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Humans coexisted with three-tonne marsupials and lizards as long as cars in ancient Australia

When people first arrived in what is now Queensland, they would have found the land inhabited by massive animals including goannas six metres long and kangaroos twice as tall as a human.

Scott Hocknull [*] Anthony Dosseto [**] Gilbert Price [***] Lee Arnold [****] Patrick Moss [*****] Renaud Joannes-Boyau [******]

We have studied fossil bones of these animals for the past decade. Our findings, published today in Nature Communications, shed new light on the mystery of what drove these ancient megafauna to extinction.

The first bones were found by the Barada Barna people during cultural heritage surveys on their traditional lands about 100 kilometres west of Mackay, at South Walker Creek Mine. Our study shares the first reliable glimpse of the giants that roamed the Australian tropics between 40,000 and 60,000 years ago.

These megafauna were the largest land animals to live in Australia since the time of the dinosaurs. Understanding the ecological role they played and the environmental impact of their loss remains their most valuable untold story.

Fossils are found eroding out of the ancient flood plains of South Walker Creek. Rochelle Lawrence, Queensland Museum.

While megafauna lived at South Walker Creek, people had arrived on the continent and were spreading across it. Our study adds new evidence to the ongoing megafauna extinction debate, but importantly underscores how much is left to learn from the fossil record.

The megafauna welcoming party

We excavated fossils from four sites and made detailed studies of the sites themselves to find the age of the fossils and understand what the environment was like in the past.

Our findings give us an idea of what megafaunal life was like in the tropical Australian savanna over a period of about 20,000 years, from around 60,000 to 40,000 years ago. During this time, the northern megafauna were different to those from the south.

Mega-reptiles of Pleistocene tropical Australia. **V. Konstantinov, A. Atuchin, R. Allen, S. Hocknull. Queensland Museum.**

We have found at least 13 extinct species so far at South Walker Creek, with mega-reptiles as apex predators, and mega-mammals their prey. Many of the species discovered are likely new species or northern variations of their southern counterparts.

Mega-mammals from Pleistocene tropical Australia. **V. Konstantinov, A. Atuchin, S. Hocknull. Queensland Museum.**

Some, like the extinct crocodiles, were thought to have gone extinct long before people were on the scene. However, we now know they survived in at least one place 60,000-40,000 years ago.

Imagine first sighting a six-metre goanna and its Komodo Dragon-sized relative, or bumping into a land-dwelling crocodile and its plate-mail armoured aquatic cousin. The mammals were equally bizarre, including a giant bucktoothed wombat, a strange “bear-sloth” marsupial, and enormous kangaroos and wallabies.

A yet-to-be named giant kangaroo is the largest ever found. With an estimated mass of 274 kg, it beats the previous contender, the goliath short-faced kangaroo, *Procoptodon goliah*.

The biggest of all the mammals was the three-tonne marsupial *Diprotodon*, and the deadliest was the pouched predator *Thylacoleo*. Living alongside these giants were other megafauna species that still survive today: the emu, the red kangaroo and the saltwater crocodile.

***The giant kangaroo of South Walker Creek may be the largest kangaroo ever found. Pictured here next to the previous titleholder, Procoptodon goliah. Scale bar equals 1 m. V.* Konstantinov, A. Atuchin, R. Allen, S. Hocknull. Queensland Museum.**

Whodunnit? The evidence points to environmental change

Why did these megafauna become extinct? It has been argued that the extinctions were due to over-hunting by humans, and occurred shortly after people arrived in Australia.

However, this theory is not supported by our finding that a diverse collection of these ancient giants still survived 40,000 years ago, after humans had spread around the continent.

The extinctions of these tropical megafauna occurred sometime after our youngest fossil site formed, around 40,000 years ago. The timeframe of their disappearance coincided with sustained regional changes in available water and vegetation, as well as increased fire frequency. This combination of factors may have proven fatal to the giant land and aquatic species.

The megafauna extinction debate will no doubt continue for years to come. New discoveries will plug up the key gaps in the record. With the gaps in the north of the continent the greatest yet to fill.

With an overlap between people and megafauna of some 15,000–20,000 years, new questions arise about co-habitation. How did people live with these giants during a period of such drastic environmental change?

How much more change can Australia bear?

Major environmental change and extinctions are not an unusual part of our geological past, but this time it's personal; it involves us. Throughout the Pleistocene (the time that ended with the most recent ice age), Australia has undergone major climatic and environmental change.

Within the same catchment of these new megafauna sites, one study shows how major climatic upheaval beginning around 280,000 years ago caused the disappearance of a diverse rainforest fauna. This set in motion a sequence of changes to the ecosystem that culminated in the loss of the megafauna at South Walker Creek around 40,000 years ago.

It's still unclear what impact these long-term environmental changes and the loss of the megafauna had on the species that survived.

This long-term trend of extinctions has now been given a kick along by the major changes to the environment created by humans which continue today. In the early 21st century in Australia we have seen increases in floods, droughts and bushfires, and we expect these increases to continue.

The fossil record provides us with a window into our past that can help us understand our present. As our study shows, dramatic environmental change takes a heavy toll on species survival especially for those at the top of the food chain. Will we heed the warnings from the past or suffer the consequences?

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Why cats have more lives than dogs when it comes to snakebite

Cats are twice as likely to survive a venomous snakebite than dogs, and the reasons behind this strange phenomenon have been revealed by University of Queensland research.

The research team, led by PhD student Christina Zdenek and Associate Professor Bryan Fry, compared the effects of snake venoms on the blood clotting agents in dogs and cats, hoping to help save the lives of our furry friends.

In Australia, the eastern brown snake (Pseudonaja textilis) alone is responsible for an estimated 76 per cent of reported domestic pet snakebites each year. **Credit: Stewart Macdonald**

"Snakebite is a common occurrence for pet cats and dogs across the globe and can be fatal," Dr Fry said. "This is primarily due to a condition called 'venom-induced consumptive coagulopathy' - where an animal loses its ability to clot blood and sadly bleeds to death.

"In Australia, the eastern brown snake (Pseudonaja textilis) alone is responsible for an estimated 76 per cent of reported domestic pet snakebites each year. "And while only 31 per cent of dogs survive being bitten by an eastern brown snake without antivenom, cats are twice as likely to survive - at 66 per cent."

Cats also have a significantly higher survival rate if given antivenom treatment and, until now, the reasons behind this disparity were unknown.

Dr Fry and his team used a coagulation analyser to test the effects of eastern brown snake venom - as well as 10 additional venoms found around the world - on dog and cat plasma in the lab.

"All venoms acted faster on dog plasma than cat or human," Mrs Zdenek said. "This indicates that dogs would likely enter a state where blood clotting fails sooner and are therefore more vulnerable to these snake venoms. "The spontaneous clotting time of the blood - even without venom - was dramatically faster in dogs than in cats.

"This suggests that the naturally faster clotting blood of dogs makes them more vulnerable to these types of snake venoms.

"And this is consistent with clinical records showing more rapid onset of symptoms and lethal effects in dogs than cats."

Several behavioural differences between cats and dogs are also highly likely to increase the chances of dogs dying from venomous snake bite. "Dogs typically investigate with their nose and mouth, which are highly vascularised areas, whereas cats often swat with their paws," Dr Fry said.

"And dogs are usually more active than cats, which is not great after a bite has taken place because the best practice is to remain as still as possible to slow the spread of venom through the body."

The researchers hope their insights can lead to a better awareness of the critically short period of time to get treatment for dogs envenomed by snakes.

"As dog lovers ourselves, this study strikes close to home but it also has global implications," Dr Fry said.

"I've had two friends lose big dogs to snakebites, dying in less than ten minutes even though the eastern brown snakes responsible were not particularly large specimens. "This underscores how devastatingly fast and fatal snake venom can be to dogs."

The research has been published in Comparative Biochemistry and Physiology (DOI: 10.1016/j.cbpc.2020.108769).

https://bit.ly/3bUN1c0

New Antibody Completely Neutralizes SARS-CoV-2 Coronavirus

A team of researchers from Sorrento Therapeutics, Inc. has isolated a new antibody that completely inhibits the SARS-CoV-2 coronavirus virus in cell culture.

"Our antibody shows exceptional therapeutic potential and could potentially save lives following receipt of necessary regulatory approvals," said Dr. Henry Ji, Chairman and CEO of Sorrento.

"We at Sorrento are working day and night to complete the steps necessary to get this product candidate approved and available to the waiting public."

The scientists screened their library of human antibodies and identified hundreds of candidates that bind to the S1 subunit of the SARS-CoV-2 spike protein.

One dozen of these antibodies had the ability to block the S1 protein's interaction with angiotensin-converting enzyme 2 (ACE2), the receptor that acts as an entry point into human lung cells for the SARS-CoV-2 virus.

These blocking antibodies were further tested for their ability to inhibit SARS-CoV-2 infection in an in vitro infection model.

Among the antibodies showing neutralizing activity, one antibody stood out for its ability to completely block SARS-CoV-2 infection of healthy cells in the experiments.

Dubbed STI-1499, this antibody completely neutralized the SARS-CoV-2 infectivity at a very low antibody dose.

Biochemical and biophysical analyses also indicate STI-1499 is a potentially strong antibody drug candidate.

"STI-1499 will likely be the first antibody in the antibody cocktail Sorrento is developing," the researchers said.

"This antibody is also expected to be developed as a stand-alone therapy because of the high potency it has exhibited in experiments to date."

"Sorrento plans to request priority evaluation and accelerated review from regulators to determine the best pathway to make any potential treatment available as soon as possible."

https://bit.ly/36pUIFO

COVID-19: UW study reports 'staggering' death rate in US among those infected who show symptoms

Is COVID-19 more deadly than the flu?

It's a lot more deadly, concludes a new study by the University of Washington published May 7 in the journal *Health Affairs*. The study's results also project a grim future if the U.S. doesn't put up a strong fight against the spread of the virus.

The national rate of death among people infected with the novel coronavirus -- SARS-CoV-2 -- that causes COVID-19 and who show symptoms is 1.3%, the study found. The comparable rate of death for the seasonal flu is 0.1%.

"COVID-19 infection is deadlier than flu -- we can put that debate to rest," said study author Anirban Basu, professor of health economics and Stergachis Family Endowed Director of the CHOICE Institute at the UW School of Pharmacy.

The School of Pharmacy and Basu have developed a website that explores the infection and fatality rates by U.S. counties for people with symptoms. For this study, 116 counties in 33 states had COVID-19 data that fit Basu's robust criteria for inclusion in the analysis. The site's projections will be updated as new data becomes available, Basu said.

Basu stresses that this website is not a forecasting tool -- it does not predict what will happen in the future. Rather, it uses the estimated death rate among symptomatic COVID-19 cases to project what is happening currently in these communities, such as what are the

likely numbers for total infections and symptomatic cases. The tool will also detail how the daily incidence of infections changes.

In the state of Washington, for example, the county-specific fatality estimates ranged from 0.5% to 3.6%. King County at 3.6% is the highest among all 116 U.S. counties studied. Among the state's other counties that could be included in this analysis were Chelan County at 2.3%, Island County at 2.2% and Spokane County at 2%.

The COVID-19 death rate, the study adds, means that if the same number of people in the U.S. are infected by the end of the year as were infected with the influenza virus -- roughly 35.5 million in 2018-2019 -- then nearly 500,000 people will die of COVID-19.

However, the novel coronavirus is more infectious than the influenza virus, Basu noted. So, a conservative estimate of 20% of the U.S. population becoming infected by the end of the year -- with the current trends in social distancing and health care supply continuing, while accounting for those infected who will recover asymptomatically -- could result in the number of deaths climbing to between 350,000 and 1.2 million.

"This is a staggering number, which can only be brought down with sound public health measures," Basu said.

To build county-by-county models that could more accurately show how deadly the pandemic is, Basu used publicly reported data on the total COVID-19 cases and deaths. Realizing that both of these reported quantities likely are undercounts and change over time, Basu looked at the trends in the ratio of these two numbers, or the reported "case fatality rates," to more accurately reflect how deadly the virus is among those who fall sick because of it.

"Our hope is that our study results can help inform local and national policies that will save lives in the future," said Basu. "Ultimately, we want this work to advance the health of people around the world."

Basu also noted that the model should not be viewed as the "last word" on estimating the COVID-19 fatality rate, but as one of several methods used to measure the impact of the virus.

"The infection fatality ratio estimate is itself dynamic in nature," Basu said. "The overall estimate can both increase or decrease in the future, depending on the demographics where the infections will be spreading. It is possible, as the infection spreads to more rural counties of the country, the overall infection fatality rate will increase due to the lack of access to necessary health care delivery."

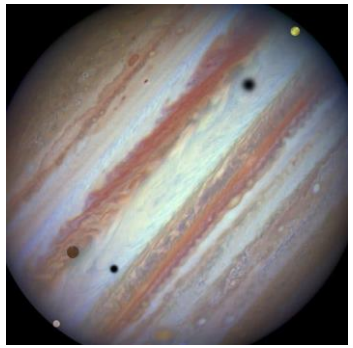
This research was funded by the UW CHOICE Institute and the School of Pharmacy.

https://nyti.ms/2WZqEVn

Jupiter's Biggest Moons Started as Tiny Grains of Hail

A new model offers an explanation for how the Galilean satellites formed around the solar system's largest world.

By Shannon Stirone



Konstantin Batygin did not set out to solve one of the solar system's most puzzling mysteries when he went for a run up a hill in Nice, France. Dr. Batygin, a Caltech researcher, best known for his contributions to the search for the solar system's missing "Planet Nine," spotted a beer bottle. At a steep, 20 degree grade, he wondered why it wasn't rolling down the hill.

From left, Europa, Callisto and Io, three of the four largest moons of Jupiter, and their shadows crossing the red giant in an image captured by the Hubble Space Telescope in 2015.**Credit...NASA Goddard**

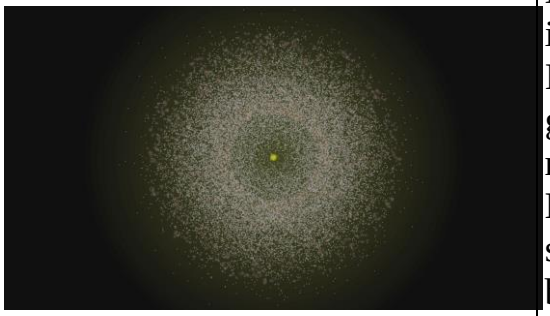
He realized there was a breeze at his back holding the bottle in place. Then he had a thought that would only pop into the mind of a theoretical astrophysicist: "Oh! This is how Europa formed."

