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Clues to how birds migrate using Earth's magnetic field

The mystery of how birds migrate long distances over land and sea is a step closer to being cracked.

By Helen Briggs

By studying robins, scientists have found clues to how birds sense the Earth's magnetic field.

Just as you might reach for a magnetic compass to find which way is north or south, birds are thought to have an in-built "living compass". A chemical in the eye that is sensitive to magnetism could be proof of this theory, according to a new study.

Peter Hore, professor of chemistry at the University of Oxford, said it could be that birds can "see" the Earth's magnetic field, although we don't know that for sure. "We think we may have identified the molecule that allows small migratory songbirds to detect the direction of the Earth's magnetic field, which they undoubtedly can do, and use that information to help them navigate when they migrate thousands of kilometres," he told BBC News.

For decades, scientists have been investigating how animals such as birds, sea turtles, fish and insects sense the Earth's magnetic field and use it to find their way.

The European robin is a stalwart of studies into the in-built "living compass" birds may use to orient themselves using the Earth's magnetic field. One chemical contender is a molecule in the retina of the eye known as a cryptochrome.

The Oxford team studied a purified form of the molecule in the lab to see whether it was fit for purpose as a magnetic sensor. They found it had the ability to form pairs of "radicals" that have high magnetic sensitivity. A radical is an atom or molecule that is highly chemically reactive.

Prof Hore said the mechanism they have been investigating involves magnetically-sensitive chemical reactions initiated by light inside the bird's eyes - in their retinas, to be precise. "It looks possible - and I would put it no stronger than that at the moment - that these highly-specialised chemical reactions could give the bird information about the direction of the Earth's magnetic field and in that way constitute a magnetic compass," he explained.

It's thought that light striking the retina causes electrons to move within the cryptochrome molecule, triggering the production of a pair of short-lived high energy radicals, which act like microscopic magnets.

The scientists caution that there is more work to do before they can be sure of the correct mechanism and the correct molecule. But they're heartened by the fact that the molecule is more magnetically-sensitive in robins than in birds such as chickens, that don't migrate.

The robin is a familiar sight in many UK gardens, with most spending the winter in Britain. But some robins do migrate, covering more than a hundred miles a night on migrations to warmer climes from Europe, Scandinavia and Russia.

The research is published in the journal Nature.

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Tasmanian devils devastate penguin population on Australian island

A project to preserve endangered Tasmanian devils on a small island has backfired after the predators killed seabirds in large numbers, a conservation group says.

A small number of devils were shipped to Maria Island east of Tasmania, Australia, in 2012.

The move aimed to protect the mammals from a deadly facial cancer that had driven them towards extinction. The devils have recovered since, but the island project has come at a cost.

The introduction of the devils to the island has had "a catastrophic impact on one or more bird species", according to BirdLife

Tasmania, a local conservation organisation.

Citing a government survey, BirdLife Tasmania said a population of little penguins that numbered 3,000 breeding pairs in 2012 had disappeared from the island.

The Tasmanian devil is classified as endangered

"Losing 3,000 pairs of penguins from an island that is a national park that should be a refuge for this species basically is a major blow," said Dr Eric Woehler, a researcher for the group.

Dr Woehler said the outcome was no surprise given what research shows about the introduction of mammals to oceanic islands.

In 2011, a report by the Tasmanian Department of Primary Industries, Parks, Water and Environment suggested the introduction of devils would have "a negative impact on little penguin and shearwater colonies on Maria Island".

Last year, a paper published in the Biological Conservation journal said the devils had "eliminated" a colony of shearwater, a species of sea bird.

"It's very clear that the devils have had a catastrophic ecological impact on the bird fauna on Maria Island," Dr Woehler said.

Tasmanian devils at a glance:

- ***The Tasmanian devil is the world's largest surviving carnivorous marsupial, a type of mammal***
- ***They can live for more than five years in the wild, if they avoid catching cancer***
- ***Males weigh up to 12kg, females up to 8kg***
- ***Hearing is considered to be their strongest sense***
- ***Devils have at least 11 distinct vocal calls***
- ***They were given their name in 1803 when sailors reported "unearthly" calls***

The mammals were moved to the island under the Save the Tasmanian Devil Program (STDP), a joint initiative of the Australian and Tasmanian governments. Tasmanian devils are classified as an endangered species by the IUCN Red List, which keeps a database on the conservation status of animals.

But Dr Woehler said their numbers had recovered in Tasmania and on the Australian mainland, where devils were born for the first time in thousands of years last month.

Given this, Dr Woehler said removing the mammals from Maria Island would "not have any adverse consequences for the devil".

A Tasmanian government spokesperson said the programme would "continue to evolve in line with new knowledge in science and emerging priorities".

However, the spokesperson said, "Maria Island remains an important part of the broader devil programme to help restore and maintain an enduring and resilient wild devil population in Tasmania."

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When an Eel Climbs a Ramp to Eat Squid From a Clamp, That's a Moray

Moray eels can hunt on land, and footage from a recent study highlights how they accomplish this feat with a sneaky second set of jaws.

By Sabrina Imbler

In the video, forceps nudge a piece of squid that sits on a ramp as an offering. Suddenly, a snowflake moray eel named Qani heaves its muscled bucatini of a body out of the water and onto the ramp. It opens its mouth and bites the squid. The eel pauses a moment, opens its mouth again and, as if its tongue were a conveyor belt, sucks the squid even deeper into its mouth using a secret second set of jaws in its throat.

This particular eel *mukbang*, to Rita S. Mehta, an evolutionary biologist at the University of California, Santa Cruz, was cinematic

gold: footage that showed the bite, the prey transport with secondary jaws and the swallow. Her team had taped loads of footage of the eels feeding on the ramp, but none that showed the act from beginning to end.

Dr. Mehta first described the moray eel's second set of choppers, known as pharyngeal jaws, in 2007. When a moray hunts, it seizes its prey with the teeth of its outer jaw, and then its pharyngeal jaws leap forward out of the throat and into the mouth to grasp the prey and drag it deeper into the eel's body.

Now, Dr. Mehta has described how snowflake eels and other morays use their pharyngeal jaws to feed just as effectively on land as in water, according to a study published this month in The Journal of Experimental Biology.

Like many other fish, morays will eventually dry out if they leave water for too long. But Dr. Mehta and her colleagues cite a study from 1979 that suggests a moray's outermost layer of skin contains certain mucus glands that may make these eels more resilient to time spent on land.

And morays climbing out of water came as no surprise to some observers. Lana Sinapayen, an artificial life researcher who grew up in the Caribbean island of Martinique, said local fishermen often caught morays by placing squids on the shore and waiting for the eels to arrive. "You only need a solid stick to take your pick," she wrote in an email. Dr. Sinapayen was not involved in the research but wanted to emphasize that many local people have long known that morays can hunt on land.

Such behavior has also long been reflected in scientific studies. One paper from 1971 describes a moray that clambered into the same tide pool to hunt for five days straight.

When Dani Rabaiotti, an environmental scientist based in London, volunteered at an aquarium as a teenager, she met a moray eel who knew how to slither onto a ledge and wait to be hand-fed. "He'd learned it was easier than hanging out in the water with all the other hungry animals," she said.

Dr. Mehta had also seen morays hunting on land — snagging land crabs on a beach in Bali — but the real question of her research was what the eels did with their prey after they bit down. Did the eels have to return to the water? Or could they swallow on land?

"Fish are mostly suction feeders and catch prey by sucking water in the mouth," said Peter Wainwright, a fish biomechanics expert at the University of California, Davis, who has previously worked with Dr. Mehta but was not involved with the new research. He added that "morays have evolved away from suction feeding."

In 2014, Dr. Mehta decided to train a small cohort of eels to feed on land and to film them in the act. She sourced snowflake moray eels from an aquarium wholesaler, and two of her former graduate students, Benjamin Higgins and Jacob Harrison, designed and installed a sand-covered Plexiglas ramp in each eel tank.

Over six years, Dr. Mehta and a rotating cast of students trained seven eels to feed on the ramp. By the end of the project, Kyle Donohoe, Dr. Mehta's former lab technician and a co-author on the study, had developed a rigid ramp regimen for the eels.

Mr. Donohoe, who once worked in a lab where he trained seals and sea lions, proved a wildly effective trainer. As it turns out, training an eel is much like training a seal.

"Consistent feeding, increasing chances of reinforcement and patience," Mr. Donohoe said. He trained Qani to wiggle farther and farther up the ramp and feed from forceps in just three weeks — the fastest of any eel in the study.

Another eel, named Benjen, joined Dr. Mehta's lab early on. Benjen, who was nearly twice as long as Qani and the largest eel in the study, eventually refused to climb the ramp for the uniformly measured 1.1-inch pieces of squid that all of the other trained eels received. The mammoth moray would ascend the ramp only for

chunks of squid so large and disproportionate to the eel's body that one of the paper's reviewers requested Benjen be stricken from the statistical analysis of the paper.

"But he's the star of the lab," Dr. Mehta said.

In Dr. Mehta's eyes, one unexpected insight of the experiment was the resilience of eel memory. School breaks and holidays often interrupted eel training, but still, Benjen remembered the ramp. In the future, Dr. Mehta hopes a student will come along who wants to teach Benjen new tasks. He continues to live in the lab, where he still undulates, uninvited, onto the ramp, awaiting big squid.

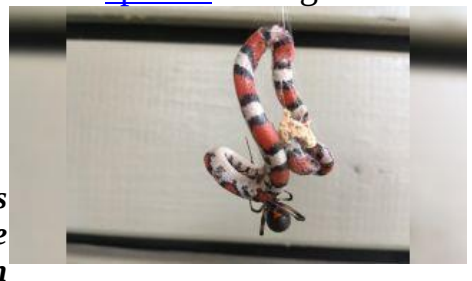
https://bit.ly/3jtubAf

These spiders take down snakes hundreds of times their size

Venomous spiders prey upon snakes many times their size, a new study finds — and often emerge victorious against snakes as venomous as they are.

By Stephanie Pappas - Live Science Contributor

The study researchers found 319 records of spiders killing and feasting upon snakes, 297 of which were naturally occurring events in the wild. (The remaining 22 were staged in captivity.)



