of the subgroups varied between 18 and 30 percent, which means that all these variants of Alzheimer's are actually quite common and no single one dominates as we previously thought", says Oskar Hansson.

*** Variant one:** tau spreads mainly within the temporal lobe and primarily affects memory. Variant one occurred in 33 percent of all cases.

*** Variant two:** In contrast to variant one, this variant spreads in the rest of the cerebral cortex. The individual has less memory problems than in the first variant, but on the other hand has greater difficulties with executive functions, that is, the ability to plan and perform an action. Variant two occurred in 18 percent of all cases.

*** Variant three:** The accumulation of tau takes place in the visual cortex, i.e. in the part of the cerebrum where information from the optic nerve is processed and classified. The visuospatial processing of sensory impressions in the brain is affected in individuals with this pattern. They have difficulty orienting themselves, distinguishing shapes and contours, distance, movement and the location of objects in relation to other objects. Variant three occurred in 30 percent of all cases.

*** Variant four:** Tau spreads asymmetrically in the left hemisphere and primarily affects the individual's language ability. Variant four occurred in 19 percent of all cases.

"The varied and large databases of tau-PET that exist today, along with newly developed methods for machine learning that can be applied to large amounts of data made it possible for us to discover and characterize these four subtypes of Alzheimer's. However, we need a longer follow-up study over five to ten years to be able to confirm the four patterns with even greater accuracy", says Oskar Hansson. The researchers believe that this new knowledge can give patients more individualized treatment methods in the future.

https://bbc.in/3xFL13e

Billion-year-old fossil found preserved in Torridon rocks

A billion-year-old fossil found in the Highlands could be the earliest multicellular animal recorded by science so far.

The microscopic fossil was discovered at Loch Torridon in Wester Ross by researchers led by the University of Sheffield and the US's Boston College.

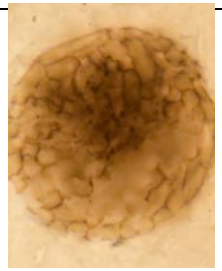
Scientists said it could prove a new link in the evolution of animals.

Researchers could identify it contained two distinct cell types thanks to the fossil's "exceptional preservation".

The fossil gives a new insight into the transition of single-celled organisms to complex multicellular animals.

It has been named Bicellum Brasieri and is described in a new

research paper published in Current Biology.



Prof Charles Wellman, of the University of Sheffield, said: "The origins of complex multicellularity and the origin of animals are considered two of the most important events in the history of life on Earth, our discovery sheds new light on both of these.

The microfossil has two distinct cell types **Paul Strother/The University of Sheffield**

"We have found a primitive spherical organism made up of an arrangement of two distinct cell types, the first step towards a complex multicellular structure, something which has never been described before in the fossil record.

"The discovery suggests that the evolution of multicellular animals occurred at least one billion years ago and that early events prior to the evolution of animals may have occurred in freshwater like lakes, rather than the ocean."

The research team now hopes to examine other samples taken from the Torridon area's ancient rocks and find more fossils that could provide further insights into the evolution of multicellular organisms.

https://bit.ly/33aNyVi

How long is a day on Venus? Scientists crack mysteries of our closest neighbor

New observations from the safety of Earth are lifting the veil on some of Venus' most basic properties

by Christopher Crockett, University of California, Los Angeles

Venus is an enigma. It's the planet next door and yet reveals little about itself. An opaque blanket of clouds smothers a harsh landscape pelted by acid rain and baked at temperatures that can liquify lead.

Now, new observations from the safety of Earth are lifting the veil on some of Venus' most basic properties. By repeatedly bouncing radar off the planet's surface over the last 15 years, a UCLA-led team has pinned down the precise length of a day on Venus, the tilt of its axis and the size of its core. The findings are published today in the journal *Nature Astronomy*. "Venus is our sister planet, and yet these fundamental properties have remained unknown," said Jean-Luc Margot, a UCLA professor of Earth, planetary and space sciences who led the research.

Earth and Venus have a lot in common: Both rocky planets have nearly the same size, mass and density. And yet they evolved along wildly different paths. Fundamentals such as how many hours are in a Venusian day provide critical data for understanding the divergent histories of these neighboring worlds.

Changes in Venus' spin and orientation reveal how mass is spread out within. Knowledge of its internal structure, in turn, fuels insight into the planet's formation, its volcanic history and how time has altered the surface. Plus, without precise data on how the planet moves, any future landing attempts could be off by as much as 30 kilometers. "Without these measurements," said Margot, "we're essentially flying blind."