Europa is one of Jupiter's four large Galilean moons. And in a paper published Monday in the Astrophysical Journal, Dr. Batygin

and a co-author, Alessandro Morbidelli, a planetary scientist at the Côte d'Azur Observatory in France, present a theory explaining how some moons form around gas giants like Jupiter and Saturn, suggesting that millimeter-sized grains of hail produced during the solar system's formation became trapped around these massive worlds, taking shape one at a time into the potentially habitable moons we know today.

Dr. Batygin and Dr. Morbidelli say earlier theories explain only a part of how the solar system's many objects formed. The two researchers set out to present the rest of the story with equations explaining how a new planet transitions from being surrounded by its disk of matter, to creating satellite building blocks, all the way to the formation of moons like Europa.

When Dr. Batygin and Dr. Morbidelli ran computer simulations of their proposed theory, they found that they'd accidentally re-created Jupiter's small innermost moons as well as the four Galilean satellites, much as we see them today.



"I thought I was still dreaming when I saw the results," Dr. Batygin said.

***Video* A visualization of a computer model shows the dust and gas around Jupiter forming into small icy satellites, which over thousands of years transform into the two innermost Galilean moons, Io and Europa. Ganymede and Callisto would form by a similar process in the millions of years that followed.** **Video by Batygin/Caltech et al.**

The equations amount to a recipe for how to make a moon. It starts with a mix of hydrogen and helium gas raining down onto Jupiter from above. Some of the gas gets swept out and away, spreading viscously as it goes into orbit around Jupiter in a process called decretion.

At this point in Jupiter's formation, the only solid particles that orbited it were smaller than one millimeter across. Because this dust is very small — tiny grains about two parts ice to one part rock — it can couple itself to the gas washing away from Jupiter.

"The disk around Jupiter acts a little bit like a vacuum cleaner, where it sources small dust from the protoplanetary disk," Dr. Batygin said.

As this material builds up over the course of about a million years, he says, it eventually reaches a mass that approximately matches Io, Europa, Ganymede and Callisto today.

The dust clumps together into a massive carpet of icy asteroids, some of which slow down, growing larger as they consume some of the other objects.

"Once the moon is big enough to ship, it gets on the conveyor belt," Dr. Batygin said, and eventually moves in closer to Jupiter, parking into its orbit around the planet.

In this model, Io was formed in about 1,000 years and then quickly got ejected from the satellite feeding zone, leaving behind a mess of remaining icy asteroids in wonky orbits. Around 10,000 years later, Europa grows over about the course of a millennium and does the same thing. After a 30,000-year break, Ganymede begins to form, but takes 2,000 years to grow. Callisto, however, begins to form when the material from Jupiter is nearly depleted, so it takes much longer, around eight million years.

The model offers a similar explanation for Saturn and its largest moon, Titan.

Jonathan Lunine, an astronomer at Cornell University who has studied the Galilean satellites' formation, says the paper "sketches out a scenario more like the formation of the terrestrial planets," than other theories. But he thinks that "it doesn't solve head-on the curious fact that Ganymede, Callisto and Titan (Titan being the big

moon of Saturn) all have very similar sizes and densities and yet totally different geologic histories."

Closer study will be needed to fully explain these moons' history. Luckily, missions planned to Saturn's moon Titan and Jupiter's moons Callisto, Europa and Ganymede in the next 20 years will yield more data to test theories like this one. And this research may aid our understanding about whether life is possible around other stars.

"If we're going to find life, arguably the best place to look are the icy satellites of the giant planets," Dr. Batygin said. If similar moons are likely to form around other stars' gas giants, it raises the question of whether "life in the universe is actually pretty common" he said. "I don't know, of course, but it's an exciting thing to think about."

https://go.nature.com/2AVLMMS

Carbon dating, the archaeological workhorse, is getting a major reboot

A long-anticipated recalibration of radiocarbon dating could shift the age of some prehistoric samples hundreds of years

Nicola Jones

Radiocarbon dating — a key tool used for determining the age of prehistoric samples — is about to get a major update. For the first time in seven years, the technique is due to be recalibrated using a slew of new data from around the world. The result could have implications for the estimated ages of many finds — such as Siberia's oldest modern human fossils, which according to the latest calibrations are 1,000 years younger than previously thought.

The work combines thousands of data points from tree rings, lake and ocean sediments, corals and stalagmites, among other features, and extends the time frame for radiocarbon dating back to 55,000 years ago — 5,000 years further than the last calibration update in 2013.

Archaeologists are downright giddy. "Maybe I've been in lockdown too long," tweeted Nicholas Sutton, an archaeologist at the University of Otago in New Zealand, "but … I'm really excited about it!"

Although the recalibration mostly results in subtle changes, even tiny tweaks can make a huge difference for archaeologists and paleo-ecologists aiming to pin events to a small window of time. A new calibration curve "is of key importance" for understanding prehistory, says Tom Higham, archaeological chronologist and director of the Oxford Radiocarbon Accelerator Unit, UK.

Dating games

The basis of radiocarbon dating is simple: all living things absorb carbon from the atmosphere and food sources around them, including a certain amount of natural, radioactive carbon-14. When the plant or animal dies, they stop absorbing, but the radioactive carbon that they've accumulated continues to decay. Measuring the amount left over gives an estimate as to how long something has been dead.

But this basic calculation assumes that the amount of carbon-14 in the environment has been constant in time and space — which it hasn't. In recent decades, the burning of fossil fuel and tests of nuclear bombs have radically altered the amount of carbon-14 in the air, and there are non-anthropogenic wobbles going much further back. During planetary magnetic-field reversals, for example, more solar radiation enters the atmosphere, producing more carbon-14. The oceans also suck up carbon — a little more so in the Southern Hemisphere, where there is more ocean — and circulate it for centuries, further complicating things.

As a result, conversion tables are needed that match up calendar dates with radiocarbon dates in different regions. Scientists are releasing new curves for the Northern Hemisphere (IntCal20), Southern Hemisphere (SHCal20), and marine samples

(MarineCal20). They will be published in the journal *Radiocarbon* in the next few months.

Since the 1960s, researchers have mainly done this recalibration with trees, counting annual rings to get calendar dates and matching those with measured radiocarbon dates. The oldest single tree for which this has been done, a bristlecone pine from California, was about 5,000 years old. By matching up the relative widths of rings from one tree to another, including from bogs and historic buildings, the tree record has now been pushed back to 13,910 years ago.

Since 1998 there have been four official IntCal calibrations, adding in data from laminated lake and marine sediments, cave stalagmites and corals (which can be both radiocarbon dated and independently assessed using techniques such as radioactive thorium/uranium dating). In 2018, some stalagmites in Hulu Cave in China provided a datable record stretching back 54,000 years[1].

IntCal20 is based on 12,904 data points, nearly double the size of 2013's data set. The results are far more satisfying, says Paula Reimer, who heads the IntCal working group and leads the radiocarbon-dating Chrono Centre at Queen's University Belfast, UK. For a known, brief magnetic field reversal 40,000 years ago, for example, the 2013 curve's carbon-14 peak was too low and too old by 500 years — an annoyance fixed by the new curve.

Higham says the recalibration is fundamental for understanding the chronology of hominins living 40,000 years ago. "I am really excited about calibrating our latest data using this curve," he says.

Recalibrate and reassess

IntCal20 revises the date for a *Homo sapiens* jawbone found in Romania called Oase 1, potentially making it hundreds of years older than previously thought[2]. Genetic analyses of Oase 1 have revealed that it had a Neanderthal ancestor just four to six generations back, says Higham, so the older the Oase 1 date, the further back Neanderthals were living in Europe. Meanwhile, the oldest *H. sapiens* fossil found in Eurasia — Ust'-Ishim, unearthed in Siberia — is almost 1,000 years younger according to the new conversion curves. "It changes the earliest date we can place on modern humans in central Siberia," says Higham. He cautions, however, that there are more sources of error in such measurements than just radiocarbon calibration: "Contamination is the biggest influence for dating really old bones like these."

Others will use the recalibration to assess environmental events. For example, researchers have been arguing for decades over the timing of the Minoan eruption at the Greek island of Santorini. Until now, radiocarbon results typically gave a best date in the low 1600s BC, about 100 years older than given by most archaeological assessments. IntCal20 improves the accuracy of dating but makes the debate more complicated: overall, it bumps the calendar dates for the radiocarbon result about 5–15 years younger, but — because the calibration curve wiggles around a lot — it also provides six potential time windows for the eruption, most likely in the low 1600s BC, but maybe in the high 1500s BC[2].

So the two groups still disagree, says Reimer, but less so, and with more complications. "Some of them are still arguing," says Reimer. "There's no hard answer."

Nevertheless, anyone looking at practically anything relating to human history from the past 50,000 years will be enthusiastic about the new calibration, says Higham: "This is a particularly exciting time to be working on the past."

https://bit.ly/2LUhr3m

Researchers reveal origins of complex hemoglobin by resurrecting ancient proteins

Evolutionary "missing link" through which hemoglobin evolved from simple precursors.

Most biological processes are carried out by complexes of multiple proteins that work together to carry out some function. How these

complicated structures could have evolved is one of modern biology's great puzzles, because they generally stick together using elaborate molecular interfaces, and the intermediate forms through which they came into being have been lost without a trace.

Now an international team of researchers led by University of Chicago Professor Joseph Thornton, PhD, and graduate student Arvind Pillai has revealed that complexity can evolve through surprisingly simple mechanisms. The group identified the evolutionary "missing link" through which hemoglobin -- the essential four-part protein complex that transports oxygen in the blood of virtually all vertebrate animals -- evolved from simple precursors. And they found that it took just two mutations more than 400 million years ago to trigger the emergence of modern hemoglobin's structure and function.

The study, "Origin of complexity in haemoglobin evolution," will be published online in the journal *Nature* on May 20. The team also includes scientists at Texas A&M University, University of Nebraska-Lincoln, and Oxford University (UK).

Each hemoglobin molecule is a four-part protein complex made up of two copies each of two different proteins, but the proteins to which they are most closely related do not form complexes at all. The team's strategy, pioneered in Thornton's lab over the last two decades, was a kind of molecular time travel: use statistical and biochemical methods to reconstruct and experimentally characterize ancient proteins before, during and after the evolution of the earliest forms of hemoglobin. This allowed them to identify the missing link during hemoglobin evolution - a two-part complex, consisting of two copies of a single protein, which existed before the last common ancestor of humans and sharks.

This ancient two-part complex did not yet possess any of modern hemoglobin's critical properties that allow it to bind oxygen in the lungs and deliver it to distant cells in the brain, muscles and other tissues.

By introducing into this missing link protein various mutations that occurred during the next historical interval, they found that just two mutations on the protein's surface triggered formation of the four-part complex and imparted the critical changes in its oxygen-binding function.

The traditional view of the evolution of biological complexity -- first proposed by Charles Darwin and elaborated recently by Richard Dawkins -- is that complexity increases gradually through a long journey of many mutations, each of which is favored by natural selection because it causes small improvements in function and fitness. The new research shows that, at the molecular level at least, new complex forms can be brought into being very quickly.

"We were blown away when we saw that such a simple mechanism could confer such complex properties," Thornton said. "This suggests that jumps in complexity can happen suddenly and even by chance during evolution, producing new molecular entities that eventually become essential to our biology."

The project began when Pillai, a graduate student in the Department of Ecology and Evolution, approached Thornton and Georg Hochberg, PhD, a postdoctoral scholar in his laboratory, with the idea that hemoglobin could be a test case to see how complex molecules evolved throughout history.

"Hemoglobin's structure and function has been studied more than perhaps any other molecule," said Pillai. "But nothing was known about how it originated during evolution. It's a great model because hemoglobin's components are part of a larger protein family in which the closest relatives don't form complexes but function in isolation. Their history can be reconstructed from the sequences of its modern descendants, and there are great laboratory tools for characterizing their properties."

Thornton said that Pillai's idea was "brilliant, and it inspired a massive amount of experimental work by Arvind and the rest of the team." Speculation about how hemoglobin might have evolved goes back at least 60 years to Linus Pauling and Max Perutz, the founding fathers of protein biochemistry, but until now there was no way to study the problem experimentally.

Analysis of the ancient proteins' atomic structures showed how the two mutations took advantage of even more ancient features to assemble the intermediate two-part complex into the four-part complex. The mutations introduced two changes on the protein surface that allowed it to bind tightly to the surface of the other protein, which remained unchanged as it was recruited into the new interaction.

Other ancient parts of the two surfaces also stuck together simply by chance, adding further strength to the interaction that was triggered by the two new mutations. Those older elements, Thornton pointed out, and even the two-part complex itself, must have existed then by chance, rather than because they enhanced the protein's final structure or function, because they evolved before those properties came into being.

Perhaps the most surprising result was that the two critical mutations, by inducing formation of the four-part structure, also triggered the critical changes in the complex's oxygen-binding functions. Hemoglobin can perform its physiological function because its affinity for oxygen is high enough to bind oxygen in the lungs, but low enough to release it in the tissues elsewhere in the body. It also binds oxygen cooperatively: When one of the four components takes up a molecule of oxygen, the other components tend to do the same - and this happens in the reverse direction, as well -- so the whole complex becomes even more effective at recruiting oxygen and releasing it in the right places.

Hemoglobin's ancient precursors - including the missing link two-part complex - bound oxygen too tightly and were not cooperative, so they could not have effectively performed the oxygen-exchange function. The researchers found that the two key mutations not only conferred the four-part structure but also imparted hemoglobin's critical oxygen-binding properties. Although the mutations are on the part of the protein's surface that assemble the complex together - not at its oxygen-binding site - the two regions are connected by an ancient string of amino acids found in all members of the globin protein family.