A black widow spider (Latrodectus geometricus) enjoys a meal of juvenile scarlet snake (Cemophora coccinea) in Georgia. **(Image credit: Daniel R. Crook)**

About a third of those examples came from scientific observations published in journals, while the rest were found on news or social media sites. "The longer I deal with this problem, the more I realize that certain spiders accomplish such incredible feats," said study senior author Martin Nyffeler, a conservation biologist at the University of Base who has previously reported on spiders eating bats and other vertebrates.

Mighty spiders

Snacking on snakes was remarkably widespread, with more than 30 spider species engaging in the practice in natural conditions, and another 11 taking the opportunity in captivity, Nyffeler and University of Georgia herpetologist J. Whitfield Gibbons reported this month in the Journal of Arachnology.

Widow spiders were the most frequent spider-killers, responsible for about half of the snake deaths; this group includes the infamous hourglass-marked black widows (*Latrodectus mactans, L. Hesperus, L. variolus)* as well as relatives like the African button spider (*L. indistinctus*).

These spiders are small, 0.4 inches (1.1 centimeters) in size at most, and they typically target small, young snakes, but their venom is deadly enough to kill much larger animals.

Members of the tarantula family were responsible for another 10% of snake kills. These larger spiders do not build webs, but hunt prey actively on the ground or in trees. Another 8.5% of predation incidents were carried out by large orb-weaver spiders, which are also known to catch and eat bats and birds.

These spiders weave large and very strong circular webs. Once the spiders kill the snakes, they suck out their innards just as they would an insect.

Reports of spiders eating snakes came from every continent except Antarctica, though half of the events reported occurred in the United States and almost a third occurred in Australia.

Sinuous victims

The researchers found evidence of spiders preying on 86 different species of snake, with snakes of the colubrid family being the most common victims.

This family includes common species such as garter snakes (*Thamnophis cyrtopsis*) and rat snakes (*Pantherophis guttatus*), and

their prevalence among spider victims likely reflects the fact that they are the most abundant snake family on all continents except Australia, Nyffeler and Gibbons wrote.

Most of the snakes attacked by spiders were babies or juveniles weighing less than a gram. But snakes sometimes took down large serpents, too: The largest victims were up to 3.25 feet (100 centimeters) long and weighed several ounces. Snakes that large were typically killed by orb-weavers or large tarantulas.

Black widows could overcome snakes up to 30 times their own size by weight, and in one report, a cobweb spider (*Steatoda triangulosa*) entangled a 6-inch-long (15 cm) garter snake that was 355 times the spider's weight. "Such an achievement is truly surprising," Nyffeler told Live Science.

"It is almost unbelievable."

It could take anywhere from hours to days for the spider venom to kill the snakes, 30% of which were venomous themselves.

Spider attacks were fatal to snakes in 86% of the reported incidents, while only 1.5% of snakes escaped on their own. Another 11% were rescued by human observers.

Once a spider vanquishes a snake, it might take days to finish the meal. In most cases, the researchers wrote, snakes are likely a rare and lucky meal for spiders that typically subsist on insects. But some spiders, particularly tarantulas, might make snakes a regular part of their diet.

Australian redback spiders (*Latrodectus hasselti*), too, have been seen eating both lizards and snakes in large quantities.

Nyffeler has a snake phobia, he said, but the research mixed fear with fascination. "After studying the 'world of spiders' for a lifetime, it was very fascinating to get a glimpse into a parallel world, the 'world of snakes,'" he said.

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Siberian Volcanic Eruptions Triggered End-Permian Mass Extinction, New Study Confirms

The end-Permian mass extinction — the most severe extinction event in the past 540 million years — was caused by massive volcanic eruptions in what is now Siberia, according to new research.

Nickel isotopes link aerosol particles from the Siberian Traps igneous province to the end-Permian mass extinction. Image credit: Margaret Weiner / University of Cincinnati Creative Services.

“The end-Permian mass extinction, which occurred about 252 million years ago, was the most severe biotic crisis in the Phanerozoic Eon, eliminating more than 90% of marine and 75% of terrestrial species,” said senior author Dr. Yanan Shen from the University of Science and Technology of China and colleagues.

“The Siberian Traps large igneous province is widely hypothesized to have been the primary trigger for the catastrophic environmental deterioration driving the extinction event.”

“Potential kill mechanisms triggered by emplacement of the Siberian Traps magmas include global warming, ultraviolet radiation exposure, hypercapnia, ocean acidification and anoxia, and toxic metal release.”

In the study, the researchers analyzed the Permian-Triassic sedimentary rocks from the Buchanan Lake section in the Sverdrup Basin, Canadian High Arctic. They found that the samples have the lightest nickel isotope ratios ever measured in sedimentary rocks.

The only plausible explanation is that the nickel was sourced from the volcanic terrain, very likely carried by aerosol particles and deposited in the ocean, where it dramatically changed the chemistry of seawater and severely disrupted the marine ecosystem.

“The study results provide strong evidence that nickel-rich particles were aerosolized and dispersed widely, both through the

atmosphere and into the ocean," said co-author Dr. Laura Wasylenki, a researcher at Northern Arizona University.

"Nickel is an essential trace metal for many organisms, but an increase in nickel abundance would have driven an unusual surge in productivity of methanogens, microorganisms that produce methane gas. Increased methane would have been tremendously harmful to all oxygen-dependent life."

"Our data provide a direct link between global dispersion of nickel-rich aerosols, ocean chemistry changes and the mass extinction event," she added. "The data also demonstrate that environmental degradation likely began well before the extinction event — perhaps starting as early as 300,000 years before then."

"Prior to this study, the connection between Siberian Traps flood basalt volcanism, marine anoxia and mass extinction was rather vague, but now we have evidence of a specific kill mechanism."

"This finding demonstrates the power of nickel isotope analyses, which are relatively new, to solve long-standing problems in the geosciences."

The results were published in the journal *Nature Communications*.

M. Li et al. 2021. Nickel isotopes link Siberian Traps aerosol particles to the end-Permian mass extinction. Nat Commun 12, 2024; doi: 10.1038/s41467-021-22066-7

https://go.nature.com/2T7wiPe

The 2,000 stars where aliens would catch a glimpse of Earth

Scientists searching for extraterrestrial life should narrow their hunt to stars and planetary systems that have an occasional view of the Earth as it passes in front of the Sun.

Astronomers have pinpointed more than 2,000 stars from where, in the not-too-distant past or future, Earth can occasionally be detected transiting across the face of the Sun.

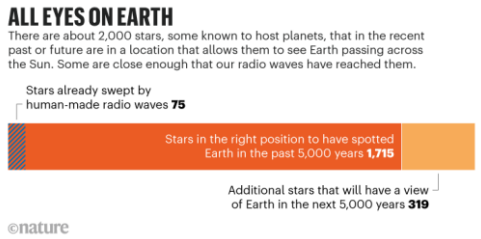
If there are aliens living on planets around those stars, with at least a similar level of technological advancement to our own species, then they would theoretically be able to spot us.

They could even have observed as the amount of carbon dioxide in Earth's atmosphere increased over the past several hundred years, since the industrial revolution.

The work, reported in this week's *Nature*[1], offers a new way of thinking about the search for extraterrestrial life, says Lisa Kaltenegger, an astronomer at Cornell University in Ithaca, New York, who led the analysis.

"Who has the cosmic front seat to see us?" she asks. "For whom would we be the aliens?"

Those aliens would be the natural choice for Earthlings to look for, say the scientists — because they may have already had a chance to spot us, and thus might be primed to be ready for communications from Earth.



Movement of stars over time

Although previous studies have considered this question[2,3,4], this is the first to incorporate the movement of stars over time, because stars can slide in or out of the narrow slice of the sky that happens to line up with both Earth and the Sun.

With this information, the scientists were able to predict where Earth was visible from over the past 5,000 years or so of human civilization — and also predict where it will be visible another 5,000 years into the future.

In doing so, the study expands astronomers' thinking about which stars have "a better-than-average shot of discovering and characterizing the Earth," says Sofia Sheikh, an astrobiologist at the Berkeley SETI Research Center in California.

The discovery was made possible by the European Space Agency's Gaia space observatory, which has compiled the best three-dimensional map of stars to date. Working with Jackie Faherty, an

astronomer at the American Museum of Natural History in New York City, Kaltenegger analysed the Gaia map to see which stars have been, or will be, in a position where Earth briefly moves between them and our Sun.

Because most of the sky lies in other planes to that of our Solar System, there's just a tiny sliver where this is possible, she says. Of the more than 330,000 stars in the Gaia catalogue that are within 100 parsecs of Earth, just 2,043 happen to have the perfect viewing geometry.

Of those, 1,715 are in the right locations to have spotted Earth in the past 5,000 years, and an additional 319 will have vantage points in the next 5,000 years (see 'All eyes on Earth').

Seven of the 2,034 are already known to host planets — but many more are likely to have worlds orbiting them, some of which may be suitable for life.

The method assumed for spying Earth from elsewhere in the Galaxy is the same one that Earth-bound astronomers have used to discover thousands of exoplanets: detecting the light of a distant star dimming slightly and regularly, as an orbiting planet passes across its face.

Good alien targets

With the results of this study, astronomers searching for extraterrestrial life can now focus on stars and planetary systems that have a view of Earth and thus might already expect to hear from us.

"It really helps in the hunting if you know where the prey is located," says Seth Shostak, an astronomer at the SETI Institute in Mountain View, California.

Of those stars, the authors further identified 75 that are close enough — within 30 parsecs — for radio waves from Earth to already have washed over them since humans started to produce them. Those might be particularly good targets, Kaltenegger says, because aliens there could have both seen and heard us by now.

But other stars assume new prominence. For instance, astronomers know of seven Earth-sized planets orbiting the star TRAPPIST-1, 12 parsecs from Earth. TRAPPIST-1 will move into a position to see Earth as a transiting planet in the year 3663, say the study authors (see 'Some of the stars with known exoplanets that have a view of Earth').

Some of the stars with known exoplanets that have a view of Earth

Star	Begin	End	Total	When
Ross 128	3,057 years ago	900 years ago	2,158 years	Past
Teegarden's Star	29 years from now	438 years from now	410 years	Future
GJ 9066	846 years from now	1,777 years from now	932 years	Future
TRAPPIST-1	1,642 years from now	4,012 years from now	2,371 years	Future

Source: Kaltenegger, L. & Faherty, J. K. *Nature* 594, 505–507 (2021).