The new radar measurements show that an average day on Venus lasts 243.0226 Earth days—roughly two-thirds of an Earth year. What's more, the rotation rate of Venus is always changing: A value measured at one time will be a bit larger or smaller than a previous value. The team estimated the length of a day from each of the individual measurements, and they observed differences of at least 20 minutes. "That probably explains why previous estimates didn't agree with one another," Margot said.

Venus' heavy atmosphere is likely to blame for the variation. As it sloshes around the planet, it exchanges a lot of momentum with the solid ground, speeding up and slowing down its rotation. This happens on Earth too, but the exchange adds or subtracts just one millisecond from each day. The effect is much more dramatic on

Venus because the atmosphere is roughly 93 times as massive as Earth's, and so it has a lot more momentum to trade.

The UCLA-led team also reports that Venus tips to one side by precisely 2.6392 degrees (Earth is tilted by about 23 degrees), an improvement on the precision of previous estimates by a factor of 10. The repeated radar measurements further revealed the glacial rate at which the orientation of Venus' spin axis changes, much like a spinning child's top. On Earth, this "precession" takes about 26,000 years to cycle around once. Venus needs a little longer: about 29,000 years.

With these exacting measurements of how Venus spins, the team calculated that the planet's core is about 3,500 kilometers across—quite similar to Earth—though they cannot yet deduce whether it's liquid or solid.

Venus as a giant disco ball

On 21 separate occasions from 2006 to 2020, Margot and his colleagues aimed radio waves at Venus from the 70-meter-wide Goldstone antenna in California's Mojave Desert. Several minutes later, those radio waves bounced off Venus and came back to Earth. The radio echo was picked up at Goldstone and at the Green Bank Observatory in West Virginia.

"We use Venus as a giant disco ball," said Margot, with the radio dish acting like a flashlight and the planet's landscape like millions of tiny reflectors. "We illuminate it with an extremely powerful flashlight—about 100,000 times brighter than your typical flashlight. And if we track the reflections from the disco ball, we can infer properties about the spin [state]."

The complex reflections erratically brighten and dim the return signal, which sweeps across Earth. The Goldstone antenna sees the echo first, then Green Bank sees it roughly 20 seconds later. The exact delay between receipt at the two facilities provides a snapshot of how quickly Venus is spinning, while the particular window of time in which the echoes are most similar reveals the planet's tilt.

The observations required exquisite timing to ensure that Venus and Earth were properly positioned. And both observatories had to be working perfectly—which wasn't always the case. "We found that it's actually challenging to get everything to work just right in a 30-second period," Margot said. "Most of the time, we get some data. But it's unusual that we get all the data that we're hoping to get."

Despite the challenges, the team is forging ahead and has turned its sights on Jupiter's moons Europa and Ganymede. Many researchers strongly suspect that Europa, in particular, hides a liquid water ocean beneath a thick shell of ice. Ground-based radar measurements could fortify the case for an ocean and reveal the thickness of the ice shell.

And the team will continue bouncing radar off of Venus. With each radio echo, the veil over Venus lifts a little bit more, bringing our sister planet into ever sharper view.

More information: *Jean-Luc Margot et al. Spin state and moment of inertia of Venus, Nature Astronomy (2021).* *DOI: 10.1038/s41550-021-01339-7*

https://bit.ly/3nEC3yM

Three new studies suggest Z-genome is much more widespread in bacteria-invading viruses than thought

Three teams working independently have found evidence that suggests the Z-genome in bacteria-invading viruses is much more widespread than thought.

by Bob Yirka , Phys.org

All three of the groups have used a variety of genomic techniques to identify parts of the pathways that lead development of the Z-genome in bacteria-invading viruses known as bacteriophages. The first team was made up of researchers from several institutions in China and one in Singapore, the second with members from several institutions in France; the third was an international effort. All three

teams have published their results in the journal *Science*. Michael Grome and Farren Isaacs with Yale University have also published a Perspectives piece in the same journal issue outlining the work of all three teams.

The genomic DNA of most living things has four distinct nucleotides: adenine, thymine, cytosine and guanine, respectively labeled ATCG. But back in 1977, scientists learned that most bacteriophages have a slightly different alphabet, one that typically omits adenine and adds diaminopurine, which has subsequently been labeled Z. After this discovery, it was thought that the alphabet was so rare little work was done to learn more about it; thus, little is known about how bacteriophages function without adenine in their genome. In this new effort, all three teams sought to learn more about the Z nucleotide and how it works in bacteriophages.