When the four-part complex assembles, this string moves, and the oxygen-binding site is reshaped in a way that makes it bind oxygen more loosely. And when one component of the hemoglobin complex does bind oxygen, the string moves back, reshaping the surface that binds the neighboring proteins together, which allows the neighbor to get better at binding oxygen, too. In this way, complex functional properties appeared as an immediate side effect when hemoglobin's ability to assemble first evolved.

"Imagine if those two mutations never occurred, or if the structural features that they took advantage of weren't in place at the time," Thornton said. "Hemoglobin as we know it would not have evolved, and neither would many of the subsequent innovations that depend on efficient oxygen transport, like rapid metabolism and the ability to grow much larger and move much faster than our ancient marine ancestors."

The study will be released on May 20, 2020, on the *Nature* website and on May 28 in the journal's print issue. Co-authors along with Pillai, Hochberg and Thornton include University of Chicago graduate student Carlos Cortez-Romero, Yang Liu and Arthur Laganowsky of Texas A&M University, Anthony Signore and Jay F. Storz of University of Nebraska-Lincoln, and Shane Chandler and Justin Benesch of Oxford University (UK).

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Biogen Uses its Own Superspreader Event to Aid COVID-19 Research

A blood biobank allows scientists to study the immune responses to the coronavirus among infected Biogen employees and their contacts.

Claire Jarvis

In late February, as the first cases of COVID-19 were detected in the US, the biotech company Biogen became an unwitting superspreader. More than 100 Biogen leaders and executives had attended a leadership meeting in Massachusetts on February 26 and 27.

When the executives flew home—to Europe, Asia, and across the US—they spread SARS-CoV-2 to their families and coworkers, seeding new outbreaks. According to the official count, 99 people living in Massachusetts alone were infected with SARS-CoV-2 as a result of the Biogen meeting. The total number of people infected in the US and around the world is higher.

The company chose to capitalize on its early COVID-19 misfortune by helping others with their research. "Several Biogen employees, who at the time were still recovering from COVID-19, began to consider ways they could offer their own anonymized medical information to research efforts," explains Maha Radhakrishnan, the chief medical officer at Biogen, in an email to *The Scientist*.

"We realized we were in a unique position to contribute to advancing COVID-19 science in an organized and deliberate way."

On April 16, Biogen announced a collaboration with the Broad Institute of MIT and Harvard, Partners HealthCare, and several local hospitals to develop a COVID-19 biobank. Biogen employees and their close contacts could volunteer to donate blood samples to researchers at the Broad Institute, who would use the tissue to study immune responses to SARS-CoV-2.

Researchers at the Broad Institute collect blood and clinical history from volunteers. Those with high titers of SARS-CoV-2 antibodies are called back to give additional samples.

The Biogen cohort was of particular interest to researchers for several reasons. As Ramnik Xavier, an immunologist at the Broad Institute and a member of the COVID-19 Biobank Steering Committee, explains, the infections occurred during a defined time frame within a closed environment. This makes it possible to study patterns of infection.

Another unique feature of the Biogen cohort is that among employees and contacts known to be infected, the cases were nearly all mild and didn't require hospitalization.

As Xavier explains, people infected with SARS-CoV-2 produce antibodies in response, but only a subset of those people produce antibodies capable of neutralizing the virus, according to data from the Biogen biobank and other studies.

"A question out there is, do patients make high-titer neutralizing antibodies following a mild infection, or is it less common than after a severe infection that requires hospitalization?"

The biobank also collects blood from Biogen employees and close contacts who were exposed to SARS-CoV-2 but didn't develop an infection. Researchers are using those samples to search for determinants of COVID-19 infection and disease severity.

To date, around 150 volunteers have signed up: an anonymized mix of Biogen employees and their close contacts. Over the past few weeks, about 30 volunteers have given blood samples, and Xavier says the team plans to finish the first round of sampling within the next few weeks.

Although Biogen spearheaded the development of the project, Radhakrishnan explains over email that the biobank is structured to protect the privacy of Biogen employees who take part. "Biogen will have the same level of access to the Biobank as researchers

around the world, which means it will not have access to identifiable information."

Academic groups wishing to use the biobank data for their own research can submit proposals to the steering committee.

There are several other COVID-19 biobanks, such as the Massachusetts Consortium on Pathogenic Readiness, collecting samples from hospitalized patients.

Researchers around the US are using biobank samples to develop monoclonal antibody treatments for COVID-19 and to standardize serological assays.

Correction (May 19): The article now notes that the biobank is collecting samples from employees and their close contacts, not strictly family members. The Scientist *regrets the error.*

https://bit.ly/2AWvMdt

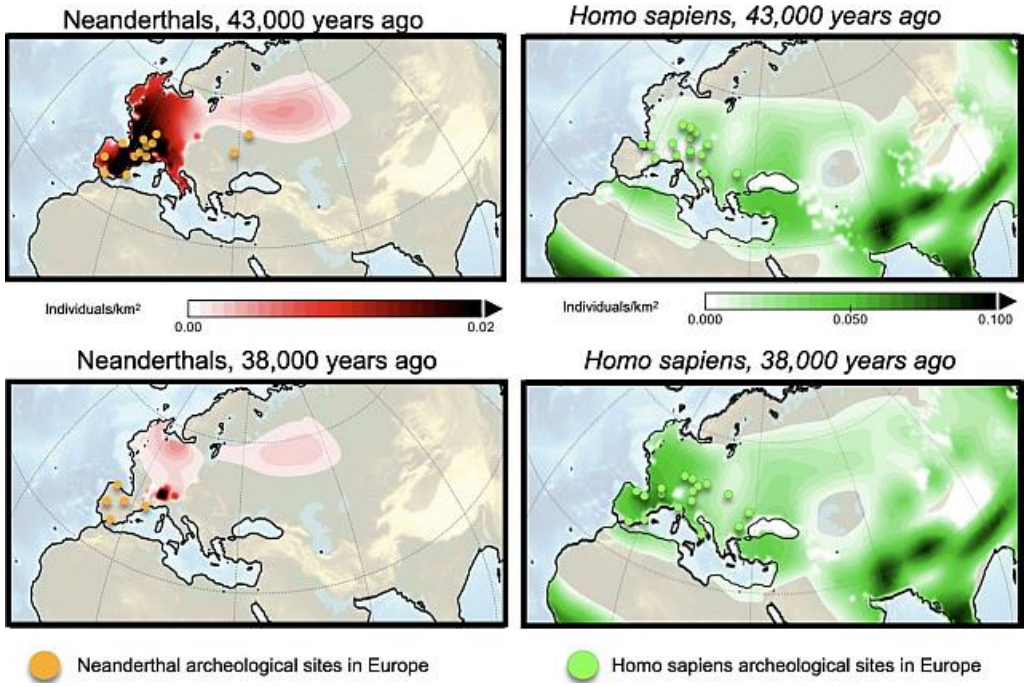
Supercomputer model simulations reveal cause of Neanderthal extinction

Only competition between Neanderthals and Homo sapiens can explain the rapid demise of Neanderthals

Climate scientists from the IBS Center for Climate Physics discover that, contrary to previously held beliefs, Neanderthal extinction was neither caused by abrupt glacial climate shifts, nor by interbreeding with *Homo sapiens*. According to new supercomputer model simulations, only competition between Neanderthals and *Homo sapiens* can explain the rapid demise of Neanderthals around 43 to 38 thousand years ago.

Neanderthals lived in Eurasia for at least 300,000 years. Then, around 43 to 38 thousand years ago they quickly disappeared off the face of the earth, leaving only weak genetic traces in present-day *Homo sapiens* populations. It is well established that their extinction coincided with a period of rapidly fluctuating climatic conditions, as well as with the arrival of *Homo sapiens* in Europe. However, determining which of these factors was the dominant cause, has remained one of the biggest challenges of evolutionary anthropology.

To quantify which processes played a major role in the collapse of Neanderthal populations one needs to use mathematical models that can realistically simulate the migration of Neanderthals and *Homo sapiens*, their interactions, competition and interbreeding in a changing climatic environment. Such models did not exist previously.



Computer simulations of population density of Neanderthals (left) and Homo sapiens (right) 43,000 years ago (upper) and 38,000 years ago (lower). Orange (green) circles indicate archeological sites of Neanderthals (Homo sapiens) during 5,000-year-long intervals centered around 43 and 38 thousand years before present. **Credit: IBS**

In a new paper published in the journal *Quaternary Science Review*, Axel Timmermann, Director of the IBS Center for Climate Physics at Pusan National University, presents the first realistic computer

model simulation of the extinction of Neanderthals across Eurasia (Figure 1). The model which is comprised of several thousands of lines of computer code and is run on the IBS supercomputer Aleph, solves a series of mathematical equations that describe how Neanderthals and *Homo sapiens* moved in a time-varying glacial landscape and under shifting temperature, rainfall and vegetation patterns. In the model both hominin groups compete for the same food resources and a small fraction is allowed to interbreed. The key parameters of the model are obtained from realistic climate computer model simulations, genetic and demographic data.

"This is the first time we can quantify the drivers of Neanderthal extinction," said Timmermann. "In the computer model I can turn on and off different processes, such as abrupt climate change, interbreeding or competition" he said. By comparing the results with existing paleo-anthropological, genetic and archeological data (e.g. Figure 1), Timmermann demonstrated that a realistic extinction in the computer model is only possible, if *Homo sapiens* had significant advantages over Neanderthals in terms of exploiting existing food resources. Even though the model does not specify the details, possible reasons for the superiority of *Homo sapiens* could have been associated with better hunting techniques, stronger resistance to pathogens or higher level of fecundity.

What exactly caused the rapid Neanderthal demise has remained elusive for a long time. This new computer modeling approach identifies competitive exclusion as the likely reason for the disappearance of our cousins. "Neanderthals lived in Eurasia for the last 300,000 years and experienced and adapted to abrupt climate shifts, that were even more dramatic than those that occurred during the time of Neanderthal disappearance. It is not a coincidence that Neanderthals vanished just at the time, when *Homo sapiens* started to spread into Europe" says Timmermann. He adds "The new computer model simulations show clearly that this event was the first major extinction caused by our own species".

A research team at the IBS Center for Climate Physics is now improving the computer model to also include megafauna and implement more realistic climate forcings. "This is a new field of research in which climate scientists can interact with mathematicians, geneticists, archeologists and anthropologists", said Axel Timmermann.

https://bit.ly/2M0sVCl

How cosmic rays may have shaped life

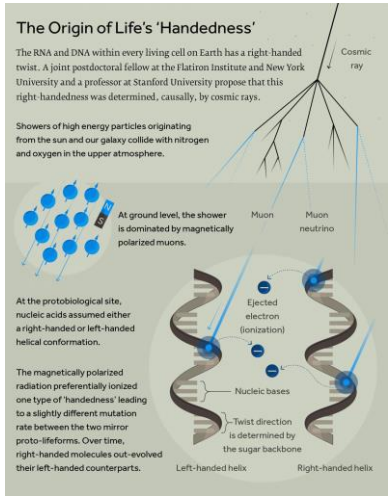
Interaction between ancient proto-organisms and cosmic rays may be responsible for chirality

Before there were animals, bacteria or even DNA on Earth, self-replicating molecules were slowly evolving their way from simple matter to life beneath a constant shower of energetic particles from space.

In a new paper, a Stanford professor and a former post-doctoral scholar speculate that this interaction between ancient proto-organisms and cosmic rays may be responsible for a crucial structural preference, called chirality, in biological molecules. If their idea is correct, it suggests that all life throughout the universe could share the same chiral preference.

Chirality, also known as handedness, is the existence of mirror-image versions of molecules. Like the left and right hand, two chiral forms of a single molecule reflect each other in shape but don't line up if stacked. In every major biomolecule - amino acids, DNA, RNA - life only uses one form of molecular handedness. If the mirror version of a molecule is substituted for the regular version within a biological system, the system will often malfunction or stop functioning entirely. In the case of DNA, a single wrong handed sugar would disrupt the stable helical structure of the molecule.

Louis Pasteur first discovered this biological homochirality in 1848. Since then, scientists have debated whether the handedness of life was driven by random chance or some unknown deterministic influence. Pasteur hypothesized that, if life is asymmetric, then it may be due to an asymmetry in the fundamental interactions of physics that exist throughout the cosmos.



"We propose that the biological handedness we witness now on Earth is due to evolution amidst magnetically polarized radiation, where a tiny difference in the mutation rate may have promoted the evolution of DNA-based life, rather than its mirror image," said Noémie Globus lead author of the paper and a former Koret Fellow at the Kavli Institute for Particle Astrophysics and Cosmology (KIPAC).

Showers of high energy particles originating from the sun and our galaxy collide with nitrogen and oxygen in the upper atmosphere. At ground level, the shower is dominated by magnetically polarized muons. At the protobiological site, nucleic acids assumed either a right-handed or left-handed helical conformation. The magnetically polarized radiation preferentially ionized one type of 'handedness' leading to a slightly different mutation rate between the two mirror proto-lifeforms. Over time, right-handed molecules out-evolved their left-handed counterparts. **Simons Foundation**

In their paper, published on May 20 in *Astrophysical Journal Letters*, the researchers detail their argument in favor of cosmic rays as the origin of homochirality. They also discuss potential experiments to test their hypothesis.

Magnetic polarization from space

Cosmic rays are an abundant form of high-energy radiation that originate from various sources throughout the universe, including stars and distant galaxies. After hitting the Earth's atmosphere, cosmic rays eventually degrade into fundamental particles. At ground level, most of the cosmic rays exist only as particles known as muons.

Muons are unstable particles, existing for a mere 2 millionths of a second, but because they travel near the speed of light, they have been detected more than 700 meters below Earth's surface. They are also magnetically polarized, meaning, on average, muons all share the same magnetic orientation. When muons finally decay, they produce electrons with the same magnetic polarization. The researchers believe that the muon's penetrative ability allows it and its daughter electrons to potentially affect chiral molecules on Earth and everywhere else in the universe.

"We are irradiated all the time by cosmic rays," explained Globus, who is currently a post-doctoral researcher at New York University and the Simons Foundation's Flatiron Institute. "Their effects are small but constant in every place on the planet where life could evolve, and the magnetic polarization of the muons and electrons is always the same. And even on other planets, cosmic rays would have the same effects."