Astronomers and science-fiction writers have noted that civilizations could signal their existence by constructing artificial 'megastructures' that pass in front of their stars, briefly dimming their light in a characteristic way.

Perhaps, some say, humanity should plan ahead for when eyes from the TRAPPIST-1 system might be cast in our direction.

"Maybe we should think about installing a transiting megastructure for them to observe," says René Heller, an astrophysicist at the Max Planck Institute for Solar System Research in Göttingen, Germany.

doi: https://doi.org/10.1038/d41586-021-01692-7

References

*1.Kaltenegger, L. & Faherty, J. K. Nature **594**, 505–507 (2021). Article Google Scholar*

2.Shostak, S. & Villard, R. Symp. Int. Astron. Union 213, 409–414 (2004). PubMed Article Google Scholar

3.Heller, R. & Pudritz, R. E. Astrobiology 16, 259–270 (2016). PubMed Article Google Scholar

*4. Kaltenegger, L. & Pepper, J. Mon. Not. R. Astron. Soc. Lett. **499**, L111-L115 (2020). Article Google Scholar*

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Dirty secrets: sediment DNA reveals a 300,000-year timeline of ancient and modern humans living in Siberia

Only site in the world known to have been inhabited by Denisovans, the Neanderthals — which overlapped at times — as well as by the earliest modern humans

Elena Zavala [1] Matthias Meyer [2] Richard 'Bert' Roberts [3] Zenobia Jacobs [4]

In the foothills of the Altai Mountains in southern Siberia lies Denisova Cave. It is the only site in the world known to have been inhabited by the eponymous Denisovans and their close relatives the Neanderthals (*Homo neanderthalensis*) — which overlapped at times — as well as by some of the earliest modern humans (*Homo sapiens*) to have dispersed into northern Asia.

Our new study pieces together the history of this site over the past 300,000 years from fragments of ancient DNA that survived in the cave sediments. Our findings reveal multiple turnovers of archaic and modern humans during this period, as well as major changes in the diversity of other animals.

We discovered Denisovans were the earliest toolmakers at the site, while Neanderthals were the sole human occupants between about 130,000 and 80,000 years ago. The first modern humans arrived much later, just as the last Denisovans and Neanderthals were leaving the scene.

We also detected marked changes in the types of human and animal DNA around 200,000 and 100,000 years ago, coincident with major shifts in climate and environmental conditions.

Genetic ghosts

Excavations in the cave by our Russian colleagues have unearthed about a dozen fossils of Denisovans and Neanderthals over the past 40 years, but none of modern humans. Rather, the presence of modern humans at the cave has been surmised based on the recovery of artefacts made from stone, animal bones and teeth, mammoth ivory, ostrich eggshells, marble and gemstones.

The rarity of fossils at the site has also meant that questions persist about when different groups of humans occupied the cave, and which of them was responsible for making specific artefacts.

We managed to put flesh on the missing bones by using genetic traces of ancient humans and various other mammals preserved in the cave sediments. And we did so without having to find more fossils.

Our latest work is the most comprehensive study yet of ancient DNA extracted from sediment at any single site in the world. It builds on our trailblazing research published in 2017.

We extracted mitochondrial DNA from more than 700 samples and anchored them to a timeline for Denisova Cave, generating a detailed picture of which humans and animals were present at this famous site at various times in the past.

Turbulent times

We retrieved ancient human DNA from 175 sediment samples — more than ten times the number of human fossils found at the site. Several interesting findings emerged from our genetic analyses.

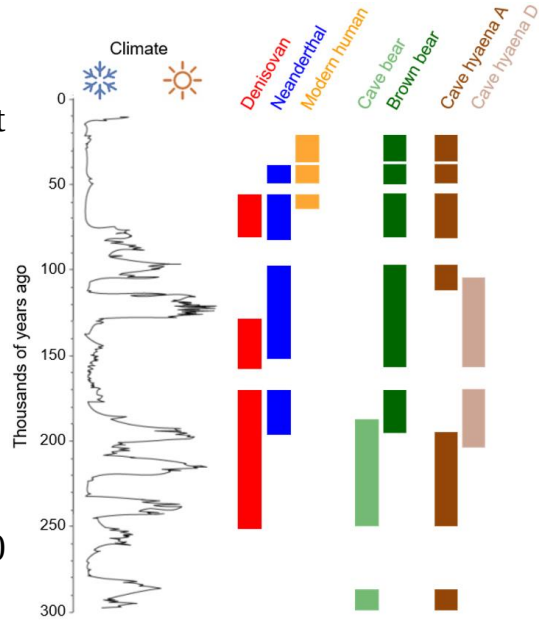
We found Denisovans were present at the cave, on and off, from 250,000 years ago until 60,000 years ago. And they were the only humans at the site between 250,000 and 200,000 years ago, so we can now say with more confidence they likely produced the stone tools recovered from these layers.

Denisovan fossils and ancient DNA have been found at only one other site, on the edge of the Tibetan Plateau.

Meanwhile, Neanderthals first appeared at Denisova Cave about 200,000 years ago, with a variety of DNA that was previously unknown. They vanished from the site about 40,000 years ago, around the same time Neanderthals disappeared in other parts of Eurasia.

Importantly, we could only find traces of Neanderthal DNA in sediments dated to between 130,000 and 80,000 years ago at Denisova Cave — and none of Denisovans.

This time interval coincides with a major change in Earth's climate: the start of the last interglacial. This was a relatively warm period similar to the present. It marked a switch from one type of Denisovan DNA before 130,000 years ago to another after 80,000 years ago.



Summary timeline of the different types of human, bear and hyaena DNA in sediments at Denisova Cave. White gaps indicate missing parts of the sedimentary sequence. The graph on the left shows the changes in climate between relatively cold and warm conditions recorded in drill cores from Lake Baikal, also in southern Siberia. **Bert Roberts**

This matches previous findings from genetic analysis of Denisovan fossils, which indicated a possible turnover in Denisovan populations. It also coincides with a population replacement of Neanderthals in Spain about 100,000 years ago — again identified from ancient DNA in cave sediments.

We also recovered the ancient DNA of modern humans from sediments deposited at Denisova Cave within the last 60,000 years. No modern human fossils have been found at the site, so these traces of DNA — from the same layers as the jewellery and pendants made from stone, bone, tooth and ivory — are the first direct evidence of *Homo sapiens*' presence at the cave.

Denisova zoo

We recovered other ancient animal DNA from 94% of the sediment samples. This is providing new vistas into cave use by more than 12 taxonomic families of mammals, including species such as bear, hyena, wolf and woolly mammoth.

Previous studies have shown the cave was occupied at times by hyenas and bears. Our findings take this further, revealing cave bears dominated between 300,000 and 200,000 years ago, after which brown bears became more abundant.

Selection of stone tools and personal ornaments made from bone, tooth and ivory recovered from the same sediment layers as modern human ancient DNA. **Institute of Archaeology and Ethnography of the Siberian Branch of the Russian Academy of Sciences.**

We also identified two major shifts in the types of hyena present at different times, with turnovers occurring when climatic conditions changed from relatively warm to cold 200,000 years ago, and from relatively cold to warm 100,000 years ago.

The timing of these turnovers, coupled with the patterns we discovered for Denisovans and Neanderthals, suggests these events were likely connected to environmental changes.

Sediment diaries

The power of sediment DNA lies in the fact that sediments are ubiquitous at archaeological and palaeontological sites. Even tiny samples can contain genetic traces of a variety of animals — including humans — in the absence of fossils.

Sediments also often contain plant remains and other materials that can be used to reconstruct ancient environments, with timelines obtained by directly dating sediment grains.

By sampling sites with high densities of sediment DNA, the ebb and flow of humans and other animals can be compared to records

of past environmental change. Making these crucial connections can help illuminate the dark corners of our planet's history.

[1]*PhD Student, Max Planck Institute for Evolutionary Anthropology*
[2]*Group Leader, Advanced DNA Sequencing Techniques Group, Max Planck Institute for Evolutionary Anthropology*
[3]*Director, ARC Centre of Excellence for Australian Biodiversity and Heritage (CABAH), University of Wollongong*
[4]*Professor, University of Wollongong*

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https://bit.ly/3qsXwvY

All Types of Coffee are Protective against Chronic Liver Disease, Study Shows

Drinking caffeinated or decaf coffee (ground or instant) was associated with a reduced risk of developing and dying from chronic liver disease compared to not drinking coffee

In a study involving almost 500,000 adults from the United Kingdom, a team of scientists from the University of Southampton and the University of Edinburgh Centre for Inflammation Research found that drinking coffee that is caffeinated (ground or instant) or decaffeinate was associated with a reduced risk of developing and dying from chronic liver disease compared to not drinking coffee, with the benefit peaking at three to four cups per day.

Chronic liver disease is a major health problem worldwide, particularly in low to middle-income countries with high disease burden and limited treatment availability.

The commonest aetiologies of chronic liver disease are alcohol-related liver disease, chronic hepatitis B and C infection, and non-alcoholic fatty liver disease. These conditions involve destruction and regeneration of liver parenchyma leading to liver fibrosis and then cirrhosis.

Coffee is a popular beverage in most societies. It comprises hundreds of chemical compounds, some of which are thought to have *in vivo* properties, including caffeine, chlorogenic acid, kahweol and cafestol. Coffee consumption has been linked with lower rates of chronic liver disease, but little is known about the effects of different coffee types.

"The aim of our study was to investigate associations of coffee consumption, including the effects of different coffee types — and, thus, composition — with chronic liver disease outcomes in a large prospective cohort," said lead author Dr. Oliver Kennedy from the Faculty of Medicine at the University of Southampton and his colleagues.

The researchers analyzed UK Biobank data on 495,585 participants with known coffee consumption, who were followed over a median of 10.7 years to monitor who developed chronic liver disease and related liver conditions.

Of all participants included in the study, 78% (384,818) consumed ground or instant caffeinated or decaffeinated coffee, while 22% (109,767) did not drink any type of coffee.