In the first, effort, the researchers studied the composition of a phage called Vibrio and discovered that it had the Z nucleotide rather than A. They also described the structure of an enzyme that is encoded by a gene similar to one known as PurA, which they called PurZ. They then showed that it functioned in ways much like the Z pathway in PurA. The second team found phage genes that encode DNA polymerases that select for diaminopurine rather than adenine. And the third team found an enzyme that plays a main role in putting together DNA molecules from parent molecules. They also discovered that it worked as a gate, excluding A nucleotides and instead adding Zs.

The work by the three teams suggests that the Z nucleotide is much more prevalent in bacteriophages than thought—further study could lead to new and improved ways to combat bacterial infections.

More information: *Yan Zhou et al. A widespread pathway for substitution of adenine by diaminopurine in phage genomes, Science (2021). DOI: 10.1126/science.abe4882*

Dona Sleiman et al. A third purine biosynthetic pathway encoded by aminoadenine-based viral DNA genomes, Science (2021). DOI: 10.1126/science.abe6494

Valerie Pezo et al. Noncanonical DNA polymerization by aminoadenine-based siphoviruses, Science (2021). DOI: 10.1126/science.abe6542

https://wb.md/3vDwjIa

Swollen Lymph Nodes After COVID Vaccine May Mean Previous Infection

People with side effects after receiving COVID-19 vaccine, such as swollen lymph nodes, may have had coronavirus

Carolyn Crist

People who experience particular side effects after receiving a COVID-19 vaccine, such as swollen lymph nodes, may have previously been infected with the coronavirus, according to a new study published on the medRxiv preprint server. The study hasn't yet been peer-reviewed.

Common side effects such as fever, fatigue, muscle pain and joint pain were also more common among those who had previous infections.

An earlier COVID-19 infection, but not what's known as "long-haul COVID-19"' was associated with increased risk of swollen lymph nodes after receiving the vaccination, the study authors wrote.

Researchers at three hospitals in the U.K. surveyed health care workers after the first dose of the Pfizer vaccine. Among 974 health care workers surveyed, 265 reported a positive COVID-19 test or antibodies before being vaccinated.

Women and younger people were more likely to report more side effects, higher severity and a longer duration of symptoms, the authors wrote.

About 4% of those who had already recovered from COVID-19 experienced swollen lymph nodes after vaccination, as compared with less than 1% of those who didn't have a previous infection. In addition, 8% of those who had contracted COVID-19 reported fever as a side effect, as compared with 2% of those who had never been infected.

Muscle pain and fatigue were also reported more frequently. About 30% of those who had already been infected reported muscle pain, as compared with 15% who didn't have a previous infection. About 29% who contracted COVID-19 reported fatigue, as compared with 20% who didn't contract the virus.

Injection site pain and gastrointestinal symptoms were about the same in both groups.

Among the 265 health care workers who had previous COVID-19 infections, 30 people reported long-haul COVID-19 symptoms that were ongoing months after being sick. Long-haul COVID-19 wasn't associated with more severe side effects from the vaccine.

In addition, the research team didn't find a significant difference in the number or severity of side effects based on the timeline of when people were infected and when they received the vaccine.

"There are public health implications with regards to vaccine hesitancy, which is somewhat driven by fear of [adverse effects]," the study authors wrote.

"This data can support education around vaccine-associated [adverse effects] and, through improved understanding, help to combat vaccine hesitancy," they added.

Source *medRxiv: "Previous COVID-19 infection but not Long-COVID is associated with increased adverse events following BNT162b2/Pfizer vaccination."*

https://bit.ly/2QOHcIw

One incredible ocean crossing may have made human evolution possible

Primates appear to have evolved in Asia before colonizing Africa. Around 50 million years ago, Africa was isolated from the rest of the world by ocean—so how did primates get there?

by Nicholas R. Longrich, The Conversation

Humans evolved in Africa, along with chimpanzees, gorillas and monkeys. But primates themselves appear to have evolved elsewhere—likely in Asia—before colonizing Africa. At the time, around 50 million years ago, Africa was an island isolated from the rest of the world by ocean—so how did primates get there?

A land bridge is the obvious explanation, but the geological evidence currently argues against it. Instead, we're left with a far more unlikely scenario: early primates may have rafted to Africa, floating hundreds of miles across oceans on vegetation and debris.