The researchers' hypothesis is that, at the beginning of life of on Earth, this constant and consistent radiation affected the evolution of the two mirror life-forms in different ways, helping one ultimately prevail over the other. These tiny differences in mutation rate would have been most significant when life was beginning and the molecules involved were very simple and more fragile. Under these circumstances, the small but persistent chiral influence from cosmic rays could have, over billions of generations of evolution, produced the single biological handedness we see today.

"This is a little bit like a roulette wheel in Vegas, where you might engineer a slight preference for the red pockets, rather than the black pockets," said Roger Blandford, the Luke Blossom Professor

in the School of Humanities and Sciences at Stanford and an author on the paper. "Play a few games, you would never notice. But if you play with this roulette wheel for many years, those who bet habitually on red will make money and those who bet on black will lose and go away."

Ready to be surprised

Globus and Blandford suggest experiments that could help prove or disprove their cosmic ray hypothesis. For example, they would like to test how bacteria respond to radiation with different magnetic polarization. "Experiments like this have never been performed and I am excited to see what they teach us. Surprises inevitably come from further work on interdisciplinary topics," said Globus.

The researchers also look forward to organic samples from comets, asteroids or Mars to see if they too exhibit a chiral bias.

"This idea connects fundamental physics and the origin of life," said Blandford, who is also Stanford and SLAC professor of physics and particle physics and former director of KIPAC. "Regardless of whether or not it's correct, bridging these very different fields is exciting and a successful experiment should be interesting."

This research was funded by the Koret Foundation, New York University and the Simons Foundation.

https://bit.ly/3bZBzLW

Recovered COVID-19 patients test positive but not infectious, data finds

"Re-positive" cases didn't spread disease or shed virus.

Beth Mole

People who recover from COVID-19 but test positive for the virus again days or weeks later are not shedding viral particles and are not infectious, according to data released Tuesday by the Korea Centers for Disease Control and Prevention.

The so-called "re-positive" cases have raised fears that an infection with the new coronavirus, SARS-CoV-2, could "reactivate" in recovered patients or that recovering from the infection may fail to produce even short-lived immunity, allowing patients to immediately become re-infected if they are exposed.

The new data from Korea should ease those concerns.

KCDC researchers examined 285 cases that had previously recovered from COVID-19 but then tested positive again. The patients tested positive again anywhere from one to 37 days after recovering from their first infection and being discharged from isolation. The average time to a second positive was about 14 days.

Of those cases, researchers checked for symptoms in 284 of them. They found that 126 (about 48 percent) did indeed have symptoms related to COVID-19.

But none of them seemed to have spread the infection. KCDC investigated 790 people who had close contact with the 285 cases and found that none of them had been infected by the "re-positive" cases.

Crucially, additional testing of 108 "re-positive" cases found that none of them were shedding infectious virus.

KCDC on RT-PCR for SARS-CoV-2

The type of tests that suggested the 285 people were positive for COVID-19 a second time were what's called RT-PCR tests (reverse transcription polymerase chain reaction). These tests are typically used to diagnose a COVID-19 infection. They do so by recognizing and making copies of unique, targeted fragments of SARS-CoV-2's genetic material.

It's a precise and effective way to determine if someone's been infected with the virus. If someone has SARS-CoV-2 genetic material in their airways, they've been infected. That said, having genetic material doesn't necessarily mean that the person still has an active infection and infectious viral particles. They may just

have lingering fragments of genetic material from destroyed viral particles.

That appears to be the case here. When KCDC researchers tried to isolate and grow whole, infectious particles of SARS-CoV-2 from the 108 cases they were able to test—all 108 were negative for whole virus.

Further, when they did further blood work on 23 of the re-positive cases, nearly all of them (96 percent) had neutralizing antibodies against SARS-CoV-2. This hints that they may have some immunity to a reinfection with the virus.

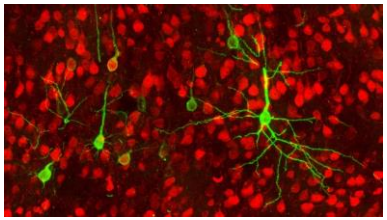
It's unclear what was causing symptoms in many of the patients. A few cases tested positive for other respiratory viruses, but many did not. Still, based on the data, the KCDC determined that re-positive cases are not infectious and do not need to re-enter isolation.

https://go.nature.com/36s2VcP

These brain regions are the stomach's master controllers

Rabies virus helps to trace the nerve network that keeps the stomach in good form.

As unemployment levels rise, so does stress — and the number of deaths from stomach ulcers. Researchers have now identified brain regions that control stomach function, findings that could explain how stress contributes to ulcers and other gastrointestinal disorders.



Neurons (green) in a brain region called the insula send projections to the stomach. **David Levinthal and Peter Strick**

To map the nerves that feed the stomach, David Levinthal and Peter Strick at the University of Pittsburgh in Pennsylvania injected rabies virus, which infects nerve cells, into the stomachs of rats. The rabies virus can travel along connected neurons from any organ in the body towards the brain.

By tracking the virus's progress, the researchers found that neurons in a brain area called the rostral insula, which is involved in regulating emotion, stimulate the stomach to digest food. But cells in the brain's primary motor cortex, which provides commands to move the body, inhibit the production of stomach acid and the contraction of the digestive tract.

These brain signals could contribute to the likelihood of developing ulcers, because changes in stomach acidity can influence the growth of ulcer-causing bacteria, the researchers say.

Proc. Natl Acad. Sci. USA (2020)

https://bit.ly/2B0tRVr

Elimination of human African trypanosomiasis within reach, study finds

Elimination of the disease as a public health problem is within reach, with fewer than 1,000 new cases reported in 2018

Over the past twenty years, huge efforts by a broad coalition of stakeholders, coordinated by the World Health Organization have curbed the latest epidemic of human African trypanosomiasis, a lethal disease transmitted by tsetse flies.

Now, public health officials report in *PLOS Neglected Tropical Diseases* that the elimination of the disease as a public health problem is within reach, with fewer than 1,000 new cases reported in 2018.

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a parasitic infection that has wreaked havoc across Africa at different times in the 20th century.

A slow-progressing form of the pathogen, Trypanosoma brucei gambiense, is found in western and central Africa, while a faster-progressing form, T. b. rhodesiense, occurs in eastern and southern Africa.

Following a resurgence of the disease in the late 1990s, strengthened control and surveillance activities were put in place

with the coordination of the World Health Organization. In 2012, the WHO's Neglected Tropical Diseases roadmap targeted HAT for elimination as a public health problem by 2020.

In the new work, Jose Ramon Franco of the World Health Organization in Geneva, Switzerland, and colleagues studied global indicators and milestones collected between 2017 and 2018 to monitor progress toward the 2020 goal of HAT elimination.

The team also developed new country-level indicators to be used by endemic countries to track HAT and validate their elimination status.

977 cases of HAT were reported in 2018, down from 2,164 in 2016, and the area at moderate or high risk of HAT has shrunk to less than 200,000 square kilometers, the team reported.

More than half of this area is in the Democratic Republic of the Congo.

Eight countries meet the requirements to request validation of gambiense HAT elimination as a public health problem.

In addition, health facilities providing diagnosis and treatment for gambiense HAT have increased since the last survey, while rhodesiense HAT facilities decreased in number.

"The 2020 goal of HAT elimination as a public health problem is within grasp, and eligible countries are encouraged to request validation of their elimination status," the authors say.

"Beyond 2020, the HAT community must gear up for the elimination of gambiense HAT transmission (2030 goal) by preparing for both the expected challenges and the unexpected ones."

Citation: Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, et al. (2020) Monitoring the elimination of human African trypanosomiasis at continental and country level: Update to 2018. PLOS Neglected Tropical Diseases 14(5): e0008261. https://doi.org/10.1371/journal.pntd.0008261

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https://bit.ly/2Zw2bBL

Oldest cousin of Native Americans found in Russia

14,000-year-old tooth belonging to a close cousin of today's Native Americans, found thousands of kilometers from Beingia

By Michael Price

A new study has revealed the oldest link yet between Native Americans and their ancestors in East Asia: a 14,000-year-old tooth belonging to a close cousin of today's Native Americans, found thousands of kilometers from the landmass that once connected Eurasia and the Americas.

"It's very cool," says Jennifer Raff, a geneticist at the University of Kansas, Lawrence, who studies the peopling of the Americas. The work suggests the Siberian ancestors of North America's Indigenous peoples were more widespread and mobile than previously believed, she says. It may also indirectly support the hypothesis that Native Americans' ancestors became isolated from their Asian forebears on Beringia, an ancient land bridge that connected Siberia to Alaska.

Sometime about 20,000 years ago, people began to cross the eastern tip of Siberia onto Beringia. Exactly where they lived and roamed in Siberia before that, however, has long been a mystery.

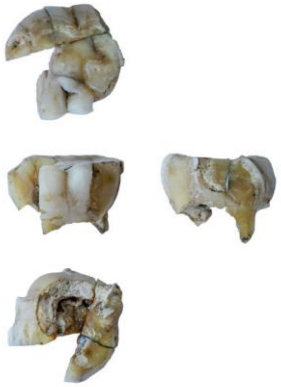
The new study provides the oldest evidence yet of a close genetic ancestor to Native Americans in Eurasia. It's also much farther from Beringia that many would have suspected, says the study's senior author, Johannes Krause, an archaeogeneticist and director of the Max Planck Institute (MPI) for the Science of Human History.

In the 1970s, Russian archaeologists excavated a site called Ust-Kyakhta sandwiched between the southern banks of Lake Baikal and the Mongolian border in south-central Russia. They recovered thousands of stone and bone tools, ceramics, and reindeer and fish bones—plus a sliver of a human tooth.

The tooth sat in a collections drawer for decades, until Svetlana Shnaider, an archaeologist at the Russian Academy of Sciences, brought it to the attention of ancient DNA experts at MPI. “Initially I was quite skeptical” that it could still contain DNA, Krause says.

But Siberia’s cold, dry environment favors DNA preservation, and the team succeeded in sequencing the tooth bearer’s genome from dental pulp.

Based on radiocarbon dates of charcoal and bones found alongside the tooth, researchers calculated it to be about 14,000 years old. The genome showed the individual was a man—one who shared the same distinctive mixture of East Asian and Eurasian ancestry as today’s Native Americans. That makes him the oldest known close relative of Native Americans outside the Americas, the researchers report today in *Cell*.



A fragmented tooth belonging to a close cousin of today’s Native Americans
G. Pavlenok

The man lived 4500 kilometers from Beringia and nearly 3200 kilometers from a woman in northeastern Siberia who shared about two-thirds of her genome with living Native Americans. This suggests the source population from which Native Americans emerged occupied a vast region of northeastern Eurasia, Krause says.

That impressive range, in turn, implies that the group directly ancestral to Native Americans became genetically isolated in Beringia, not in Siberia, where they had been moving around for thousands of years, Raff says. Today, the people near Lake Baikal have virtually none of the genetic hallmarks of that older population, indicating it was replaced by migrants of primarily northeast Asian ancestry about 10,000 years ago.

People around Lake Baikal continued to move around and interact with other groups for thousands of years, according to additional findings in the paper. Two of them, buried side by side about 4200 years ago, bore the DNA signature of the plague-causing bacteria *Yersinia pestis*, which until now had only been found much farther west, in people with a genetic connection to the Eurasian steppe.

“That [the bacterium] moved all the way from the Baltic to the Baikal over more or less 100 years is a bit of a surprise,” Krause says. “Today, we see something like coronavirus that went everywhere within 3 months, but the Bronze Age was not such a globalized world.”

The combination of both human and pathogen ancient DNA offers a rare historical window into a place critical to understanding Native American, Asian, and European genetics, says Priya Moorjani, a geneticist at the University of California, Berkeley. “Every sample thus far from this region has helped to refine our understanding of human history and evolution.”

Posted in: Archaeology doi:10.1126/science.abc9124

https://bit.ly/2Zz6GLY

When plant pollen scarce, bumblebees biting leaves causes flowers to bloom early

Intentional damage accelerates the production of flowers

Facing a scarcity of pollen, bumblebees will nibble on the leaves of flowerless plants, causing intentional damage in such a way that accelerates the production of flowers, according to a new study, which reports on a previously unknown behavior of bumblebees. The leaf-damaging bumblebee bites have a drastic effect on plant flowering, compelling some to bloom two weeks to a full month earlier. Although the mechanisms by which deliberate bee damage accelerate flowering remain unclear, the results reveal bumblebees as powerful agents in influencing the local availability of floral

resources. "An encouraging interpretation of the new findings is that behavioral adaptations of flower-visitors can provide pollination systems with more plasticity and resilience to cope with climate change than hitherto suspected," writes Lars Chittka in a related Perspective. Plants and pollinators rely on one another for survival. Just as pollinators, like bumblebees, depend on flowers for crucial nutrition, plants need pollinators to reproduce. This symbiotic relationship is kept in balance by the synchronous timing of the emergence of hibernating insects and spring blossoms as spring temperatures rise and the days get longer. But this fragile arrangement is threatened by climate change. For instance, warming early season temperatures could cause pollinators to wake up too soon, before the springtime bloom and without a source of food. Foteini Pashalidou and colleagues discovered an adaptive strategy used by food-deprived bumblebees to manipulate the timing of a plant's flowering. Pashalidou et al. observed bumblebee workers from pollen-starved colonies use their mouthparts to cut distinctively shaped holes in the leaves of flowering plants, which resulted in them flowering significantly earlier. The authors were not able to reproduce the flower-stimulating effects by mimicking the damage on their own, however, suggesting a yet-unknown feature distinct to the bees' approach. "Understanding the molecular pathways by which one could accelerate flowering by a full month, as reported [by Pashalidou et al.], would be a horticulturalist's dream," Chittka writes.

https://wb.md/2TwtHLS

ACE Inhibitors Protective Against Severe COVID-19?

A new nationwide US observational study suggests that ACE inhibitors may protect against severe illness in older people with COVID-19, prompting the start of a randomized clinical trial to test the strategy.

Sue Hughes

In addition, a new meta-analysis of all the available data on the use of ACE inhibitors and angiotensin-receptor blockers (ARBs) in COVID-19–infected patients has concluded that these drugs are not associated with more severe disease and do not increase susceptibility to infection.