During the study period, there were 3,600 cases of chronic liver disease, including 301 deaths. Additionally, there were 5,439 cases of chronic liver disease or steatosis, and 184 cases of hepatocellular carcinoma.

Compared to non-coffee drinkers, coffee-drinkers had a 21% reduced risk of chronic liver disease, a 20% reduced risk of chronic or fatty liver disease, and a 49% reduced risk of death from chronic liver disease.

The maximum benefit was seen in the group who drank ground coffee, which contains high levels of kahweol and cafestol.

Instant coffee, which has low levels of these compounds, was also associated with a reduced the risk of chronic liver disease.

While the reduction in risk was smaller than that associated with

ground coffee, the finding may suggest that other ingredients, or potentially a combination of ingredients, may be beneficial.

"Coffee is widely accessible and the benefits we see from our study may mean it could offer a potential preventative treatment for chronic liver disease," Dr. Kennedy said. "This would be especially valuable in countries with lower income and worse access to healthcare and where the burden of chronic liver disease is highest."

The results appear in the journal *BMC Public Health*.

O.J. Kennedy et al. 2021. All coffee types decrease the risk of adverse clinical outcomes in chronic liver disease: a UK Biobank study. BMC Public Health 21, 970; doi: 10.1186/s12889-021-10991-7

https://nyti.ms/3dqUJk7

Scientist Finds Early Virus Sequences That Had Been Mysteriously Deleted

By rooting through files stored on Google Cloud, a researcher says he recovered 13 early coronavirus sequences that had disappeared from a database last year.

By Carl Zimmer

About a year ago, more than 200 data entries from the genetic sequencing of early cases of Covid-19 in Wuhan disappeared from an online scientific database.

Now, by rooting through files stored on Google Cloud, a researcher in Seattle reports that he has recovered 13 of those original sequences — intriguing new information for discerning when and how the virus may have spilled over from a bat or another animal into humans.

The new analysis, released on Tuesday, bolsters earlier suggestions that a variety of coronaviruses may have been circulating in Wuhan before the initial outbreaks linked to animal and seafood markets in December 2019.

As the Biden administration investigates the contested origins of the virus, known as SARS-CoV-2, the study neither strengthens nor discounts the hypothesis that the pathogen leaked out of a famous Wuhan lab. But it does raise questions about why original sequences were deleted, and suggests that there may be more revelations to recover from the far corners of the internet.

"This is a great piece of sleuth work for sure, and it significantly advances efforts to understand the origin of SARS-CoV-2," said Michael Worobey, an evolutionary biologist at the University of Arizona who was not involved in the study.

Jesse Bloom, a virologist at the Fred Hutchinson Cancer Research Center who wrote the new report, called the deletion of these sequences suspicious. It "seems likely that the sequences were deleted to obscure their existence," he wrote in the paper, which has not yet been peer-reviewed or published in a scientific journal.

Dr. Bloom and Dr. Worobey belong to an outspoken group of scientists who have called for more research into how the pandemic began. In a letter published in May, they complained that there wasn't enough information to determine whether it was more likely that a lab leak spread the coronavirus, or that it leapt to humans from contact with an infected animal outside of a lab.

The genetic sequences of viral samples hold crucial clues about how SARS-CoV-2 shifted to our species from another animal, most likely a bat. Most precious of all are sequences from early in the pandemic, because they take scientists closer to the original spillover event.

As Dr. Bloom was reviewing what genetic data had been published by various research groups, he came across a March 2020 study with a spreadsheet that included information on 241 genetic sequences collected by scientists at Wuhan University. The spreadsheet indicated that the scientists had uploaded the sequences to an online database called the Sequence Read Archive, managed by the U.S. government's National Library of Medicine.

But when Dr. Bloom looked for the Wuhan sequences in the

database earlier this month, his only result was “no item found.”

Puzzled, he went back to the spreadsheet for any further clues. It indicated that the 241 sequences had been collected by a scientist named Aisi Fu at Renmin Hospital in Wuhan. Searching medical literature, Dr. Bloom eventually found another study posted online in March 2020 by Dr. Fu and colleagues, describing a new experimental test for SARS-CoV-2. The Chinese scientists published it in a scientific journal three months later.

In that study, the scientists wrote that they had looked at 45 samples from nasal swabs taken “from outpatients with suspected Covid-19 early in the epidemic.” They then searched for a portion of SARS-CoV-2’s genetic material in the swabs. The researchers did not publish the actual sequences of the genes they fished out of the samples. Instead, they only published some mutations in the viruses.

But a number of clues indicated to Dr. Bloom that the samples were the source of the 241 missing sequences. The papers included no explanation as to why the sequences had been uploaded to the Sequence Read Archive, only to disappear later.

Perusing the archive, Dr. Bloom figured out that many of the sequences were stored as files on Google Cloud. Each sequence was contained in a file in the cloud, and the names of the files all shared the same basic format, he reported.

Dr. Bloom swapped in the code for a missing sequence from Wuhan. Suddenly, he had the sequence. All told, he managed to recover 13 sequences from the cloud this way.

With this new data, Dr. Bloom looked back once more at the early stages of the pandemic. He combined the 13 sequences with other published sequences of early coronaviruses, hoping to make progress on building the family tree of SARS-CoV-2.

Working out all the steps by which SARS-CoV-2 evolved from a bat virus has been a challenge because scientists still have a limited number of samples to study. Some of the earliest samples come from the Huanan Seafood Wholesale Market in Wuhan, where an outbreak occurred in December 2019.

But those market viruses actually have three extra mutations that are missing from SARS-CoV-2 samples collected weeks later. In other words, those later viruses look more like coronaviruses found in bats, supporting the idea that there was some early lineage of the virus that did not pass through the seafood market.

Dr. Bloom found that the deleted sequences he recovered from the cloud also lack those extra mutations. “They’re three steps more similar to the bat coronaviruses than the viruses from the Huanan fish market,” Dr. Bloom said.

This suggests, he said, that by the time SARS-CoV-2 reached the market, it had been circulating for awhile in Wuhan or beyond. The market viruses, he argued, aren’t representative of full diversity of coronaviruses already loose in late 2019.

“Maybe our picture of what was present early in Wuhan from what has been sequenced might be somewhat biased,” he said.

In his report, Dr. Bloom acknowledged that this conclusion would have to be confirmed with a deeper analysis of the virus sequences.

Dr. Worobey said that he and his colleagues are working on a large-scale study of SARS-CoV-2 genes to better understand its origin and that they’ll now add Dr. Bloom’s 13 recovered sequences.

“These additional data will play a big role in that effort,” Dr. Worobey said.

It’s not clear why this valuable information went missing in the first place. Scientists can request that files be deleted by sending an email to the managers of the Sequence Read Archive. The National Library of Medicine, which manages the archive, said that the 13 sequences were removed last summer.

“These SARS-CoV-2 sequences were submitted for posting in SRA in March 2020 and subsequently requested to be withdrawn by the submitting investigator in June 2020,” said Renate Myles, a

spokeswoman for the National Institutes of Health.

She said that the investigator, whom she did not name, told the archive managers that the sequences were being updated and would be added to a different database. But Dr. Bloom has searched every database he knows of, and has yet to find them. “Obviously I can’t rule out that the sequences are on some other database or web page somewhere, but I have not been able to find them any of the obvious places I’ve looked,” he said.

Three of the co-authors of the 2020 testing study that produced the 13 sequences did not immediately respond to emails inquiring about Dr. Bloom’s finding. That study did not give contact information for another co-author, Dr. Fu, who was also named on the spreadsheet from the other study.

Some scientists are skeptical that there is anything sinister behind the removal of the sequences. “I don’t really understand how this points to a cover-up,” said Stephen Goldstein, a virologist at the University of Utah.

Dr. Goldstein noted that the testing paper listed the individual mutations the Wuhan researchers found in their tests. Although the full sequences are no longer in the archive, the key information has been public for over a year, he said. It was just tucked away in a format that is hard for researchers to find.

“We all missed this relatively obscure paper,” Dr. Goldstein said.

“You can’t really say why they were removed,” Dr. Bloom acknowledged in an interview.

“You can say that the practical consequence of removing them was that people didn’t notice they existed.” He also noted that the Chinese government ordered the destruction of a number of early samples of the virus and barred the publication of papers on the coronavirus without its approval.

For his part, Dr. Worobey still wants answers. “I hope we hear from the authors who generated, but then deleted, these crucial sequences so we can understand more about their motivation for doing so,” he said. “It certainly is strange at face value and really demands an explanation.”

Regardless of what happened to these 13 sequences, Dr. Bloom now wonders what other clues might be discovered online. In order to reconstruct the origin of Covid-19, all those clues potentially matter. “Ideally, we need to try to find as many other early sequences as possible,” he said. “And I think this study suggests that we should look everywhere.”

https://bit.ly/3xWUaDS

Being Anglo-Saxon was a matter of language and culture, not genetics

A new study from archaeologists at University of Sydney and Simon Fraser University in Vancouver, has provided important new evidence to answer the question "Who exactly were the Anglo-Saxons?"

New findings based on studying skeletal remains clearly indicates the Anglo-Saxons were a melting pot of people from both migrant and local cultural groups and not one homogenous group from Western Europe.

Professor Keith Dobney at the University of Sydney said the team's results indicate that "the Anglo-Saxon kingdoms of early Medieval Britain were strikingly similar to contemporary Britain—full of people of different ancestries sharing a common language and culture".

The famous Anglo-Saxon Sutton Hoo helmet from about 625 CE, part of the British Museum collection.Photo: Elissa Blake/University of Sydney. **Credit: Elissa Blake/University of Sydney**

The Anglo-Saxon (or early medieval) period in England runs from the 5th-11th centuries AD. Early Anglo-Saxon dates from around 410-660 AD—with migration occurring throughout all but the final 100 years (ie 410-560AD).

Studying ancient skulls

Published in *PLOS ONE*, the collaborative study by Professor Dobney at University of Sydney and Dr. Kimberly Plomp and Professor Mark Collard at Simon Fraser University in Vancouver, looked at the three-dimensional shape of the base of the skull.

"Previous studies by palaeoanthropologists have shown that the base of the human skull holds a shape signature that can be used to track relationships among human populations in a similar way to ancient DNA," Dr. Plomp said.