Such oceanic dispersal was once seen as far-fetched and wildly speculative by many scientists. Some still support the land bridge theory, either disputing the geological evidence, or arguing that primate ancestors crossed into Africa long before the current fossil record suggests, before the continents broke up.

But there's an emerging consensus that oceanic dispersal is far more common than once supposed. Plants, insects, reptiles, rodents and primates have all been found to colonize island continents in this way—including a remarkable Atlantic crossing that took monkeys from Africa to South America 35 million years ago. These events are incredibly rare but, given huge spans of time, such freak events inevitably influence evolution—including our own origins.

Primate origins

Humans appeared in southern Africa between 200,000-350,000 years ago. We know we come from Africa because our genetic diversity is highest there, and there are lots of fossils of primitive humans there.

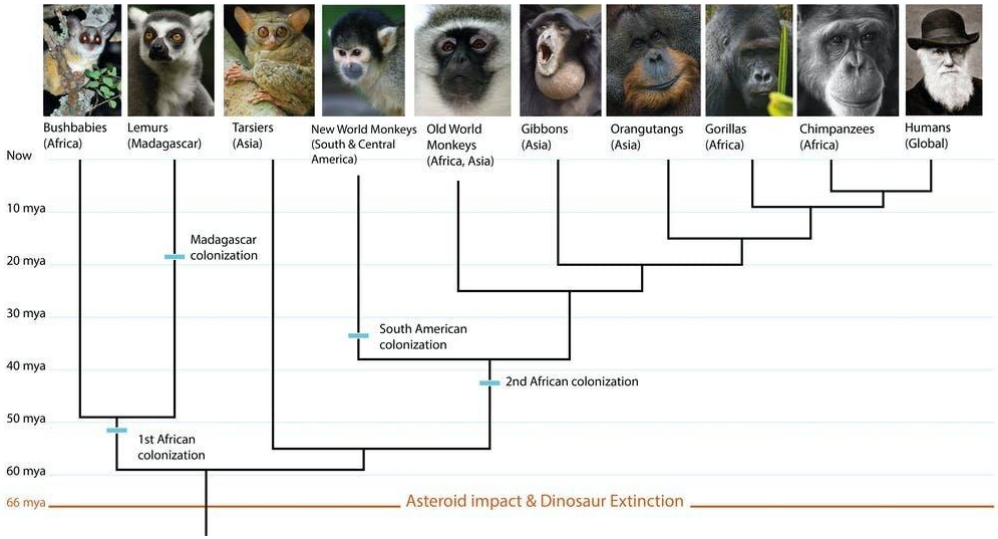
Our closest relatives, chimps and gorillas, are also native to Africa, alongside baboons and monkeys. But primates' closest living relatives—flying lemurs, tree shrews and rodents—all inhabit Asia or, in the case of rodents, evolved there. Fossils provide somewhat conflicting evidence, but they also suggest primates arose outside of Africa.

The oldest primate relative, *Purgatorius*, lived 65 million years ago, just after the dinosaurs disappeared. It's from Montana.

The oldest true primates also occur outside Africa. *Teilhardina*,

related to monkeys and apes, lived 55 million years ago, throughout Asia, North America, and Europe. Primates arrived in Africa later. Lemur-like fossils appear there 50 million years ago, and monkey-like fossils around 40 million years ago.

But Africa split from South America and became an island 100 million years ago, and only connected with Asia 20 million years ago. If primates colonized Africa during the 80 million years the continent spent isolated, then they needed to cross water.



Primates have differentiated over tens of millions of years. **Credit: Nicholas R. Longrich/Wikimedia**

Ocean crossings

The idea of oceanic dispersal is central to the theory of evolution. Studying the Galapagos Islands, Darwin saw only a few tortoises, iguanas, snakes, and one small mammal, the rice rat. Further out to sea, on islands like Tahiti, were only little lizards.

Darwin reasoned that these patterns were hard to explain in terms of Creationism—in which case, similar species should exist everywhere—but they made sense if species crossed water to colonize islands, with fewer species surviving to colonize more distant islands.

He was right. Studies have found tortoises can survive weeks afloat without food or water—they probably bobbed along until hitting the Galapagos. And in 1995, iguanas swept offshore by hurricanes washed up 300km away, very much alive, after riding on debris. Galapagos iguanas likely traveled this way.

The odds are against such crossings. A lucky combination of conditions—a large raft of vegetation, the right currents and winds, a viable population, a well-timed landfall—is needed for successful colonization. Many animals swept offshore simply die of thirst or starvation before hitting islands. Most never make landfall; they disappear at sea, food for sharks. That's why ocean islands, especially distant ones, have few species.