The observational study, which was published on the MedRxiv preprint server on May 19 and has not yet been peer reviewed, was conducted by the health insurance company United Heath Group and by the Yale University School of Medicine, in New Haven, Connecticut.

The investigators analyzed data from 10,000 patients from across the United States who had tested positive for COVID-19, who were enrolled in Medicare Advantage insurance plans or were commercially insured, and who had received a prescription for one or more antihypertensive medications.

Results showed that the use of ACE inhibitors was associated with an almost 40% lower risk for COVID-19 hospitalization for older people enrolled in Medicare Advantage plans. No such benefit was seen in the younger commercially insured patients or in either group with ARBs.

At a telephone media briefing on the study, senior investigator Harlan Krumholz, MD, said: "We don't believe this is enough info to change practice, but we do think this is an interesting and intriguing result. "These findings merit a clinical trial to formally test whether ACE inhibitors - which are cheap, widely available, and well-tolerated drugs - can reduce hospitalization of patients infected with COVID-19," he added.

Krumholz is professor of medicine at Yale and is the director of the Yale New Haven Hospital Center for Outcomes Research.

A pragmatic clinical trial is now being planned. In this trial, 10,000 older people who test positive for COVID-19 will be randomly assigned to receive either a low dose of an ACE inhibitor or

placebo. It is hoped that recruitment for the trial will begin within the next 3 to 4 weeks. It is open to all eligible Americans who are older than 50 years, who test negative for COVID-19, and who are not taking medications for hypertension. Prospective patients can sign up at a dedicated website.

The randomized trial, also conducted by United Health Group and Yale, is said to be "one of the first virtual COVID-19 clinical trials to be launched at scale."

For the observational study, the researchers identified 2263 people who were receiving medication for hypertension and who tested positive for COVID-19. Of these, approximately two thirds were older, Medicare Advantage enrollees; one third were younger, commercially insured individuals.

In a propensity score–matched analysis, the investigators matched 441 patients who were taking ACE inhibitors to 441 patients who were taking other antihypertensive agents; and 412 patients who were receiving an ARB to 412 patients who were receiving other antihypertensive agents.

Results showed that during a median of 30 days after testing positive, 12.7% of the cohort were hospitalized for COVID-19. In propensity score–matched analyses, neither ACE inhibitors (hazard ratio [HR], 0.77; *P* = .18) nor ARBs (HR, 0.88; *P* =.48) were significantly associated with risk for hospitalization.

However, in analyses stratified by insurance group, ACE inhibitors (but not ARBs) were associated with a significant lower risk for hospitalization among the Medicare group (HR, 0.61; *P* = .02) but not among the commercially insured group (HR, 2.14; *P* = .12).

A second study examined outcomes of 7933 individuals with hypertension who were hospitalized with COVID-19 (92% of these patients were Medicare Advantage enrollees). Of these, 14.2% died, 59.5% survived to discharge, and 26.3% underwent ongoing hospitalization. In propensity score–matched analyses, use of neither an ACE inhibitor (HR, 0.97; *P* = .74) nor an ARB (HR, 1.15; *P* = .15) was associated with risk of in-hospital mortality.

The researchers say their findings are consistent with prior evidence from randomized clinical trials suggesting a reduced risk for pneumonia with ACE inhibitors that is not observed with ARBs.

They also cite some preclinical evidence that they say suggests a possible protective role for ACE inhibitors in COVID-19: that ACE inhibitors, but not ARBs, are associated with the upregulation of ACE2 receptors, which modulate the local interactions of the renin-angiotensin-aldosterone system in the lung tissue.

"The presence of ACE2 receptors, therefore, exerts a protective effect against the development of acute lung injury in infections with SARS coronaviruses, which lead to dysregulation of these mechanisms and endothelial damage," they add.

"Further, our observations do not support theoretical concerns of adverse outcomes due to enhanced virulence of SARS coronaviruses due to overexpression of ACE2 receptors in cell cultures – an indirect binding site for these viruses."

The authors also note that their findings have "important implications" for four ongoing randomized trials of ACE inhibitors/ARBs in COVID-19, "as none of them align with the observations of our study."

They point out that of the four ongoing trials, three are testing the use of ACE inhibitors or ARBs in the treatment of hospitalized COVID-19 patients, and one is testing the use of a 10-day course of ARBs after a positive SARS-CoV-2 test to prevent hospitalization.

Experts Cautious

However, two cardiovascular experts who were asked to comment on this latest study for *Medscape Medical News* were not overly optimistic about the data.

Michael Weber, MD, professor of medicine at the State University of New York, said: "This report adds to the growing number of

observational studies that show varying effects of ACE inhibitors and ARBs in increasing or decreasing hospitalizations for COVID-19 and the likelihood of in-hospital mortality. Overall, this new report differs from others in the remarkable effects of insurance coverage: in particular, for ACE inhibitors, there was a 40% reduction in fatal events in Medicare patients but a twofold increase in patients using commercial insurance — albeit the test for heterogeneity when comparing the two groups did not quite reach statistical significance. "In essence, these authors are saying that ACE inhibitors are highly protective in patients aged 65 or older but bordering on harmful in patients aged below 65. I agree that it's worthwhile to check this finding in a prospective trial...but this hypothesis does seem to be a reach."

Weber noted that both ACE inhibitors and ARBs increase the level of the ACE2 enzyme to which the COVID-19 virus binds in the lungs. "The ACE inhibitors do so by inhibiting the enzyme's action and thus stimulate further enzyme production; the ARBs block the effects of angiotensin II, which results in high angiotensin II levels that also upregulate ACE2 production," he said.

"Perhaps the ACE inhibitors, by binding to the ACE enzyme, can in some way interfere with the enzyme's uptake of the COVID virus and thus provide some measure of clinical protection. This is possible, but why would this effect be apparent only in older people?"

John McMurray, MD, professor of medical cardiology at the University of Glasgow, added: "This looks like a subgroup of a subgroup type analysis based on small numbers of events — I think there were only 77 hospitalizations among the 722 patients treated with an ACE inhibitor, and the Medicare Advantage subgroup was only 581 of those 722 patients. "The hazard ratio had wide 95% CI [confidence interval] and a modest *P* value," Murray added. "So yes, interesting and hypothesis-generating, but not definitive."

New Meta-analysis

The new meta-analysis of all data so far available on ACE inhibitor and ARB use for patients with COVID-19 was published online in *Annals of Internal Medicine* on May 15.

The analysis is a living systematic review with ongoing literature surveillance and critical appraisal, which will be updated as new data become available. It included 14 observational studies.

The authors, led by Katherine Mackey, MD, VA Portland Health Care System, Oregon, conclude: "High-certainty evidence suggests that ACE-inhibitor or ARB use is not associated with more severe COVID-19 disease, and moderate certainty evidence suggested no association between use of these medications and positive SARS-CoV-2 test results among symptomatic patients. Whether these medications increase the risk for mild or asymptomatic disease or are beneficial in COVID-19 treatment remains uncertain."

In an accompanying editorial, William G. Kussmaul, MD, Drexel University College of Medicine, Philadelphia, Pennsylvania, says that initial fears that these drugs may be harmful for patients with COVID-19 now seem to have been unfounded.

"We now have reasonable reassurance that drugs that alter the renin angiotensin system do not pose substantial threats as either COVID-19 risk factors or severity multipliers," he writes.

MedRxiv. Published online May 19, 2020. Full text

Ann Intern Med 2020. Published online May 15, 202. Full text, Editorial

https://nyti.ms/3bVonrL

Elephants Really Can't Hold Their Liquor

Humans and other species have a gene mutation that lets them digest alcohol. In other species, it's missing.

By Rachel Nuwer

Humans are not the only animals that get drunk. Birds that gorge on fermented berries and sap are known to fall out of trees and crash into windows. Elk that overdo it with rotting apples get stuck in

trees. Moose wasted on overripe crab apples get tangled in swing sets, hammocks and even Christmas lights.

Elephants, though, are the animal kingdom's most well-known boozers. One scientific paper describes elephant trainers rewarding animals with beer and other alcoholic beverages, with one elephant in the 18th century said to have drunk 30 bottles of port a day. In 1974, a herd of 150 elephants in West Bengal, India, became intoxicated after breaking into a brewery, then went on a rampage that destroyed buildings and killed five people.

Despite these widespread reports, scientists have questioned whether animals — especially large ones such as elephants and elk — actually become inebriated. In 2006, researchers calculated that based on the amount of alcohol it takes to get a human drunk, a 6,600-pound elephant on a bender would have to quickly consume up to 27 liters of seven percent ethanol, the key ingredient in alcohol. Such a quantity of booze is unlikely to be obtained in the wild. Intoxicated wild elephants, the researchers concluded, must be a myth. As the lead author said at the time, "People just want to believe in drunken elephants."

***A herd of wild elephants was reportedly on a drunken rampage outside the village of Tundi, India, in 2006.*...Sasanka Sen/Associated Press**

If you are one who wanted to believe, a study published in April in Biology Letters might serve as your vindication. A team of scientists say that the earlier myth-busting researchers made a common mistake: They assumed that elephants would have to consume as much alcohol to get drunk as humans do. In fact, elephants are likely exceptional lightweights because they — and many other mammals — lack a key enzyme that quickly metabolizes ethanol. The findings highlight the need to consider species on an individual basis.

"You can't just assume that humans are just like every other mammal and the physiological abilities of all these mammals are comparable," said Mareike Janiak, a postdoctoral scholar in evolutionary anthropology at the University of Calgary and the lead author of the study. "Simply scaling up to body size doesn't account for differences that exist between different mammal species."

Humans, chimpanzees, bonobos and gorillas have an unusually high tolerance for alcohol because of a shared genetic mutation that allows them to metabolize ethanol 40 times faster than other primates. The mutation occurred around 10 million years ago, coinciding with an ancestral shift from arboreal to terrestrial living and, most likely, a diet richer in fallen, fermenting fruit on the forest floor.

To test whether other species independently evolved the same adaptation, Dr. Janiak and her colleagues searched the genomes of 85 mammals that eat a variety of foods and located the ethanol-metabolizing gene in 79 species. But they identified the same or similar mutation as humans in just six species — mostly those with a diet high in fruit and nectar, including flying foxes and aye-aye lemurs. But most other mammals did not possess the mutation, and in some species, including elephants, dogs and cows, the ethanol-metabolizing gene had lost all function.

"It was far more likely for animals that eat the leafy part of plants or for carnivores to lose the gene," said Amanda Melin, a molecular ecologist at the University of Calgary and a co-author of the study. "The takeaway is that diet is important in what we see happening in molecular evolution."

Some results were unexpected. Tree shrews, for example, drink "copious amounts" of fermented nectar with ethanol content

equivalent to weak beer, Dr. Melin said, but they never show signs of inebriation. Yet tree shews do not share the same enzyme-producing mutation as humans. This implies that "there's multiple, different ways to solve this problem," she said.

Nathaniel Dominy, a biological anthropologist at Dartmouth College who was not involved in the research, said the new paper "highlights the novel adaptations of humans by putting our metabolic proficiency in broader evolutionary context." He said it also "exemplifies the power of comparative biology" for teasing out the underlying function of specific genetic traits.

The elephant findings, in particular, are "interesting but confusing," said Chris Thouless, the head of research at Save the Elephants, a nonprofit in Kenya. Forest elephants today regularly seek and eat fruit, but their ancestors became grass eaters around eight million years ago. Evidence indicates they then switched to a mixed diet around one million years ago.

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"Maybe they lost the ability to efficiently metabolize alcohol, but either continued to have, or regained, a taste for and the ability to locate fruit," Dr. Thouless said. He compared it with people who have very low tolerance for alcohol but still desire and drink it.

While the new study reveals the means by which elephants and other mammals may become inebriated, it does not explicitly confirm the phenomena in nature. "The persistent myth of drunken elephants remains an open and tantalizing question, and a priority for future research," Dr. Dominy said.

https://bit.ly/2TzbUDQ

This Bionic Eye Is Better Than a Real One, Scientists Say

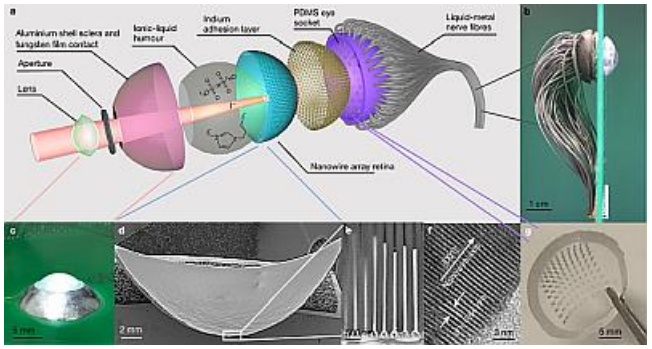
"A human user of the artificial eye will gain night vision capability."

Victor Tangermann

Researchers say they've created a proof-of-concept bionic eye that could surpass the sensitivity of a human one.

"In the future, we can use this for better vision prostheses and humanoid robotics," researcher Zhiyong Fan, at the Hong Kong University of Science and Technology, told *Science News*.

The eye, as detailed in a paper published in the prestigious journal *Nature* today, is in essence a three dimensional artificial retina that features a highly dense array of extremely light-sensitive nanowires.



a, Exploded view of EC-EYE. b, c, Side view (b) and top view (c) of a completed EC-EYE. d, Low-resolution cross-sectional SEM image of the hemispherical PAM/nanowires. e, Cross-sectional SEM images of nanowires in PAM. f, High-resolution transmission electron microscopy image of a single-crystalline perovskite nanowire. g, Photograph of the polydimethylsiloxane (PDMS) socket, which improves the alignment of the liquid-metal wires. **Back to article page Nature ISSN 1476-4687 (online)**

The team, led by Fan, lined a curved aluminum oxide membrane with tiny sensors made of perovskite, a light-sensitive material that's been used in solar cells.

Wires that mimic the brain's visual cortex relay the visual information gathered by these sensors to a computer for processing.

The nanowires are so sensitive they could surpass the optical wavelength range of the human eye, allowing it to respond to 800 nanometer wavelengths, the threshold between visual light and infrared radiation. That means it could see things in the dark when the human eye can no longer keep up. "A human user of the artificial eye will gain night vision capability," Fan told *Inverse*.