"Based on this, we collected 3D data from suitably dated skeletal collections from Britain and Denmark, and then analysed the data to estimate the ancestry of the Anglo-Saxon individuals in the sample."

The researchers found that between two-thirds and three-quarters of early Anglo-Saxon individuals were of continental European ancestry, while between a quarter and one-third were of local ancestry.

When they looked at skeletons dated to the Middle Anglo-Saxon period (several hundred years after the original migrants arrived), they found that 50 to 70 percent of the individuals were of local ancestry, while 30 to 50 percent were of continental European ancestry, which probably indicates a change in the rate of migration and/or local adoption of culture over time.

"These findings tell us that being Anglo-Saxon was more likely a matter of language and culture, not genetics," Professor Collard said.

The debate about Anglo-Saxons

Although Anglo-Saxon origins can clearly be traced to a migration of Germanic-speaking people from mainland Europe between the 5th and 7th centuries AD, the number of individuals who settled in Britain is still contested, as is the nature of their relationship with the pre-existing inhabitants of the British Isles, most of whom were Romano-Celts.

The ongoing and unresolved argument is whether hordes of European invaders largely replaced the existing Romano-British inhabitants, or did smaller numbers of migrants settle and interact with the locals, who then rapidly adopted the new language and culture of the Anglo-Saxons?

"The reason for the ongoing confusion is the apparent contradiction between early historical texts (written sometime after the events that imply that the newcomers were both numerous and replaced the Romano-British population) and some recent biomolecular markers directly recovered from Anglo-Saxon skeletons that appears to suggest numbers of immigrants were few," said Professor Dobney.

"Our new data sits at the interface of this debate and implies that early Anglo-Saxon society was a mix of both newcomers and immigrants and, instead of wholesale population replacement, a process of acculturation resulted in Anglo-Saxon language and culture being adopted wholesale by the local population."

"It could be this new cultural package was attractive, filling a vacuum left at the end of the Roman occupation of Britain. Whatever the reason, it lit the fuse for the English nation we have today—still comprised of people of different origins who share the same language," Professor Dobney said.

More information: *Plomp KA, Dobney K, Collard M (2021) A 3D basicranial shape-based assessment of local and continental northwest European ancestry among 5th to 9th century CE Anglo-Saxons. PLoS ONE 16(6): e0252477.* *doi.org/10.1371/journal.pone.0252477*

https://bit.ly/3wY2SBH

Why One Particular Strain of COVID-19 Could Represent Its 'Peak Fitness'

Delta is the "fittest" variant to date

Aria Bendix, Business Insider

No coronavirus variant spotted so far is more concerning than Delta, the strain first identified in India in February. World Health Organization officials on Monday said Delta is the "fittest" variant to date, since it spreads even more easily than other variants and may lead to more severe cases among unvaccinated people.

"Delta is a superspreader variant, the worst version of the virus we've seen," Eric Topol, director of the Scripps Research Translational Institute, tweeted last week.

But it's possible that Delta is the worst the coronavirus is going to throw at us – that the virus, in other words, has reached what epidemiologists call "peak fitness."

Topol and Italian virologist Roberto Burioni explore that scenario in a letter published in the journal *Nature* on Monday.

The virus, they wrote, is likely to hit a point after which it no longer mutates to become more infectious. In that case, they said, "a 'final' variant will prevail and become the dominant strain, experiencing only occasional, minimal variations."

It's too soon to know whether that's happened, since Delta isn't yet dominant worldwide. But it likely will be soon – Delta has been detected in more than 80 countries so far and is already dominant in India and the UK.

"Delta is absolutely going up the fitness peak – whether it's at the top, I think that's very hard to say until we just don't see any further change," Andrew Read, who studies the evolution of infectious diseases at Pennsylvania State University, told Insider.

"If Delta takes over the world and nothing changes," he added, "then we'll know in a while – a year or two – that it is the most fit."

The fittest variants are the best at spreading

The coronavirus is constantly mutating in relatively harmless ways, but every once in a while, a mutation turns the virus into a more menacing threat.

A new variant develops that can evade antibodies generated in response to a vaccine or prior infection, results in more serious illness, or spreads more easily. Emerging research indicates that Delta checks at least two of those boxes.

Public Health England found that Delta is associated with a 60 percent increased risk of household coronavirus transmission compared to Alpha, the variant discovered in the UK. Alpha is already around 50 percent more transmissible than the original strain, according to the Centers for Disease Control and Prevention.

Researchers in Scotland also found that getting infected with Delta doubles the risk of hospital admission relative to Alpha. (Previous studies have suggested that Alpha may be 30 to 70 percent deadlier than the original strain.)

What's more, emerging research indicates that a single vaccine dose doesn't hold up as well against Delta as it does against other coronavirus strains. Recent Public Health England analyses found that two doses of Pfizer's vaccine were 88 percent effective at preventing symptomatic COVID-19 from Delta, while a single shot was just 33 percent effective. That's compared to 95 percent efficacy against the original strain, with 52 percent after one shot.

The best way for the coronavirus to achieve peak fitness, Topol and Burioni wrote in their letter, is to become more contagious. If a variant is already spreading quickly, there's no urgent need for it to evade the body's immune response; it can simply jump to another person. "Increasing rate of transmission from person to person is what we're looking for," Read said.

So far, Delta is by far the most transmissible variant. The US's Delta cases appear to have tripled in just 11 days, from 10 percent

of all cases sequenced in early June to 31 percent last week, according to a recent estimate from the *Financial Times*.

At that rate, experts predict Delta will become the nation's dominant strain in weeks.

That doesn't necessarily mean the coronavirus has reached maximum transmission, though. Read said Delta could still acquire combinations of mutations that make it even better at spreading (what he called a "Delta-plus" variant).

It's also possible that two separate variants – Delta and Alpha, for instance – could combine mutations to produce an even more infectious strain. Under a third scenario, Read said, an entirely new lineage might replace Delta as the dominant variant.

"The biggest concern at the moment is just the sheer number of people that have the virus and therefore the sheer number of variants that are being generated," Read said. "Some of those might be the jackpot which are even fitter than Delta."

Still, vaccines will likely provide at least some protection against whatever strain represents the coronavirus' peak fitness.

"No human vaccine has ever been undermined by a variant to the point where the vaccine was completely useless," Read said.

https://bit.ly/3qTsf26

Researchers find 3,000-year-old shark attack victim

Researchers reveal their discovery of a 3,000-year-old victim—attacked by a shark

Newspapers regularly carry stories of terrifying shark attacks, but in a paper published today, Oxford-led researchers reveal their discovery of a 3,000-year-old victim—attacked by a shark in the Seto Inland Sea of the Japanese archipelago.

The research in *Journal of Archeological Science: Reports*, shows that this body is the earliest direct evidence for a shark attack on a human and an international research team has carefully recreated what happened—using a combination of archeological science and forensic techniques.

The grim discovery of the victim was made by Oxford researchers J. Alyssa White and Professor Rick Schulting while investigating evidence for violent trauma on the skeletal remains of prehistoric hunter-gatherers at Kyoto University. They came upon No. 24, from the previously excavated site of Tsukumo, an adult male riddled with traumatic injuries.

Original excavation photograph of Tsukumo No. 24, courtesy of the Laboratory of Physical Anthropology, Kyoto University. **Credit: Kyoto University**

"We were initially flummoxed by what could have caused at least 790 deep, serrated injuries to this man," say the Oxford pair. "There were so many injuries and yet he was buried in the community burial ground, the Tsukumo Shell-mound cemetery site."

They continue, "The injuries were mainly confined to the arms, legs, and front of the chest and abdomen. Through a process of elimination, we ruled out human conflict and more commonly-reported animal predators or scavengers."

Since archeological cases of shark reports are extremely rare, they turned to forensic shark attack cases for clues and worked with expert George Burgess, Director Emeritus of the Florida Program for Shark Research. And a reconstruction of the attack was put together by the international team.

The team concluded that the individual died more than 3,000 years ago, between 1370 to 1010 BC. The distribution of wounds strongly suggest the victim was alive at the time of attack; his left hand was sheared off, possibly a defense wound.

Individual No. 24's body had been recovered soon after the attack and buried with his people at the cemetery. Excavation records

showed he was also missing his right leg and his left leg was placed on top of his body in an inverted position.

According to the pair, "Given the injuries, he was clearly the victim of a shark attack. The man may well have been fishing with companions at the time, since he was recovered quickly. And, based on the character and distribution of the tooth marks, the most likely species responsible was either a tiger or white shark."

Co-author Dr. Mark Hudson, a researcher with the Max Planck Institute, says, "The Neolithic people of Jomon Japan exploited a range of marine resources... It's not clear if Tsukumo 24 was deliberately targeting sharks or if the shark was attracted by blood or bait from other fish. Either way, this find not only provides a new perspective on ancient Japan, but is also a rare example of archeologists being able to reconstruct a dramatic episode in the life of a prehistoric community."

More information: *J. Alyssa White et al, 3000-year-old shark attack victim from Tsukumo shell-mound, Okayama, Japan, Journal of Archaeological Science: Reports (2021). DOI: 10.1016/j.jasrep.2021.103065*

https://bit.ly/3x3Jq6I

Starting the day off with chocolate could have unexpected benefits

Researchers find time of day eating milk chocolate can impact regulation of body weight

WHO Frank A. J. L. Scheer, PhD, MSc, Neuroscientist and Marta Garaulet, PhD, Visiting Scientist, both of the Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital. Drs. Scheer and Garaulet are co-corresponding authors of a new paper published in The FASEB Journal.

WHAT Eating milk chocolate every day may sound like a recipe for weight gain, but a new study of postmenopausal women has found that eating a concentrated amount of chocolate during a narrow window of time in the morning may help the body burn fat and decrease blood sugar levels.

To find out about the effects of eating milk chocolate at different times of day, researchers from the Brigham collaborated with investigators at the University of Murcia in Spain. Together, they conducted a randomized, controlled, cross-over trial of 19 postmenopausal women who consumed either 100g of chocolate in the morning (within one hour after waking time) or at night (within one hour before bedtime). They compared weight gain and many other measures to no chocolate intake.