Rafting was once treated as an evolutionary novelty: a curious thing happening in obscure places like the Galapagos, but irrelevant to evolution on continents. But it's since emerged that rafts of vegetation or floating islands—stands of trees swept out to sea—may actually explain many animal distributions across the world.

Rafting

Several primate rafting events are well established. Today, Madagascar has a diverse lemur fauna. Lemurs arrived from Africa around 20 million years ago. Since Madagascar has been an island since the time of the dinosaurs, they apparently rafted the 400 kilometer-wide Mozambique Channel. Remarkably, fossils suggest the strange aye-aye crossed to Madagascar separately from the other lemurs.

Even more extraordinary is the existence of monkeys in South America: howlers, spider monkeys and marmosets. They arrived 35 million years ago, again from Africa. They had to cross the Atlantic—narrower then, but still 1,500 km wide. From South America, monkeys rafted again: to North America, then twice to the Caribbean.

But before any of this could happen, rafting events would first need to bring primates to Africa: one brought the ancestor of lemurs, another carried the ancestor of monkeys, apes, and ourselves. It may seem implausible—and it's still not entirely clear where they came from—but no other scenario fits the evidence.

Rafting explains how rodents colonized Africa, then South America. Rafting likely explains how Afrotheria, the group containing elephants and aardvarks, got to Africa. Marsupials, evolving in North America, probably rafted to South America, then Antarctica, and finally Australia. Other oceanic crossings include mice to Australia, and tenrecs, mongooses and hippos to Madagascar.

Floating 800km from the Seychelles to Africa, this tortoise washed up on shore – covered in barnacles, but alive. **Credit: Catharine Muir**

Oceanic crossings aren't an evolutionary subplot; they're central to the story. They explain the evolution of monkeys, elephants, kangaroos, rodents, lemurs—and us. And they show that evolution isn't always driven by ordinary, everyday processes but also by bizarrely improbable events.

Macroevolution

One of Darwin's great insights was the idea that everyday events—small mutations, predation, competition—could slowly change species, given time. But over millions or billions of years, rare, low-probability, high-impact events—"black swan" events—also happen.

Some are immensely destructive, like asteroid impacts, volcanic eruptions, and ice ages—or viruses jumping hosts. But others are creative, like genome duplications, gene transfer between multicellular species—and rafting.

The role rafting played in our history shows how much evolution comes down to chance. Had anything gone differently—the weather was bad, the seas rough, the raft washed up on a desert island, hungry predators waited on the beach, no males aboard—colonization would have failed. No monkeys, no apes—no humans.

It seems our ancestors beat odds that make Powerball lotteries seem like a safe bet. Had anything had gone differently, the evolution of life might look rather different than it does. At a minimum, we wouldn't be here to wonder about it.

https://wb.md/3xBqweO

Most Patients Labeled Penicillin-Allergic Really Aren't Intolerant

The mislabeling has implications for patient outcomes and efforts to fight antibiotic resistance

Marcia Frellick

Most people whose medical record says they are allergic to penicillin are not actually intolerant, an allergist said Thursday during the first day of sessions for the American College of Physicians (ACP) Internal Medicine Meeting 2021.

The mislabeling has implications for patient outcomes and efforts to fight antibiotic resistance, said Olajumoke Fadugba, MD, program director for the Allergy and Immunology Fellowship at University of Pennsylvania Health System in Philadelphia.

About 10% of the general population reports a history of penicillin allergy (up to 15% of hospitalized patients), but up to 90% of patients with that label are able to tolerate penicillin, Fadugba said. The mislabeling comes either because reactions were improperly characterized early on or people have outgrown the allergy.

"There are data that tell us penicillin IgE-mediated wanes over time and that after 10 years of avoidance of a drug, greater than 80% of patients have a resolution of their penicillin IgE."

Data also show patients outgrow their aminopenicillin reactions

(including those from amoxicillin and Ampicillin) faster than parenteral penicillin reactions, she noted.

Josune Iglesias, MD, assistant professor of internal medicine at Rush University Medical Center in Chicago, Illinois, told *Medscape Medical News* she often sees patients who said their parents told them when they were kids that they were allergic to penicillin and that information just keeps getting entered into their records.

She said physicians are aware the penicillin-allergic label is not always accurate, but there is hesitancy to challenge those labels.