The researchers also claim the eye can react to changes in light faster than a human one, allowing it to adjust to changing conditions in a fraction of the time.

Each square centimeter of the artificial retina can hold about 460 million nanosize sensors, dwarfing the estimated 10 million cells in the human retina. This suggests that it could surpass the visual fidelity of the human eye.

Fan told *Inverse* that "we have not demonstrated the full potential in terms of resolution at this moment," promising that eventually "a user of our artificial eye will be able to see smaller objects and further distance."

Other researchers who were not involved in the project pointed out that plenty of work still has to be done to eventually be able to connect it to the human visual system, as *Scientific American* reports.

But some are hopeful.

"I think in about 10 years, we should see some very tangible practical applications of these bionic eyes," Hongrui Jiang, an electrical engineer at the University of Wisconsin–Madison who was not involved in the research, told *Scientific American*.

https://bit.ly/2LX7na2

Placentas from COVID-19-positive pregnant women show injury

Findings suggests abnormal blood flow between mothers, babies in utero

CHICAGO --- The placentas from 16 women who tested positive for COVID-19 while pregnant showed evidence of injury, according to pathological exams completed directly following birth, reports a new Northwestern Medicine study.

The type of injury seen in the placentas shows abnormal blood flow between the mothers and their babies in utero, pointing to a new complication of COVID-19. The findings, though early, could help inform how pregnant women should be clinically monitored during the pandemic.

The study was published today (May 22) in the journal *American Journal of Clinical Pathology*. It is the largest study to examine the health of placentas in women who tested positive for COVID-19.

"Most of these babies were delivered full-term after otherwise normal pregnancies, so you wouldn't expect to find anything wrong with the placentas, but this virus appears to be inducing some injury in the placenta," said senior author Dr. Jeffrey Goldstein, assistant professor of pathology at Northwestern University Feinberg School of Medicine and a Northwestern Medicine pathologist. "It doesn't appear to be inducing negative outcomes in live-born infants, based on our limited data, but it does validate the idea that women with COVID should be monitored more closely."

This increased monitoring might come in the form of non-stress tests, which examine how well the placenta is delivering oxygen, or growth ultrasounds, which measure if the baby is growing at a healthy rate, said co-author Dr. Emily Miller, assistant professor of obstetrics and gynecology at Feinberg and a Northwestern Medicine obstetrician.

"Not to paint a scary picture, but these findings worry me," Miller said. "I don't want to draw sweeping conclusions from a small study, but this preliminary glimpse into how COVID-19 might cause changes in the placenta carries some pretty significant implications for the health of a pregnancy. We must discuss whether we should change how we monitor pregnant women right now."

Previous research has found that children who were in utero during the 1918-19 flu pandemic, which is often compared to the current COVID-19 pandemic, have lifelong lower incomes and higher rates of cardiovascular disease. Flu doesn't cross the placenta, Goldstein said, so whatever is causing life-long problems in those people is most likely due to immune activity and injury to the placenta.

"Our study, and other studies like it, are trying to get on the ground floor for this exposure so we can think about what research questions we should be asking in these kids and what can or should we do now to mitigate these same types of outcomes," Goldstein said.

Fifteen patients delivered live infants in the third trimester, however one patient had a miscarriage in the second trimester. "That patient was asymptomatic, so we don't know whether the virus caused the miscarriage or it was unrelated," Goldstein said, "We are aware of four other cases of miscarriage with COVID. The other reported patients had symptoms and three of four had severe inflammation in the placenta. I'd like to see more before drawing any conclusions."

The placenta is the first organ to form in fetal development. It acts as the fetus' lungs, gut, kidneys and liver, taking oxygen and nutrients from the mother's blood stream and exchanging waste. The placenta also is responsible for many of the hormonal changes within the mother's body. Examining a woman's placenta allows a pathologist to follow a retroactive roadmap of a woman's pregnancy to learn what happened to the baby in utero or what could happen to both the mother and the infant after birth.

"The placenta acts like a ventilator for the fetus, and if it gets damaged, there can be dire outcomes," Miller said. "In this very limited study, these findings provide some signs that the ventilator might not work as well for as long as we'd like it to if the mother tests positive for SARS-CoV2."

The placentas in these patients had two common abnormalities: insufficient blood flow from the mother to the fetus with abnormal blood vessels called maternal vascular malperfusion (MVM) and blood clots in the placenta, called intervillous thrombi.

In normal cases of MVM, the mother's blood pressure is higher than normal. This condition is typically seen in women with preeclampsia or hypertension. Interestingly, only one of the 15 patients in this study had preeclampsia or hypertension.

"There is an emerging consensus that there are problems with coagulation and blood vessel injury in COVID-19 patients," Goldstein said. "Our finding support that there might be something clot-forming about coronavirus, and it's happening in the placenta."

The 16 women in the study delivered their babies at Northwestern Medicine Prentice Women's Hospital. All tested positive for COVID-19. Four patients came in with flu-like symptoms three to five weeks before delivery and tested positive for the virus. The remaining patients all tested positive when they came in to deliver. Five patients never developed symptoms, others were symptomatic at delivery.

Between 30 and 40 patients deliver at Prentice daily. The team began testing placentas of COVID-19-positive mothers in early April. Fourteen of the live-born infants in the study were born full term and with normal weights and Apgar scores. One live-born infant was premature.

"They were healthy, full-term, beautifully normal babies, but our findings indicate a lot of the blood flow was blocked off and many of the placentas were smaller than they should have been," Miller said. "Placentas get built with an enormous amount of redundancy. Even with only half of it working, babies are often completely fine. Still, while most babies will be fine, there's a risk that some pregnancies could be compromised."

In February, before the pandemic was known to have reached Chicago, Goldstein assembled his research team.

"If you get the flu and you're pregnant, we know nothing about what that looks like in your placenta, so I began thinking how we'd study this flu-like epidemic if it came through Chicago," Goldstein said. "We started setting things up and then lo and behold, the epidemic came here, so we were ready."

Other Northwestern co-authors include Elisheva D. Shanes, Leena B. Mithal and Hooman A. Azad.

https://wb.md/2WXflpE

Doctor Accused of More Than 200 Misdiagnoses Gives Up License

Doctor accused of misdiagnosing epilepsy in more than 200 children surrendered his medical license

Ed White

DETROIT (AP) — A Detroit-area doctor accused of misdiagnosing epilepsy in more than 200 children surrendered his medical license and agreed to pay a $5,000 penalty under a settlement accepted Wednesday by state regulators.

"A great day for patients that was long overdue," said attorney Brian McKeen, who has won two trials so far over Dr. Yasser Awaad's treatment of children.

A disciplinary panel at the Michigan Board of Medicine accepted the agreement during a meeting held by video conference. There was no immediate response from Awaad's attorney to a request for comment.

The attorney general's office filed a complaint against Awaad in 2018, years after he treated children as a pediatric neurologist at Oakwood Healthcare in Dearborn, which is now part of Beaumont Health.

"Between 1997 and 2007, (Awaad) misdiagnosed approximately 250 patients as suffering from epilepsy or seizure disorders, based on electroencephalograms that were either not performed or not interpreted properly," the complaint said. "Some of these patients were also misdiagnosed as having attention deficit disorder or other autistic spectrum conditions."

Children were given medication that was unnecessary and sometimes harmful, the complaint said, and their actual conditions weren't addressed.

Awaad agreed with regulators that the allegations could be treated as true to resolve the complaint. He said he has not actively practiced medicine in Michigan since 2007.

McKeen represents dozens of patients who have accused Awaad of malpractice. During one trial last year, he said the doctor was running a "gravy train of fraud" by repeatedly ordering expensive EEG tests.

Awaad's attorney told jurors that it was "outrageous and preposterous" to claim Awaad intentionally harmed Mariah Martinez when she was 9 years old. Harry Sherbrook said there was more to diagnosing epilepsy than reading EEGs.

The jury awarded more than $3 million to Martinez, although a judge reduced it to $846,000 because of state caps on malpractice claims.

In a second case in October, a jury awarded nearly $2.8 million to a former Awaad patient. That verdict will likely be reduced, too.

Awaad's agreement to give up his medical license was not his first encounter with regulators. A similar complaint over his epilepsy diagnoses was filed in 2011. He paid a $10,000 fine and agreed to have his work reviewed by another doctor for a period.

https://bit.ly/2A8fyO8

'Time is vision' after a stroke

New research from the University of Rochester, published in the journal Brain, may offer hope to stroke patients in regaining vision.

A person who has a stroke that causes vision loss is often told there is nothing she can do to improve or regain the vision she has lost.

The Rochester team found that survivors of occipital strokes--strokes that occur in the occipital lobe of the brain and affect the ability to see--may retain some visual capabilities immediately after the stroke, but these abilities diminish and eventually disappear permanently after approximately six months. By capitalizing on this

initial preserved vision, early vision training interventions can help stroke patients recover more of their vision loss than if training is administered after six months.

"One of our key findings, which has never been reported before, is that an occipital stroke that damages the visual cortex causes gradual degeneration of visual structures all the way back to the eyes," says Krystel Huxlin, the James V. Aquavella, MD Professor in Ophthalmology at the University of Rochester's Flaum Eye Institute.

The Rochester research team--including Elizabeth Saionz, a PhD candidate in Huxlin's lab and the first author of the paper; Duje Tadin, professor and chair of the Department of Brain and Cognitive Sciences; and Michael Melnick, a postdoctoral associate in Tadin and Huxlin's labs--additionally discovered that early intervention in the form of visual training appears to stop the gradual loss of visual processing that stroke victims may experience. Vision stroke rehabilitation remains a developing field, and previous studies and trials of experimental therapies have focused on patients with chronic vision loss--that is, patients who are more than six months post-stroke.

"Right now, the 'standard of care' for vision stroke patients is that they don't receive any targeted therapy to restore vision," Saionz says. "They might be offered therapy to help maximize use of their remaining vision or learn how to navigate the world with their new limited vision, but there are no treatments offered that can give them back any of the vision that they lost."

The new study compared chronic patients--those who were more than six-months post-stroke--with early subacute patients, who started training within the first three months after their stroke.

The researchers trained both groups of stroke patients using a computer-based device Huxlin developed. The training is like physical therapy for the visual system and involves a set of exercises that stimulates undamaged portions of the visual cortical system to use visual information. With repeated stimulation, these undamaged parts of the brain can learn to more effectively process visual information that is not filtered by the damaged primary visual cortex, partially restoring conscious visual sensations.

The researchers discovered that the subacute patients who underwent such vision training recovered global motion discrimination--the ability to determine the direction of motion in a noisy environment--as well as luminance detection--the ability to detect a spot of light--faster and much more efficiently than the chronic patients.

Overall, the group's findings suggest that individuals may maintain visual abilities early after a stroke, indicating they have preserved some sensory information processing that may temporarily circumvent the permanently damaged regions of the brain. Early visual training may therefore be critical both to prevent vision from degrading and to enhance restoration of any preserved perceptual abilities.

"For the first time, we can now conclusively say that just as for sensorimotor stroke, 'time is vision' after an occipital stroke," Huxlin says.

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Mysterious inflammatory syndrome tied to COVID-19 is showing up in adults in their early 20s

The syndrome doesn't just affect young children, as previously reported.

By Rachael Rettner - Senior Writer

A mysterious inflammatory syndrome tied to COVID-19 that has been reported in children is now also turning up in young adults in their early 20s, according to news reports.

Doctors have now diagnosed the syndrome in a 20-year-old in San Diego and a 25-year-old in Long Island, New York, according to

The Washington Post. Several additional cases have been reported in patients in their early 20s who are hospitalized at New York University's Langone Medical Center in New York City, the Post reported.

Symptoms of the syndrome — dubbed multisystem inflammatory syndrome in children (MIS-C) — can vary. But patients tend to have symptoms similar to those found in Kawasaki disease, a rare childhood illness that causes inflammation in blood vessel walls, and in serious cases can cause heart damage, Live Science previously reported. Symptoms can include fever, abdominal pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes and fatigue, according to the Centers for Disease Control and Prevention.

CLOSE

In young children, symptoms of the syndrome seem to more classically resemble Kawasaki disease, but teens and young adults appear to have more of an overwhelming inflammatory response involving their heart and other organs, the Post reported.

"The older ones have had a more severe course," Dr. Jennifer Lighter, a pediatric infectious diseases doctor at NYU Langone, told the Post.

There is concern that the syndrome may be underdiagnosed in adults, in part because many doctors outside of the pediatric setting have never seen cases of Kawasaki disease.

Doctors at Rady Children's Hospital in San Diego, where the 20-year-old patient was diagnosed, are now setting up a system for staff to screen adults for the illness, and they are talking with health officials to try to expand warnings about the syndrome to encompass young adults, the Post reported.

Adult internal medicine doctors need to be aware "that maybe this is coming their way," said Dr. Jane Burns, director of the Kawasaki Disease Clinic at Rady Children's Hospital, as reported by the Post.

Many patients with MIS-C have antibodies against the new coronavirus, rather than an active infection, which suggests that the syndrome may be the result of a delayed immune response to the virus.

So far, more than 20 states have reported cases of MIS-C, with total U.S. cases estimated to be several hundred, the Post reported. New York City alone has reported 89 confirmed cases, with 157 cases under investigation, NBC News 4 reported.

https://bit.ly/2ZATFBA

The Lancet: First human trial of COVID-19 vaccine finds it is safe and induces rapid immune response

Found to be safe, well-tolerated, and able to generate an immune response against SARS-CoV-2 in humans

The first COVID-19 vaccine to reach phase 1 clinical trial has been found to be safe, well-tolerated, and able to generate an immune response against SARS-CoV-2 in humans, according to new research published in *The Lancet*. The open-label trial in 108 healthy adults demonstrates promising results after 28 days--the final results will be evaluated in six months [1]. Further trials are needed to tell whether the immune response it elicits effectively protects against SARS-CoV-2 infection.