Researchers report that among the women studied:

**** Morning or nighttime chocolate intake did not lead to weight gain;***

**** Eating chocolate in the morning or in the evening can influence hunger and appetite, microbiota composition, sleep and more;***

**** A high intake of chocolate during the morning hours could help to burn fat and reduce blood glucose levels.***

**** Evening/night chocolate altered next-morning resting and exercise metabolism.***

"Our findings highlight that not only 'what' but also 'when' we eat can impact physiological mechanisms involved in the regulation of body weight," said Scheer.

"Our volunteers did not gain weight despite increasing caloric intake. Our results show that chocolate reduced ad libitum energy intake, consistent with the observed reduction in hunger, appetite and the desire for sweets shown in previous studies," said Garaulet.

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A Coronavirus Epidemic Hit 20,000 Years Ago, New Study Finds

A few dozen human genes rapidly evolved in ancient East Asia to thwart coronavirus infections, scientists say. Those genes could be crucial to today's pandemic.

By Carl Zimmer

Researchers have found evidence that a coronavirus epidemic swept East Asia some 20,000 years ago and was devastating enough to

leave an evolutionary imprint on the DNA of people alive today.

The new study suggests that an ancient coronavirus plagued the region for many years, researchers say. The finding could have dire implications for the Covid-19 pandemic if it's not brought under control soon through vaccination.

"It should make us worry," said David Enard, an evolutionary biologist at the University of Arizona who led the study, which was published on Thursday in the journal Current Biology. "What is going on right now might be going on for generations and generations."

Until now, researchers could not look back very far into the history of this family of pathogens. Over the past 20 years, three coronaviruses have adapted to infect humans and cause severe respiratory disease: Covid-19, SARS and MERS. Studies on each of these coronaviruses indicate that they jumped into our species from bats or other mammals.

Four other coronaviruses can also infect people, but they usually cause only mild colds. Scientists did not directly observe these coronaviruses becoming human pathogens, so they have relied on indirect clues to estimate when the jumps happened. Coronaviruses gain new mutations at a roughly regular rate, and so comparing their genetic variation makes it possible to determine when they diverged from a common ancestor.

The most recent of these mild coronaviruses, called HCoV-HKU1, crossed the species barrier in the 1950s. The oldest, called HCoV-NL63, may date back as far as 820 years.

But before that point, the coronavirus trail went cold — until Dr. Enard and his colleagues applied a new method to the search. Instead of looking at the genes of the coronaviruses, the researchers looked at the effects on the DNA of their human hosts.

Over generations, viruses drive enormous amounts of change in the human genome. A mutation that protects against a viral infection may well mean the difference between life and death, and it will be passed down to offspring. A lifesaving mutation, for example, might allow people to chop apart a virus's proteins.

But viruses can evolve, too. Their proteins can change shape to overcome a host's defenses. And those changes might spur the host to evolve even more counteroffensives, leading to more mutations.

When a random new mutation happens to provide resistance to a virus, it can swiftly become more common from one generation to the next. And other versions of that gene, in turn, become rarer. So if one version of a gene dominates all others in large groups of people, scientists know that is most likely a signature of rapid evolution in the past.

In recent years, Dr. Enard and his colleagues have searched the human genome for these patterns of genetic variation in order to reconstruct the history of an array of viruses. When the pandemic struck, he wondered whether ancient coronaviruses had left a distinctive mark of their own.

He and his colleagues compared the DNA of thousands of people across 26 different populations around the world, looking at a combination of genes known to be crucial for coronaviruses but not other kinds of pathogens. In East Asian populations, the scientists found that 42 of these genes had a dominant version. That was a strong signal that people in East Asia had adapted to an ancient coronavirus.

But whatever happened in East Asia seemed to have been limited to that region. "When we compared them to populations around the world, we couldn't find the signal," said Yassine Souilmi, a postdoctoral researcher at the University of Adelaide in Australia and a co-author of the new study.

The scientists then tried to estimate how long ago East Asians had

adapted to a coronavirus. They took advantage of the fact that once a dominant version of a gene starts being passed down through the generations, it can gain harmless random mutations. As more time passes, more of those mutations accumulate.

Dr. Enard and his colleagues found that the 42 genes all had about the same number of mutations. That meant that they had all rapidly evolved at about the same time. “This is a signal we should absolutely not expect by chance,” Dr. Enard said.

They estimated that all of those genes evolved their antiviral mutations sometime between 20,000 and 25,000 years ago, most likely over the course of a few centuries. It’s a surprising finding, since East Asians at the time were not living in dense communities but instead formed small bands of hunter-gatherers.

Aida Andres, an evolutionary geneticist at the University College London who was not involved in the new study, said she found the work compelling. “I’m quite convinced there’s something there,” she said.

Still, she didn’t think it was possible yet to make a firm estimate of how long ago the ancient epidemic took place. “The timing is a complicated thing,” she said. “Whether that happened a few thousand years before or after — I personally think it’s something that we cannot be as confident of.”

Scientists looking for drugs to fight the new coronavirus might want to scrutinize the 42 genes that evolved in response to the ancient epidemic, Dr. Souilmi said. “It’s actually pointing us to molecular knobs to adjust the immune response to the virus,” he said.

Dr. Anders agreed, saying that the genes identified in the new study should get special attention as targets for drugs. “You know that they’re important,” she said. “That’s the nice thing about evolution.”

https://wb.md/3h80a69

Nearly All COVID Deaths in US Are Now Among Unvaccinated

An indication that deaths per day could be practically zero if everyone eligible got the vaccine.

Carla K. Johnson and Mike Stobbe

Nearly all COVID-19 deaths in the U.S. now are in people who weren't vaccinated, a staggering demonstration of how effective the shots have been and an indication that deaths per day — now down to under 300 — could be practically zero if everyone eligible got the vaccine. An Associated Press analysis of available government data from May shows that "breakthrough" infections in fully vaccinated people accounted for fewer than 1,200 of more than 853,000 COVID-19 hospitalizations. That's about 0.1%.

And only about 150 of the more than 18,000 COVID-19 deaths in May were in fully vaccinated people. That translates to about 0.8%, or five deaths per day on average.

The AP analyzed figures provided by the Centers for Disease Control and Prevention. The CDC itself has not estimated what percentage of hospitalizations and deaths are in fully vaccinated people, citing limitations in the data.

Among them: Only about 45 states report breakthrough infections, and some are more aggressive than others in looking for such cases. So the data probably understates such infections, CDC officials said. Still, the overall trend that emerges from the data echoes what many health care authorities are seeing around the country and what top experts are saying.

Earlier this month, Andy Slavitt, a former adviser to the Biden administration on COVID-19, suggested that 98% to 99% of the Americans dying of the coronavirus are unvaccinated.

And CDC Director Dr. Rochelle Walensky said on Tuesday that the vaccine is so effective that "nearly every death, especially among

adults, due to COVID-19, is, at this point, entirely preventable." She called such deaths "particularly tragic."

Deaths in the U.S. have plummeted from a peak of more than 3,400 a day on average in mid-January, one month into the vaccination drive. About 63% of all vaccine-eligible Americans — those 12 and older — have received at least one dose, and 53% are fully vaccinated, according to the CDC. While vaccine remains scarce in much of the world, the U.S. supply is so abundant and demand has slumped so dramatically that shots sit unused.

Ross Bagne, a 68-year-old small-business owner in Cheyenne, Wyoming, was eligible for the vaccine in early February but didn't get it. He died June 4, infected and unvaccinated, after spending more than three weeks in the hospital, his lungs filling with fluid. He was unable to swallow because of a stroke.

"He never went out, so he didn't think he would catch it," said his grieving sister, Karen McKnight. She wondered: "Why take the risk of not getting vaccinated?"

The preventable deaths will continue, experts predict, with unvaccinated pockets of the nation experiencing outbreaks in the fall and winter. Ali Mokdad, a professor of health metrics sciences at the University of Washington in Seattle, said modeling suggests the nation will hit 1,000 deaths per day again next year.

In Arkansas, which has one of the lowest vaccination rates in the nation, with only about 33% of the population fully protected, cases, hospitalizations and deaths are rising. "It is sad to see someone go to the hospital or die when it can be prevented," Gov. Asa Hutchinson tweeted as he urged people to get their shots.

In Seattle's King County, the public health department found only three deaths during a recent 60-day period in people who were fully vaccinated. The rest, some 95% of 62 deaths, had had no vaccine or just one shot. "Those are all somebody's parents, grandparents, siblings and friends," said Dr. Mark Del Beccaro, who helps lead a vaccination outreach program in King County. "It's still a lot of deaths, and they're preventable deaths."

In the St. Louis area, more than 90% of patients hospitalized with COVID-19 have not been vaccinated, said Dr. Alex Garza, a hospital administrator who directs a metropolitan-area task force on the outbreak. "The majority of them express some regret for not being vaccinated," Garza said. "That's a pretty common refrain that we're hearing from patients with COVID."

The stories of unvaccinated people dying may convince some people they should get the shots, but young adults — the group least likely to be vaccinated — may be motivated more by a desire to protect their loved ones, said David Michaels, an epidemiologist at George Washington University's school of public health in the nation's capital. Others need paid time off to get the shots and deal with any side effects, Michaels said.

The Occupational Safety and Health Administration this month began requiring health care employers, including hospitals and nursing homes, to provide such time off. But Michaels, who headed OSHA under President Barack Obama, said the agency should have gone further and applied the rule to meat and poultry plants and other food operations as well as other places with workers at risk.

Bagne, who lived alone, ran a business helping people incorporate their companies in Wyoming for the tax advantages. He was winding down the business, planning to retire, when he got sick, emailing his sister in April about an illness that had left him dizzy and disoriented. "Whatever it was. That bug took a LOT out of me," he wrote.