"We are cautious because of the potential side effects and the harm that we could cause if we unlabel the patient," she said. "I think having this information will help us unlabel those patients well so we don't cause harm." Also, the threat to antibiotic resistance is real, she said, when penicillin is eliminated as an option unnecessarily.

When a person is labelled allergic to penicillin, the treatment choices often go to broad-spectrum antibiotics that are more costly, have potentially worse side effects, and may contribute to resistance.

"It's really important, especially with older people, patients sicker with chronic conditions to really make sure we unlabel those patients [who are not truly penicillin-allergic]," Iglesias said.

The label can also cause harm in the hospital setting and worsen outcomes, according to Fadugba.

She notes that the penicillin allergy label has been linked with longer hospital length of stay, higher rate of readmission, acute kidney injury, multidrug-resistant organism such as MRSA, and nosocomial infections including *Clostridioides difficile*.

Getting an effective drug history is an important part of determining who really has a penicillin allergy.

A questionnaire should ask whether the patient was likely to have had an immediate hypersensitivity to penicillin, such as hives or anaphylaxis, which would be more worrisome than a delayed rash.

Knowing the timeframe of the reaction helps determine how likely or unlikely people are to still have the allergy, Fadugba said.

"We also want to ask, have they received a penicillin antibiotic since that initial reaction and have they tolerated it?" she said.

She continued, "If a patient received amoxicillin 2 weeks ago, and they tolerated it, you can essentially remove the allergy label and essentially change that patient's potential hospital course — that immediate course or future outcomes."

After obtaining the history, there are choices to make.

If a patient is not allergic, she said, the next step is removing the label and documenting why so that in the future another clinician doesn't see the deleted label and put it back.

If a person is deemed allergic by history, clinicians should document the nature of the reaction and if the patient needs a beta-lactam during a hospitalization or in clinic, make a decision based on what kind of beta-lactam they need, she said.

"Generally, for a fourth-generation cephalosporin, for a distant history of penicillin allergy, you can probably give the full dose or — if you're conservative — give it cautiously, perhaps 10% initially and then monitor because cross-reactivity is known to be low, about 2%."

If the patient needs a penicillin antibiotic specifically, options are guided by the resources. If a clinician has personnel or an allergy specialist available, skin testing may be an option and "if negative, you can rule out the allergy," Fadugba said.

"If that's not available and the patient really needs a penicillin, you can consider desensitization," she said.

However, she said, "If the patient is very high risk, then you have no choice but to use an alternative, especially if you can't desensitize."

Fadugba is a consultant for the Health Resources & Services Administration. Iglesias has disclosed no relevant financial relationships.

American College of Physicians (ACP) Internal Medicine Meeting 2021: Allergies in Adult Inpatients: Separating Fact From Fiction. Presented April 29, 2021.

https://bit.ly/3vC2hof

Novel coronavirus really is seasonal, study suggests

Warm temperatures and long hours of sunlight may reduce the spread of COVID-19, the study found.

By Rachael Rettner - Senior Writer

Warm temperatures and tropical climates may really help reduce the spread of COVID-9, a new study suggests.

The study found that places with warm temperatures and long hours of sunlight — such as countries close to the equator and those experiencing summer — had a lower rate of COVID-19 cases, compared with countries farther away from the equator and those experiencing colder weather.

The findings held even after the researchers took into account other factors that could affect both the spread of COVID-19 and the number of reported cases, such as a country's level of urbanization and the intensity of COVID-19 testing.

Still, the authors stress that their findings don't mean that summer weather will eliminate COVID-19; but it may give people a leg up against the disease.

"Our results do not imply that the disease will vanish during summer or will not affect countries close to the equator," the authors wrote in their paper, published April 27 in the journal Scientific Reports. "Rather, the higher temperatures and more intense UV [ultraviolet] radiation in summer are likely to support public health measures to contain SARS-CoV-2," the novel coronavirus causing COVID-19.

Shortly after the COVID-19 pandemic began in the winter of 2020, there was speculation that summer temperatures may bring relief from COVID-19. Indeed, many respiratory viruses, including flu viruses, show a seasonal pattern, peaking during the winter and dipping during the summer.

Scientists don't know for sure why these viruses follow a seasonal pattern, but a number of factors are thought to play a role. For example, studies suggest that many respiratory viruses are more stable and linger in the air longer in environments with cold temperatures and low humidity, Live Science previously reported. Human behaviors, such as gathering indoors in wintertime, could also boost transmission.