"These results represent an important milestone. The trial demonstrates that a single dose of the new adenovirus type 5 vectored COVID-19 (Ad5-nCoV) vaccine produces virus-specific antibodies and T cells in 14 days, making it a potential candidate for further investigation", says Professor Wei Chen from the Beijing Institute of Biotechnology in Beijing, China, who is responsible for the study. "However, these results should be interpreted cautiously. The challenges in the development of a COVD-19 vaccine are unprecedented, and the ability to trigger these immune responses does not necessarily indicate that the vaccine will protect humans from COVID-19. This result shows a

promising vision for the development of COVID-19 vaccines, but we are still a long way from this vaccine being available to all." [2]

The creation of an effective vaccine is seen as the long-term solution to controlling the COVID-19 pandemic. Currently, there are more than 100 candidate COVID-19 vaccines in development worldwide.

The new Ad5 vectored COVID-19 vaccine evaluated in this trial is the first to be tested in humans. It uses a weakened common cold virus (adenovirus, which infects human cells readily but is incapable of causing disease) to deliver genetic material that codes for the SARS-CoV-2 spike protein to the cells. These cells then produce the spike protein, and travel to the lymph nodes where the immune system creates antibodies that will recognize that spike protein and fight off the coronavirus.

The trial assessed the safety and ability to generate an immune response of different dosages of the new Ad5-nCoV vaccine in 108 healthy adults between the ages of 18 and 60 years who did not have SARS-CoV-2 infection. Volunteers were enrolled from one site in Wuhan, China, and assigned to receive either a single intramuscular injection of the new Ad5 vaccine at a low dose (5 × 1010 viral particles/0·5ml, 36 adults), middle dose (1×1011 viral particles/1.0ml, 36 adults), or high dose (1.5 x 1011 viral particles/1.5ml, 36 adults).

The researchers tested the volunteers' blood at regular intervals following vaccination to see whether the vaccine stimulated both arms of the immune system: the body's 'humoral response' (the part of the immune system that produces neutralising antibodies which can fight infection and could offer a level of immunity), and the body's cell-mediated arm (which depends on a group of T cells, rather than antibodies, to fight the virus). The ideal vaccine might generate both antibody and T cell responses to defend against SARS-CoV-2.

The vaccine candidate was well tolerated at all doses with no serious adverse events reported within 28 days of vaccination. Most adverse events were mild or moderate, with 83% (30/36) of those receiving low and middle doses of the vaccine and 75% (27/36) in the high dose group reporting at least one adverse reaction within 7 days of vaccination.

The most common adverse reactions were mild pain at the injection site reported in over half (54%, 58/108) of vaccine recipients, fever (46%, 50/108), fatigue (44%, 47/108), headache (39%, 42/108), and muscle pain (17%, 18/108). One participant given the higher dose vaccine reported severe fever along with severe symptoms of fatigue, shortness of breath, and muscle pain--however these adverse reactions persisted for less than 48 hours.

Within two weeks of vaccination, all dose levels of the vaccine triggered some level of immune response in the form of binding antibodies (that can bind to the coronavirus but do not necessarily attack it - low-dose group 16/36, 44%; medium dose 18/36, 50%; high dose 22/36, 61%), and some participants had detectable neutralising antibodies against SARS-CoV-2 (low-dose group 10/36, 28%; medium dose 11/36, 31%; high dose 15/36, 42%).

After 28 days, most participants had a four-fold increase in binding antibodies (35/36, 97% low-dose group; 34/36 (94%) middle-dose group, and 36/36, 100% in high-dose group), and half (18/36) of participants in the low- and middle-dose groups and three-quarters (27/36) of those in the high-dose group showed neutralising antibodies against SARS-CoV-2.

Importantly, the Ad5-nCoV vaccine also stimulated a rapid T cell response in the majority of volunteers, which was greater in those given the higher and middle doses of vaccine, with levels peaking at 14 days after vaccination (low-dose group (30/36; 83.3%), medium (35/36, 97.2%), and high-dose group (35/36, 97.2%) at 14 days).

Further analyses showed that 28 days after vaccination, the majority of recipients showed either a positive T cell response or had detectable neutralising antibodies against SARS-CoV-2 (low-dose group 28/36, 78%; medium-dose group 33/36, 92%; high-dose group 36/36, 100%).

However, the authors note that both the antibody and T-cell response could be reduced by high pre-existing immunity to adenovirus type 5 (the common cold virus vector/carrier)--in the study, 44%-56% of participants in the trial had high pre-existing immunity to adenovirus type 5, and had a less positive antibody and T-cell response to the vaccine.

"Our study found that pre-existing Ad5 immunity could slow down the rapid immune responses to SARS-CoV-2 and also lower the peaking level of the responses. Moreover, high pre-existing Ad5 immunity may also have a negative impact on the persistence of the vaccine-elicited immune responses", say Professor Feng-Cai Zhu from Jiangsu Provincial Center for Disease Control and Prevention in China who led the study.

The authors note that the main limitations of the trial are its small sample size, relatively short duration, and lack of randomised control group, which limits the ability to pick up rarer adverse reactions to the vaccine or provide robust evidence for its ability to generate an immune reaction. Further research will be needed before this trial vaccine becomes available to all.

A randomised, double-blinded, placebo-controlled phase 2 trial of the Ad5-nCoV vaccine has been initiated in Wuhan to determine whether the results can be replicated, and if there are any adverse events up to 6 months after vaccination, in 500 healthy adults--250 volunteers given a middle dose, 125 given a low dose, and 125 given a placebo as a control. For the first time, this will include participants over 60 years old, an important target population for the vaccine.

Peer-reviewed / Experimental study / People

NOTES TO EDITORS

The study was funded by National Key R&D Program of China, National Science and Technology Major Project, and CanSino Biologic. It was conducted by researchers from Beijing Institute of Biotechnology, Beijing, China; Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China; National Institute for Food and Drug Control, Beijing, China; Hubei Provincial Center for Disease Control and Prevention, Wuhan, China; State Key Laboratory of Pathogen and Biosecurity, Beijing, China; CanSino Biologics, Tianjin, China; Huazhong University of Science and Technology, Wuhan, China; and Shanghai Canming Medical Technology, Shanghai, China.

The labels have been added to this press release as part of a project run by the Academy of Medical Sciences seeking to improve the communication of evidence. For more information, please see: http://www.sciencemediacentre.org/wp-content/uploads/2018/01/AMS-press-release-labelling-system-GUIDANCE.pdf if you have any questions or feedback, please contact The Lancet press office pressoffice@lancet.com

[1] 'Open label' means both the participant and researcher know what the treatment that the participants are receiving. Non-randomised studies are often done to check if a treatment is safe and effective.

[2] Quotes direct from authors and cannot be found in the text of the Article.

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For access to the Article and Comment, please see: http://www.thelancet-press.com/embargo/covidvaccine.pdf

For access to the Appendix, please see: http://www.thelancet-press.com/embargo/covidvaccineAPPX.pdf

https://bit.ly/3c2bEDo

Malaria Mosquitoes Are Biting before Bed-Net Time

Mosquitoes that like to bite at night are being thwarted by bed nets, leading to the rise of populations that prefer to bite when the nets are not up yet.

By Jason G. Goldman

Listen

More than 200 million people get malaria each year. And about half a million die—mostly in Africa, many of them children. And those staggering numbers are an improvement. Malaria deaths have been cut in half since 2000. In many places, a remarkably simple tool has

led the fight: bed nets treated with a mild insecticide that stop mosquitoes from biting people in their sleep.

Both people and mosquitoes are pawns in the malaria transmission cycle. If an infected person gets bitten by a mosquito, the parasite gets picked up along within the blood meal. That mosquito can then transfer the parasite to the next person it bites. Bed nets help stop mosquitoes from easy attacks on motionless sleepers. But now some mosquitoes seem to be giving up the night shift.

"Malaria mosquitos in Africa tend to shift their biting behavior."

Entomologist Eunho Suh from Penn State University's Center for Infectious Disease Dynamics.

"Normally they tend to bite people during the night, but because of extensive use of bed nets, these mosquitoes started biting in the early evening or in the morning."

Suh and his team wanted to know whether observed change in biting time had any impact on malaria transmission. Back in the lab, they presented *Anopheles* mosquitoes with the opportunity to feed on blood at 6 P.M., at midnight and at 6 A.M. When the laboratory was kept at an even 80 degrees Fahrenheit, evening and morning biters were no more or less likely to become infectious than the midnight biters.

But in the real world of the warm and humid tropics, nighttime is slightly cooler than daytime. And when the researchers introduced that temperature variation, the evening biters were a lot more likely to have potent malaria parasites. The results are in the journal *Nature Ecology & Evolution*. [Eunho Suh et al., The influence of feeding behaviour and temperature on the capacity of mosquitoes to transmit malaria]

"Not all mosquito bites are equal. So mosquitoes biting in the evening can have the highest transmission potential, compared to mosquitoes biting at midnight or the morning."

Suh thinks that the difference in the likelihood of mosquitoes becoming infectious has to do with the way that the malaria parasite matures. The parasites have a tougher time developing when mosquitoes are too warm. But if a mosquito picks up the parasites from blood at around dusk, those parasites have more hours of cooler nighttime temps to complete their development.

Next, Suh wants to conduct a similar study of wild mosquitoes and wild malaria parasites in Africa to see if the results from his lab mosquitoes hold up.

Either way, bed nets will remain an important tool. But understanding the enemy's behavior is always crucial information in any battle.

https://bit.ly/2yArms0

Engineers Successfully Test New Chip With Download Speeds of 44.2 Terabits Per Second

Could one day replace existing internet infrastructure to hit crazy new highs in download speeds

Mike Mcrae

A tiny device called a micro-comb could one day replace existing internet infrastructure to hit crazy new highs in download speeds, providing millions with ample data at the same time even during the busiest periods.

(Monash University)

The lightweight technology has recently been put to the test in a field trial that measured data rates of an astonishing 44.2 terabits per second, all emitted from a single light source.

The micro-comb chips themselves aren't exactly new, having been invented around a decade ago. But with rising pressure on our data highways, the technology is now showing promise as a way to slim down and speed up the technology behind our internet.

"It is truly exciting to see their capability in ultra-high bandwidth fibre optic telecommunications coming to fruition," says David Moss, Director of the Optical Sciences Centre at Swinburne University.

"This work represents a world-record for bandwidth down a single optical fibre from a single chip source, and represents an enormous breakthrough for part of the network which does the heaviest lifting."

Engineers from Monash University, Swinburne University, and RMIT in Australia claim a significant benefit of the chip is its ability to make the most of existing infrastructure to meet the demands we can expect in coming years.

The development of Australia's own copper-based, multi-technology-mix national broadband network (NBN) has come under heavy criticism since the government's decision in 2013 to not run optical fibre directly to people's houses.

It was a questionable call that many felt failed to future-proof the internet against rising demands, a prediction that has only been reinforced by the pandemic crisis that's escalated our data consumption habits, as we try to squeeze countless Zoom meetings and TV show episodes through networks of copper and optical fibre.

There's a pressing concern that current systems will struggle in the years to come. Replacing highways of ageing cables to keep up with our needs is an expensive and time-demanding exercise that no doubt will be left up to future generations to figure out.

Meanwhile, there are other components that can be upgraded to help improve the flow of traffic. One of those is the way we currently generate the frequencies of light that carry the bits and bytes down the cables into our computers and smart devices.

Lasers shining at different frequencies can create a multitude of 'channels' to cram information into the tiny refracting tubes. Depending on the way the light is spaced, we can shine as many as 80 channels into the network for all our data needs.

This innovative new micro-comb chip could be set to replace existing methods for creating all of those channels, exchanging 80 separate lasers for a single crystal waveform generator that can be tuned to shape a rainbow of light waves.

On paper, it looks like a great idea. But to make sure their theory was sound, the researchers connected a prototype of the device to more than 76 kilometres (47 miles) of 'dark' optic cable run between two Melbourne university campuses.

The team found they could max out the amount of data for each channel, demonstrating a potential top speed of 44.2 terabits per second from the device. Under ideal conditions with the right system, that would theoretically allow you to download 1,000 movies in a single second. All in high definition!

The reality might not be quite as shiny as downloading all of Netflix in a blink, but with other potential improvements to internet technology on the horizon, even moderate jumps of several terabits per second over short distances are improvements worth paying attention to.

"And it's not just Netflix we're talking about here – it's the broader scale of what we use our communication networks for," says Monash University computer systems engineer Bill Corcoran.

"This data can be used for self-driving cars and future transportation and it can help the medicine, education, finance and e-commerce industries, as well as enable us to read with our grandchildren from kilometres away."

If all goes well, data centres could be using these chips to connect to one another for faster communications.

Maybe in a few years we might all say goodbye to transmitters that shunt data at a paltry few hundred gigabytes per second. Not just in Australia, but around the world.

https://wb.md/3efVHep

'Clear Signature' of ALS Found in Children's Teeth

Adults who develop amyotrophic lateral sclerosis (ALS) metabolize metals differently than those who do not develop the neurodegenerative disease, and this shows up in teeth during childhood, new research suggests.

Megan Brooks

Investigators found increased uptake of a mixture of metals — including chromium, manganese, nickel, tin, and zinc — in the teeth of those who developed ALS.

"This study shows that metal dysregulation during specific periods in childhood and early adolescence is linked with the decades-later onset of ALS," senior author Manish Arora, PhD, MPH, vice chair, environmental medicine and public health, Icahn School of Medicine at Mount Sinai, New York City, told *Medscape Medical News.*

"This is the first study to show a clear signature at birth and within the first decade of life, well before any clinical signs or symptoms of the disease," he added in a news release.

The study was published online May 21 in *Annals of Clinical and Translational Neurology*.

Dysregulated Metal Uptake

ALS typically manifests in individuals in their 50s or 60s. Deficiencies and an excess of essential elements and toxic metals are implicated in the disease, but the age when metal dysregulation appears is unknown.

The Mount Sinai team, along with colleagues at the University of Michigan in Ann Arbor, determined that metal uptake is dysregulated during childhood in adults diagnosed with ALS.

For the study, the investigators used laser ablation-inductively coupled plasma-mass spectrometry to map data of metal uptake using biomarkers in teeth from autopsies or dental extractions from 36 ALS patients and 31 controls without ALS.

They found that metal levels were higher in the ALS group compared with controls.

Specifically, in patients with ALS, they found that chromium uptake increased after age 10, whereas manganese was significantly higher from birth until approximately 6 years and it was significantly lower between age 12 and 15 years.