As his health deteriorated, a neighbor finally persuaded him to go to the hospital. "Why was the messaging in his state so unclear that he didn't understand the importance of the vaccine? He was a very bright guy," his sister said. "I wish he'd gotten the vaccine, and I'm sad he didn't understand how it could prevent him from getting

COVID."

https://bit.ly/3qv090d

The Animal Viruses Most Likely to Jump into Humans

The SpillOver tool catalogs viruses that could cause a new pandemic

By Harini Barath

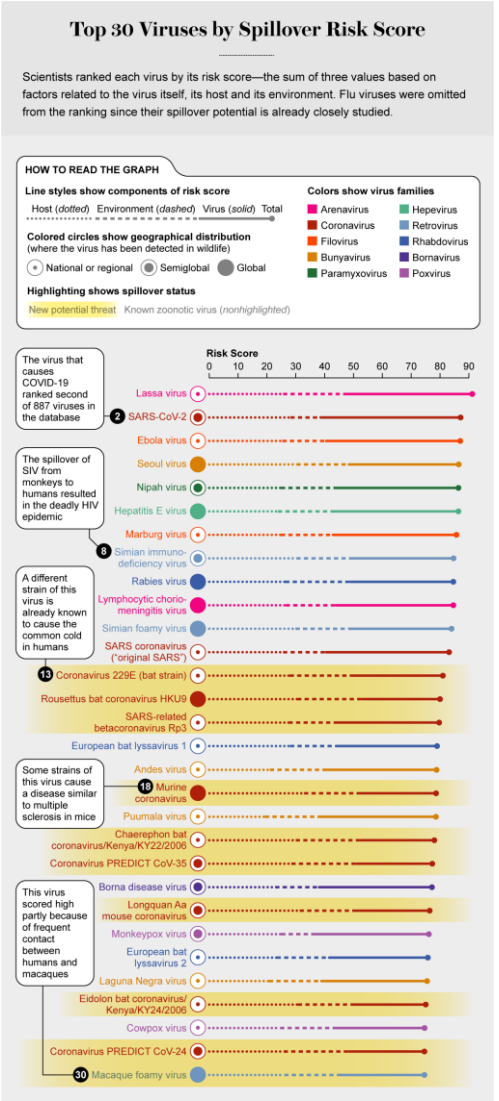
Long before COVID-19, scientists had been working to identify animal viruses that could potentially jump to people. These efforts have led to a Web-based platform called SpillOver, which ranks the risk that various viruses will make the leap. Developers hope the new tool will help public health experts and policymakers avoid future outbreaks.

Jonna Mazet, an epidemiologist and disease ecologist at the University of California, Davis, has led this work for more than a decade. It began with the USAID PREDICT project, which sought to go beyond well-tracked influenza viruses and identify other emerging pathogens that pose a risk to humans. Thousands of scientists scoured more than 30 countries to locate and identify animal viruses, discovering many new ones in the process. But not every virus is equally threatening. So Mazet and her colleagues decided to create a framework to interpret their findings. "We wanted to move beyond scientific stamp collecting [simply finding viruses] to actual risk evaluation and reduction," she says.

The team was surprised to find very little existing research on categorizing threats from viruses that are currently found only in animals but are in viral families that can likely cause disease in people. So the researchers started from scratch, identifying 31 factors pertaining to animal viruses (such as how they are transmitted), to their hosts (such as how many and varied they are), and to the environment (human population density, frequency of interaction with hosts, and more). These are summed up in a risk score out of 155; the higher the score, the more likelihood of spillover.

Cornell University virologist Colin Parrish, who was not involved in the study, says the factors examined were important in previous spillovers. But he notes that other viruses' crossover risk may be heightened by unforeseeable factors that crop up later. "It's a bit like the stock market," he says.

The new study, published in the *Proceedings of the National Academy of Sciences USA*, ranks 887 animal-borne viruses. Twelve known human pathogens scored at the top—with the virus that causes COVID-19 in second place, just under the rat-carried Lassa virus. (Influenza would have topped the list if included, Mazet says, but flu variants are already tracked elsewhere.) Parrish notes that the list also omits insect-borne viruses and those from domesticated animals. "This is a work in progress," he says. "I'm sure it will be iterated into a more powerful tool as more information and data become available.



Credit: Amanda Montañez; Source: SpillOver (https://spillover.global); data as of April 7, 2021

SpillOver is publicly editable, and scientists around the world are

already contributing their own findings. Mazet hopes it catches the attention of public health practitioners and leaders, too. With targeted action, Mazet says, “we can ensure that we don't have these spillovers at all. Or if we do, we're ready for them—because we're watching.”

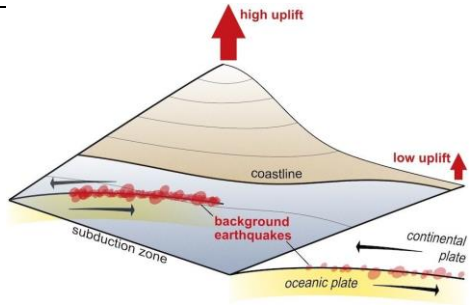
https://bit.ly/3zXeAyB

Continuous activity of small earthquakes makes mountains grow

Small earthquakes that work steadily in the background play a far greater role in shaping the landscape

From a human perspective, earthquakes are natural disasters—in the past hundred years, they have caused more than 200,000 deaths and enormous economic damage. Mega-earthquakes with a magnitude of nine or higher on the Richter scale are considered a particular threat. Yet the inconceivable energy released in these events doesn't seem to affect the uplift of mountains, according to a new study by geoscientists at the University of Tübingen. The energy of small earthquakes that work steadily in the background appears to play a far greater role in shaping the landscape. In Chile and Japan, Professor Todd Ehlers and Dr. Andrea Madella found parallels between seismic activity and the pattern and rate of mountain uplift. The results have been published in the journal *Nature Geoscience*.

Earthquakes generally occur in areas of the Earth where continental plates collide. Along the Chilean coast, for example, the Nazca plate is being pushed under the South American plate, causing the latter to be compressed and to accumulate elastic energy over hundreds of years. "The discharge of all that energy within a short time—often less than a minute—results in mega-earthquakes which can shake the ground in a terrifying way," says Todd Ehlers, "and in that time, the oceanic Nazca plate slides under the continental one."



Mountain ranges are pushed up at the edge of the compressed plate. In Peru and Chile, these are the Andes, which reach heights of more than 6,900 meters. In Japan, where several continental plates collide, mountains form a large part of the land mass.

In the time between mega-earthquakes, smaller earthquakes continuously occur between oceanic and continental plates (background earthquakes). Where a lot of energy is released through these earthquakes, we observe coastal mountains that rise faster. In contrast, slow-uplifting coastal areas coincide with fewer background earthquakes. **Credit: University of Tübingen**

Surprising patterns

In their study, the researchers examined records of earthquakes of various magnitudes along the fault lines in Chile and Japan and compared that data with the topographic patterns of the landscape. "Once we subtracted the mega-earthquakes and their smaller aftershocks from our calculations, we found that the energy released from the slow sustained activity of smaller earthquakes often matched the coastal uplift," Andrea Madella reports.

These smaller earthquakes occur mainly at depths of 30 to 60 kilometers and have a magnitude of four to five. "The correlation surprised us. These smaller earthquakes have clearly been underestimated," says Ehlers. "They occur constantly in the background without any particular spatial or temporal peaks. It seems to be their cumulative energy that makes the mountains grow over millions of years." But what happens to the energy from mega-earthquakes? "It bends the whole landscape cyclically," says Madella. "But that deformation is then reversed and often it causes no permanent uplift of mountains."

More information: *Andrea Madella et al, Contribution of background seismicity to forearc uplift, Nature Geoscience (2021).* *DOI: 10.1038/s41561-021-00779-0*

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'Dragon man' fossil may replace Neanderthals as our closest relative

Homo longi lineage may be our closest relatives--and has the potential to reshape our understanding of human evolution

A near-perfectly preserved ancient human fossil known as the Harbin cranium sits in the Geoscience Museum in Hebei GEO University. The largest of known *Homo* skulls, scientists now say this skull represents a newly discovered human species named *Homo longi* or "Dragon Man." Their findings, appearing in three papers publishing June 25 in the journal *The Innovation*, suggest that the *Homo longi* lineage may be our closest relatives--and has the potential to reshape our understanding of human evolution.

"The Harbin fossil is one of the most complete human cranial fossils in the world," says author Qiang Ji, a professor of paleontology of Hebei GEO University. "This fossil preserved many morphological details that are critical for understanding the evolution of the *Homo* genus and the origin of *Homo sapiens*."

The cranium was reportedly discovered in the 1930s in Harbin City of the Heilongjiang province of China. The massive skull could hold a brain comparable in size to modern humans' but had larger, almost square eye sockets, thick brow ridges, a wide mouth, and oversized teeth. "While it shows typical archaic human features, the Harbin cranium presents a mosaic combination of primitive and derived characters setting itself apart from all the other previously-named *Homo* species," says Ji, leading to its new species designation of *Homo longi*.

Scientists believe the cranium came from a male individual, approximately 50 years old, living in a forested, floodplain environment as part of a small community. "Like *Homo sapiens*, they hunted mammals and birds, and gathered fruits and vegetables, and perhaps even caught fish," remarks author Xijun Ni, a professor of primatology and paleoanthropology at the Chinese Academy of Sciences and Hebei GEO University. Given that the Harbin individual was likely very large in size as well as the location where the skull was found, researchers suggest *H. longi* may have been adapted for harsh environments, allowing them to disperse throughout Asia.

Using a series of geochemical analyses, Ji, Ni, and their team dated the Harbin fossil to at least 146,000 years, placing it in the Middle Pleistocene, a dynamic era of human species migration. They hypothesize that *H. longi* and *H. sapiens* could have encountered each other during this era.

"We see multiple evolutionary lineages of *Homo* species and populations co-existing in Asia, Africa, and Europe during that time. So, if *Homo sapiens* indeed got to East Asia that early, they could have a chance to interact with *H. longi*, and since we don't know when the Harbin group disappeared, there could have been later encounters as well," says author Chris Stringer, a paleoanthropologist at the Nature History Museum in London.

Looking farther back in time, the researchers also find that *Homo longi* is one of our closest hominin relatives, even more closely related to us than Neanderthals. "It is widely believed that the Neanderthal belongs to an extinct lineage that is the closest relative of our own species. However, our discovery suggests that the new lineage we identified that includes *Homo longi* is the actual sister group of *H. sapiens*," says Ni.