Studies in lab dishes have also found that high temperature and humidity reduce the survival of SARS-CoV-2, but whether this translates to real-world transmission was unclear.

In the new study, the researchers analyzed information from 117 countries, using data on the spread of COVID-19 from the beginning of the pandemic to Jan. 9, 2021. They used statistical methods to examine the relationship between a country's latitude — which affects the amount of sunlight it receives as well as temperature and humidity — and its level of COVID-19 spread. They also used data from the World Health Organization to control for factors that could affect how hard a country is hit by COVID-19, such as air travel, health care expenditure, the ratio of older adults to younger people and economic development.

They found that every 1 degree increase in a country's latitude from the equator was tied to a 4.3% increase in the number of COVID-19 cases per million people. This means that if one country is 620 miles (1,000 kilometers) closer to the equator compared with another, the country closer to the equator could expect to have 33% fewer COVID-19 cases per million people, with all other factors being equal between the countries.

"Our results are consistent with the hypothesis that heat and sunlight reduce the spread of

SARS-CoV-2 and the prevalence of COVID-19," according to the authors, from the Heidelberg Institute of Global Health in Germany and the Chinese Academy of Medical Sciences in Beijing. The findings also mean that "the threat of epidemic resurgence may

increase during winter," as was seen in many countries in the Northern Hemisphere in December 2020 and January 2021, they said.

The authors note that their study only included data up until Jan. 9, 2021, before a number of COVID-19 variants, including variants that first emerged in South Africa and the U.K., took off around the world, so it's unclear whether these variants will show similar patterns of seasonal infection.

https://bit.ly/3vBnQW3

Medieval Skeletons Might Be Hiding a Cancer Rate Far Higher Than Expected

Cancer isn't just a modern-day affliction. A new archaeological analysis suggests malignant growths in medieval Britain were not as rare as we once thought.

Carly Cassella

Even before widespread smoking, the Industrial Revolution, and the modern surge in life expectancy, it seems cancer was still a leading cause of disease.

Scanning and X-raying 143 medieval skeletons from six cemeteries in and around the city of Cambridge, archaeologists have predicted cancer cases between the 6th and the 16th century were roughly a quarter of what they are today.

That's 10 times higher than previous estimates, which had put cancer rates at less than one percent.

"Until now it was thought that the most significant causes of ill health in medieval people were infectious diseases such as dysentery and bubonic plague, along with malnutrition and injuries due to accidents or warfare," says archaeologist Jenna Dittmar from Cambridge University.

"We now have to add cancer as one of the major classes of disease that afflicted medieval people."

Past analyses of medieval skeletons in Britain have only focused on the exterior of the bone, but Dittmar and her colleagues decided to look for evidence of metastases within the bone, too.

Scanning parts of the skeleton that are more likely to hold cancerous growths, such as the spinal column, the pelvis, and the thigh bone, the team found signs of malignancy in five individuals from medieval times.

Most cases were confined to the pelvis, but there was one middle-aged man that had lesions scattered throughout his skeleton, which is indicative of blood cancer.

"Using CT scans we were able to see cancer lesions hidden inside a bone that looked completely normal on the outside," says Dittmar.

This type of scanning can detect bone metastases in patients about 75 percent of the time, and over a third of people today who die with cancer show evidence of these growths in their bones.

Based on these statistics, the authors think the minimum prevalence of all cancers in medieval Britain would have sat somewhere between 9 and 14 percent.

In the centuries since, that rate has surged. In modern Britain, where people live far longer, breathe more pollutants, and face more viruses, up to 50 percent of people have cancer by the time they die.

Figuring out how much cancer incidence has increased in recent years is important because it allows us to know where our greatest threats are coming from. Currently, it's still not completely clear how much tobacco smoking and pollutants have impacted our rates of disease as a whole because we don't have a baseline to work off.

Historic texts are not particularly trustworthy and are hard to compare to modern data, whereas archaeological remains are much more reliable, especially with the technology we've got today.

The sample size of the current study was obviously small and focused on only one region. It's also tricky business diagnosing cancer so many centuries later.

Yet even with these caveats in mind, the findings suggest we have been missing many cases of medieval cancer by not looking within the bone.

"We need further studies using CT scanning of apparently normal skeletons in different regions and time periods to see how common cancer was in key civilizations of the past," says first author of the new research, archaeologist Piers Mitchell from Cambridge University.