Nickel and tin showed discrete windows of increased uptake in the ALS group, from age 6 to 10 years for nickel and from birth to age 2 1/2 for tin. Zinc levels were significantly higher throughout the study period.

Individuals with ALS also showed an increasing trend for copper uptake between birth and 10 years and for lead from age 12 to 15 years, and a decreasing trend for lithium from birth to 15 years.

At the point of maximal difference in metal levels, compared with controls, ALS patients had higher uptake by 1.49 times for chromium (95% confidence interval [CI], 1.11 - 1.82; at 15 years), 1.82 times for manganese (95% CI, 1.34 - 2.46; at birth), 1.65 times for nickel (95% CI, 1.22 - 2.01; at 8 years), 2.46 times for tin (95% CI, 1.65 - 3.30; at 2 years) and 2.46 times for zinc (95% CI, 1.49 - 3.67; at 6 years).

The markers of metal uptake dysregulation were also found in teeth from an ALS mouse model where researchers also found differences in the distribution of metals in the brains of ALS mice compared with control mice.

"This is a small study and much more work has to be done, but the general direction we are taking is very much toward clinical application," Arora told *Medscape Medical News*. "What's exciting is that we are looking at biological pathways that we could potentially modify with drug development," he said.

Solid Research

Commenting on the study for *Medscape Medical News*, Anthony Geraci, MD, director of neuromuscular medicine at Northwell Health in Great Neck, New York, noted the "scientific rigor of this study is solid and was well-conducted."

The findings, he added, are interesting in that they are among the first to identify potential neuronal abnormalities that may occur early in life and lead to subsequent ALS.

"Metal uptake is an essential function of most cells of the human body and neurons of the central and peripheral nervous systems, which are the cells that degenerate and die, leading to ALS," explained Geraci, who was not involved with the study.

"Metal is crucial for formation of critical metalloproteinase and DNA regulation and as cofactors in many enzymatic reactions within the cell. Caution, however, should be applied as the results of this study do not establish a causative link between altered metal uptake and later expression of ALS," he added.

However, Geraci said these results are "in line with more recent theories that implicate an abnormal and imbalanced formation of excitatory and inhibitory connections in the human brain during embryogenesis, with the result of a slightly abnormal cell-signaling mechanism between neurons that, over the span of one's life, may lead to the hyperexcitability and abnormal calcium flux into neurons that die during the course of ALS."

"More research along these lines will hopefully begin to unlock the earliest origins and genetic bases for the development later in life of degenerative diseases such as ALS," Geraci added. "The hope is that earlier identification of persons with ALS may one day lead to early intervention and prevention of the devastating manifestations of this disease."

The study was funded in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institutes of Environmental Health Sciences. Arora and Geraci have disclosed no relevant financial relationships.

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https://bit.ly/3d1xvMO

Results from the remdesivir COVID-19 trial are out, and it's good news

Recovery time was shortened from 15 to 11 days.

Jonathan M. Gitlin

On Friday, some good news in the fight against SARS-CoV-2 was published in The New England Journal of Medicine. The antiviral drug remdesivir—originally developed as a potential treatment for Ebola—was shown to shorten recovery time for patients infected with the coronavirus. In late April, early results from this phase 3 clinical trial suggested that remdesivir might be of value in treating COVID-19 patients—this new paper confirms that. It's not a cure, but the drug shortened the recovery time from an average of 15 days to 11 days.

The trial involved 1,059 COVID-19 patients across 60 different sites in the United States, Europe, and Asia. Five hundred and thirty-eight patients were treated with a 10-day course of remdesivir; the other 521 patients were given a course of placebo on the same schedule. The patients were assessed daily, both to determine the severity of their symptoms as well as any side effects that could be caused by the drug, which interferes with the the virus' ability to copy its RNA.

What was this trial looking at?

The main thing being measured in this study was how long a patient took to recover, using an eight-point clinical scale that ranged from "not hospitalized," through increasing levels of care required all the way up to "death." Secondary outcomes for the trial looked at mortality at two and four weeks after treatment began, as well as any serious side effects that occurred during the trial.

There had been some controversy about the trial because when it started in February 2020, the primary outcome measurement was how well a patient was doing on day 15. However, in late March,

the trial's statisticians changed that to a secondary outcome, replacing it with the outcome described above. But these statisticians had no access to the data showing which participants were receiving the drug and which the placebo, nor any knowledge of the outcome data. The tweak to the study's parameters happened because of a growing awareness by scientists during those few weeks that COVID-19 was a more protracted disease than first thought, and therefore it made sense to study recovery over 28 days, not 15.

In late April, it was time to look at the initial results of the trial. And these results showed enough of a clinical benefit from remdesivir that the researchers had an ethical obligation to share their initial findings with the broader medical community. This also meant that patients receiving the placebo could be given the drug.

11 days < 15 days

Overall, treatment with remdesivir shortened a patient's time to recovery compared to the placebo group, from an average of 15 days to 11 days. Improvements occurred whether or not the patient was receiving supplemental oxygen. What's more, the data lays to rest any worries that remdesivir has to be given very early after the onset of symptoms. In fact, those participants who entered the trial more than 10 days after the onset of symptoms actually showed a better response to remdesivir than those who started being treated during the first 10 days of being symptomatic.

The trial's main secondary outcome—how a participant was doing on day 15—also showed that remdesivir was significantly better than placebo. And the total number of deaths was lower in the remdesivir group (21 versus 28) at this point, although that difference was not statistically significant. (An analysis of mortality at day 28 is still ongoing, given that enrollment in the study only ended in late April.)

The researchers note that remdesivir treatment is unlikely to be sufficient on its own given that it has, at best, a moderate impact on mortality, so studies that combine the drug treatment with other therapies should be explored. But in comparison to another recent study on the effect of hydroxychlorquine on COVID-19—which suggests that drug causes a marked increase in death—this work should definitely be considered a success.

The New England Journal of Medicine, 2020. DOI: 10.1056/NEJMoa2007764 (About DOIs).

https://bit.ly/3qnsGPN

This Human Brain Tissue Survived Intact For 2,600 Years, And We May Finally Know How

Researchers finally have clues explaining this remarkable instance of preservation

Mike Mcrae

Thousands of years ago, near what is today the British village of Heslington, a man's body started to decompose. Flesh and organs became mud. Hair turned to dust. In the end, bones remained, and, mysteriously, a small piece of his brain.

After months of patiently investigating the tissue's proteins, an international team of researchers finally has clues explaining this remarkable instance of preservation, and it could help us better understand how healthy (and unhealthy) brains actually work.

The 2008 discovery of the Heslington brain – one of the oldest specimens of human neural tissue ever to be uncovered in the UK – left researchers with a challenging puzzle to solve.

Within moments of a typical death, brain tissue starts to decompose. Compared with other body parts, this decay is especially rapid, with various proteins going to work demolishing cellular infrastructure.

So when archaeologists looked inside a mud-caked skull pulled from an Iron Age dig site, they were understandably shocked to see

the withered remains of what looked like a chunk of recognisable human brain.

According to carbon dating, the middle-aged man breathed his last breath somewhere between 673 and 482 BCE, most likely as the result of a fractured spine – the kind you get after a hanging.

Exactly who he was, or why he died, probably won't ever be known. Sometime after his speculated execution, though, the victim's severed head was thrown into a pit, where it was encased in a fine grain sediment.

Soft tissues can often be preserved if they're desiccated, frozen, or kept in an anaerobic, acidic environment.

What's especially strange in the case of the Heslington skull is the lack of preservation of any other part of the body, including hair. For all appearances, the firm, tofu-like material looks like a caramelised chunk of human cerebral cortex, only it's 80 percent smaller than an adult human brain.

***The Heslington brain.** (Dr Axel Petzold)*

To work out what made the remaining organic material so special, researchers took a closer look at the nature of its proteins.

Unlike most organs, the brain needs to be well supported on a cellular level to operate, maintaining connections within the complex weave of neurons and their long bodies.

A matrix of intermediate filaments (IFs) performs this task in living brains, and it seems under the right circumstances, they can retain some kind of integrity long after the cells have been reduced to molecular ashes.

We already know a fair bit about these IFs based on various pathological studies. Different cell types have their own types of filament, and this specificity has attracted research for uncovering biomarkers for neurological diseases.

In the case of the Heslington brain, microscopy revealed weaves of IFs that resembled the long threads of axons making up a living brain, only shorter and narrower, while antibody markers matching axon proteins confirmed they once housed the long neuron tails.

Further analysis with specific antibody markers revealed a disproportionate amount of neural structures belonging to 'helper' cells such as astrocytes, with fewer proteins marking out thinking grey matter tissue.

Determining why these particular astrocyte IFs in particular didn't follow the usual path of decay was never going to be simple.

There were no signs of the preserving tannins often seen in British bog bodies, and while the specimen's pH was towards the lower end, the researchers weren't confident they could use it to estimate the acidity of the body's grave.

What's more, proteins that stick around at relatively warm temperatures tend to form stable structures, and stable proteins don't unfold as easily as unstable ones.

So over the course of a year, the researchers patiently measured the slow unwinding and breakdown of proteins in a modern specimen of neural tissue and compared it with the decay within the Heslington brain.

The results invited speculation over a chemical that blocks destructive enzymes called proteases in the months following death, allowing the proteins to coalesce into stable aggregates that could persist at warmer temperatures.

"Combined, the data suggest that the proteases of the ancient brain might have been inhibited by an unknown compound which had diffused from the outside of the brain to the deeper structures," they write in their report.

What seems clear is that there was nothing particularly special about this poor Iron Age fellow's brain. Rather, something in the environment could have inhibited the chemical processes that

would ordinarily break down the protein filaments responsible for supporting the brain's 'white matter' astrocytes, at least long enough for it to clump into a more robust form.

Of course, with only this incredibly unique sample to study, it's hard to draw firm conclusions. But even if the proposed 'unknown blocker' turns out to be a red herring, research on the way that IFs form stable aggregates could inform models explaining how destructive plaques form in our brain.

And with possible scraps of protein being found in fossils from time to time, it would be good to have a sound understanding of how they might 'unfold' to deduce their original structures.

The strange brain from Heslington still has a few things to teach us yet. This research was published in *Interface*.

https://bit.ly/2A2PKTo

Fatal Lyme carditis in a 37-year-old man shows need for awareness of unusual symptoms

Physicians and the public should be aware of its different manifestations

Lyme disease can have unusual presentations. Physicians and the public should be aware of its different manifestations, as people spend more time outside in the warmer weather and as the areas in Canada where the black legged tick is found expand. Three articles in *CMAJ* (*Canadian Medical Association Journal*), whichdescribe a fatal case in a 37-year-old man, atypical skin lesions and heart abnormalities in a 56-year-old woman and severe neurological symptoms in a 4-year-old boy, illustrate the diversity in clinical presentations of Lyme disease.

Lyme disease can affect the heart (known as Lyme carditis), which can result in serious heart rhythm abnormalities in a small group of people. Clinicians should be aware of the possibility of Lyme carditis in people presenting with atrioventricular heart block, especially in areas where Lyme disease is endemic. Patients may have had a rash. Early treatment with antibiotics is recommended to avoid complications, even before a diagnosis is confirmed.

A fatal case of Lyme disease in a previously healthy 37-year-old man illustrates the challenges of diagnosing Lyme disease in the absence of classic symptoms.

http://www.cmaj.ca/lookup/doi/10.1503/cmaj.191194

The patient originally presented to his family doctor with flu-like symptoms, including fever, sore throat, nasal congestion and migratory joint pain. Several weeks earlier, he had been in contact with ticks but didn't recall removing one. His physician suspected a viral infection, and the patient's symptoms resolved.

Weeks later, he developed heart palpitations, shortness of breath and chest discomfort for which he was sent to the emergency department. Lyme disease was suspected as electrocardiography (ECG) showed complete heart block. He was admitted to hospital and started on treatment for Lyme carditis, but his condition worsened quickly. Clinicians were unable to reverse the course of illness and he died. Serology results confirmed Lyme disease, and an autopsy showed signs of Lyme carditis.

"The diagnosis of Lyme carditis is based on clinical suspicion and serology consistent with acute Lyme disease," writes Dr. Milena Semproni, Infectious Diseases fellow at the University of Manitoba and Winnipeg Regional Health Authority, Winnipeg, Manitoba, with coauthors. "Unfortunately, diagnosis can be delayed while serology is being processed, and clinical suspicion should guide empiric treatment. Given that the early diagnosis is clinical, cases may be overlooked by clinicians, especially as Lyme disease moves into new geographic areas."

In suspected cases of Lyme carditis, patients should have an urgent ECG performed and be started on antibiotics without waiting for serologic confirmation.

The authors note that serious heart rhythm abnormalities and sudden cardiac death can occur in a small group of patients, although it is uncommon. In the 10 other North American cases of sudden cardiac death attributed to Lyme carditis described in the literature, 8 patients were male, and the cases occurred between June and November, when ticks are active.

A reflection written by the man's sister, with a video testimonial, https://youtu.be/lz7e29CewE8, describes the family's initial concern that this was Lyme disease, the heartbreak caused by his death and their hope for increased awareness and understanding of the disease.

Read a related article about a patient with a large red rash (erythema migrans), aches and chills who, after a second visit for heart palpitations, was found to have Lyme carditis. The patient recovered with antibiotic treatment.

http://www.cmaj.ca/lookup/doi/10.1503/cmaj.191660

"Given that most conduction abnormalities caused by Lyme carditis resolve with appropriate antibiotic therapy, recognition of atypical dermatologic presentations in the context of Lyme carditis prevents unnecessary permanent pacemaker implantation in these young and otherwise healthy individuals," writes Dr. Adrian Baranchuk, Department of Medicine, Queen's University, Kingston, with coauthors.

While the bull's eye rash is usually considered a feature of Lyme disease, in some cases, the rash doesn't follow the usual pattern.

A third article describes a 4-year-old boy who presented to hospital with fever, vomiting, malaise, ataxia and aphasia. The article describes the differential diagnosis and investigations, which eventually led to a diagnosis of Lyme disease (neuroborreliosis). The boy recovered fully with antibiotic treatment.

http://www.cmaj.ca/lookup/doi/10.1503/cmaj.191279