The study was published in *Cancer*. The paper is unavailable as of the time of publishing, but a pre-press proof of the study can be reviewed on Academia.edu.

https://bit.ly/3udWfdn

This lab-grown meat grows on spinach skeletons

For lab-grown meat to replace a fresh steak, it needs to look like one

Kristen Witte

In the last decade, lab-grown meat has emerged a sustainable alternative to traditional livestock methods. Livestock strain Earth's land resources and account for about 14.5 percent of global greenhouse gas emissions. But while scientists can grow thin sheets of cow meat and scrape it together to form a patty, people eat with their eyes as much as their mouths. For lab-grown meat to replace a fresh steak, it needs to look like a steak.

Growing lab-based meat into 3D structures is difficult because it needs constant delivery of oxygen and nutrients. In living organisms, vascular systems fill that need. Researchers at Boston College previously showed that skeletonized spinach leaves, stripped of everything but their veiny, oxygen-dispersing, vascular system, can support patches of heart muscle cells. Now, they show that lab-grown meat can grow on skeletonized spinach, an essential step to growing steak-shaped meat in the lab.

To skeletonize the spinach leaves, the scientists "decellularized" them, stripping away the greenery and leaving behind a translucent ghost of a leaf. Then, the scientists spread cow muscle cells on the ghostly leaves, like butter on fresh bread. After two weeks, the cells not only survived and multiplied, but also organized into long strands of muscle fiber. These long strands are the building blocks of steak — whether from a cow or from a spinach leaf.

Lab-grown meat is a technological solution to the environmental crisis. And while we need new and better technology (think, solar panels and battery storage) to change the course, the technology also needs to maximize environmental sustainability. Using spinach, which is in itself environmentally sustainable, doubles down on the sustainability of lab-grown meat.

https://bit.ly/338w9wa

Same drug can have opposite effects on memory according to sexual differences

Inhibition through a drug of the Tac2 neuronal circuit, involved in the formation of the memory of fear, has opposite effects on the ability to remember aversive events in mice according to sex

A research team from the Institut de Neurociències at the Universitat Autònoma de Barcelona (INc-UAB) has showed that inhibition through a drug of the Tac2 neuronal circuit, involved in the formation of the memory of fear, has opposite effects on the ability to remember aversive events in mice according to sex: it is reduced in male mice and increased in female mice.

Is the first time that a drug has been shown to produce this opposite effect on the memory of male and female mice. The study also evidences that opposing molecular mechanisms and behaviours can occur in memory formation depending on sex. The study has been published in *Nature Communications*.

The research group on Translational mechanisms of the memory of fear led by Raül Andero, professor and researcher at ICREA, has been studying the functioning of fear memory for years to find

treatments for pathologies associated with traumatic experiences, such as post-traumatic stress and phobias.

The research team had identified that the Tac2 circuit, located in the amygdala, could be temporarily blocked by the effect of a drug they are studying. This drug, called Osanetant, was able to reduce the capacity to recall traumatic events in male mice. In the study published now, they discovered that this same drug produces the opposite effect in female mice, increasing their fear memory.

This opposite effect is explained by the fact that, in blocking the Tac2 pathway, the drug interacts with the neuronal receptors of two sex hormones: testosterone in males and estrogen in females. In addition, it has been observed that hormonal fluctuations during the oestrous cycle in female mice, equivalent to the menstrual cycle in women, vary the effects of the drug on the ability to remember aversive events.

"These results demonstrate the ability that hormones have to modulate the formation of fear memories, and show the need to consider sex differences and hormonal cycles in the design of pharmacological treatments for psychiatric disorders", says Antonio Florido, INc-UAB predoctoral researcher and first author of the article.

In the field of neurosciences, only one study in females is published for every 5.5 done in males. And research on Tac2 pathway has also been done mostly in males so far.

"Understanding how and why memory processes differ between sexes is key to designing treatments for fear disorders, especially considering that women are the ones who most often present these types of disorders. Some drugs that are already used may not have the expected effects on them", says Raül Andero, the study coordinator. "Our findings may help raise awareness of the need to do research differentiating by sex and promote basic and clinical studies that include the female sex", he adds.

The drug studied is not new, but it is safe for use in humans. However, at the moment it is not being used to treat any disease. Dr. Andero's group is now investigating its potential use in treating fear disorders differently by sex.

In this research, which has been carried out in collaboration with other INc-UAB research groups and the Hospital del Mar Medical Research Institute (IMIM), scientists show the importance of personalized medicine. "Mental health drugs that we have today, not only for memory-related disorders, are not specific enough and may be causing contrary effects to those desired", they conclude.