Their reconstruction of the human tree of life also suggests that the common ancestor we share with Neanderthals existed even further back in time. "The divergence time between *H. sapiens* and the Neanderthals may be even deeper in evolutionary history than generally believed, over one million years," says Ni. If true, we likely diverged from Neanderthals roughly 400,000 years earlier than scientists had thought.

The researchers say that findings gathered from the Harbin cranium have the potential to rewrite major elements of human evolution. Their analysis into the life history of *Homo longi* suggest they were strong, robust humans whose potential interactions with *Homo sapiens* may have shaped our history in turn. "Altogether, the Harbin cranium provides more evidence for us to understand *Homo* diversity and evolutionary relationships among these diverse *Homo* species and populations," says Ni. "We found our long-lost sister lineage."

Funding information for this research is available in the respective papers.
The Innovation, Shao et al.: "Geochemical provenancing and direct dating of the Harbin archaic human cranium" https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00056-4 DOI: 10.1016/j.xinn.2021.100131
The Innovation, Ji et al.: "Late Middle Pleistocene Harbin cranium represents a new Homo species" https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00057-6 DOI: 10.1016/j.xinn.2021.100132
The Innovation, Ni et al.: "Massive cranium from Harbin in northeastern China establishes a new Middle Pleistocene human lineage" https://www.cell.com/the-innovation/fulltext/S2666-6758(21)00055-2 DOI: 10.1016/j.xinn.2021.100130

https://bit.ly/2SC2oT6

Inflatable, shape-changing spinal implants could help treat severe pain

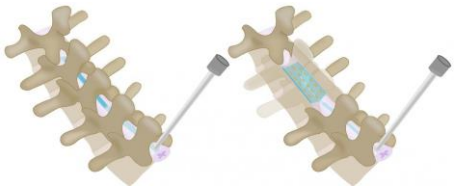
A team of engineers and clinicians has developed an ultra-thin, inflatable device that can be used to treat the most severe forms of pain without the need for invasive surgery.

The device, developed by researchers at the University of Cambridge, uses a combination of soft robotic fabrication techniques, ultra-thin electronics and microfluidics.

The device is so thin - about the width of a human hair - that it can be rolled up into a tiny cylinder, inserted into a needle, and implanted into the epidural space of the spinal column, the same area where injections are administered to control pain during childbirth.

Once correctly positioned, the device is inflated with water or air so that it unrolls like a tiny air mattress, covering a large section of the spinal cord.

When connected to a pulse generator, the ultra-thin electrodes start sending small electrical currents to the spinal cord, which disrupt pain signals.



University of Cambridge

Early tests of the device suggest that it could be an effective treatment for many forms of severe pain - including leg and back pain - which are not remedied by painkillers. It could also be adapted into a potential treatment for paralysis or Parkinson's disease. However, extensive tests and clinical trials will be required before the device can be used on patients.

Although other types of spinal cord stimulation devices are currently used to treat severe pain, the most effective of these devices are bulky and require invasive surgery, while current keyhole devices are far less effective at treating pain. By combining the clinical effectiveness of the surgical devices and the ease of implantation of the keyhole devices, the Cambridge-developed device could be an effective, long-term solution to intractable pain, which affects millions worldwide. The results are reported in the journal *Science Advances.*

Pain is something that everyone experiences, and for the vast majority of people, it is temporary and treatable. However, for some, pain becomes debilitating. In the UK, back pain is the leading cause of disability, costing the economy around £12 billion per year. In the US, the Centers for Disease Control and Prevention estimates that as many as one in 12 Americans suffer from intractable back pain, which does not respond to conventional treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) or opioids.

Spinal cord stimulation (SCS) is an option for those who suffer

from intractable back pain or other types of neuropathic pain, but despite its effectiveness, its use is limited, with just 50,000 procedures carried out worldwide each year.

"Spinal cord stimulation is a treatment of last resort, for those whose pain has become so severe that it prevents them from carrying out everyday activities," said Dr Damiano Barone from Cambridge's Department of Clinical Neurosciences, one of the paper's senior authors. "However, the two main types of SCS devices both have flaws, which may be one reason their use is limited, even though millions struggle with chronic pain every day."

The most effective SCS device in clinical use is a paddle-type device, which covers a wide area of the spinal cord but is bulky and requires invasive surgery under general anaesthetic. The other type of device can be implanted with a needle and only requires local anaesthetic, but it covers a smaller area and is less clinically effective than a paddle-type device.

"Our goal was to make something that's the best of both worlds - a device that's clinically effective but that doesn't require complex and risky surgery," said Dr Christopher Proctor from Cambridge's Department of Engineering, the paper's other senior author. "This could help bring this life-changing treatment option to many more people." "In order to end up with something that can be implanted with a needle, we needed to make the device as thin as possible," said co-first author Ben Woodington, also from the Department of Engineering.

The researchers used a combination of manufacturing techniques to build their device: flexible electronics used in the semiconductor industry; tiny microfluidic channels used in drug delivery; and shape-changing materials used in soft robotics.

Their finished device is just 60 microns thick - thin enough that it can be rolled up and placed in a needle for implantation. However, after implantation, the device expands out to cover a wide area of the spinal cord, thanks to the microfluidic channels.

"Thin-film electronics aren't new, but incorporating fluid chambers is what makes our device unique - this allows it to be inflated into a paddle-type shape once it is inside the patient," said Proctor.

"Our earlier versions were actually so thin that they were invisible to x-rays, which the surgeon would need to use to confirm they're in the right place before inflating the device," said Woodington. "We added some bismuth particles to make it visible without increasing the thickness too much. Designing a device is one thing, but putting it into surgical use is quite another."

The researchers validated their device in vitro and on a human cadaver model. They are currently working with a manufacturing partner to further develop and scale up their device and are hoping to begin tests in patients within two to three years.

"The way we make the device means that we can also incorporate additional components - we could add more electrodes or make it bigger in order to cover larger areas of the spine with increased accuracy," said Barone. "This adaptability could make our SCS device a potential treatment for paralysis following spinal cord injury or stroke or movement disorders such as Parkinson's disease. An effective device that doesn't require invasive surgery could bring relief to so many people."

The technology is being commercialised by Cambridge Enterprise, the University's commercialisation arm. The research was supported in part by the Engineering and Physical Sciences Research Council, the Borysiewicz Biomedical Science Fellowship, the Medical Research Council, Health Education England and the National Institute for Health Research.

https://bit.ly/3y3bDKO

Edible Cholera vaccine made of powdered rice proves safe in phase 1 human trials

Study points towards role of gut microbiome in vaccine effectiveness

A new vaccine to protect against deadly cholera has been made by grinding up genetically modified grains of rice. The first human trial has shown no obvious side effects and a good immune response. Researchers based at the University of Tokyo and Chiba University have published the peer-reviewed results of the Phase 1 clinical trial of the vaccine, named MucoRice-CTB, in *The Lancet Microbe*.

Vaccine manufacturing has made enormous strides in 2020, spurred on by COVID-19. However, the complexity of mRNA-based SARS-CoV-2 vaccines has highlighted the value of inoculations that can be made, transported and stored cheaply and without refrigeration. The MucoRice-CTB vaccine is stable at room temperature from start to finish.

"I'm very optimistic for the future of our MucoRice-CTB vaccine, especially because of the dose escalation results. Participants responded to the vaccine at the low, medium and high doses, with the largest immune response at the highest dose," said Professor Hiroshi Kiyono, D.D.S., Ph.D., from the Institute of Medical Science at the University of Tokyo who leads the MucoRice project. Dr. Kiyono is also a faculty member at Chiba University in Japan and the University of California, San Diego, in the U.S.

Thirty volunteers received a placebo and groups of 10 volunteers received a total of four doses spaced every two weeks of either 3 milligrams (mg), 6 mg or 18 mg each of the vaccine. Tests two and four months after receiving the last dose revealed that volunteers who responded to the vaccine had IgA and IgG antibodies - two types of proteins the immune system produces to fight infections - specific to cholera toxin B (CTB). Participants who received a higher dose of vaccine were more likely to have CTB-specific antibodies.

An independent review board found no evidence of significant side effects.

Growing a new type of vaccine Vibrio cholerae bacteria is spread most often by drinking water contaminated with sewage. Without medical attention, cholera can kill in mere hours due to diarrhea with severe dehydration. Cholera infects 1.3 million to 4 million people and causes 21,000 to 143,000 deaths each year, according to the World Health Organization.

There are four modern needle-free cholera vaccines, all of which are given as drops on the tongue, but require cold storage and are made from whole killed or live-attenuated (weakened) cholera cells; https://www.fda.gov/media/98688/download).

The new cholera vaccine grows in genetically modified Japanese short-grain rice plants that produce a nontoxic portion of CTB that can be recognized by the immune system. CTB is similar in structure to a toxin made by some types of disease-causing E. coli bacteria, so cholera vaccines often provide cross protection against travelers' diarrhea.

Researchers grow the rice plants in a purpose-built, indoor hydroponic farm that meets WHO good manufacturing practice standards for medicines, which ensures that the vaccine remains uncontaminated and that the plants are isolated from the natural environment.

The plants produce the CTB subunit in their seeds, the edible grains of rice, and store the antigens in droplets called protein bodies with membranes made of fat.

"The rice protein bodies behave like a natural capsule to deliver the antigen to the gut immune system," said Dr. Kiyono.

Other medicines have been grown in plants, most often in the leaves - including treatments for Ebola, lymphoma and flu - but the drugs have to be extracted and purified before being used. The grain-based aspect of the MucoRice system avoids those extra steps, the need for cold storage, and protects the antigens as they travel through the harsh acid of the stomach.

When the plants are mature, the rice is harvested and ground into a fine powder, then sealed in aluminum packets for storage. When people are ready to be vaccinated, the powder is mixed with about 90 milliliters (1/3 U.S. cup) of liquid and then drunk. Researchers have only tested the vaccine using saline (a salt solution equivalent to body fluids), but they expect it would work equally well with plain water.

Immunity through the gut is strong, but complicated by the microbiome

"The beautiful part of our vaccine is that it wisely uses the body's mucosal immune system through the gut for the induction of antigen-specific antibodies," said Dr. Kiyono.

MucoRice-CTB enters the body through intestinal mucosal membranes, mimicking a natural way of encountering and responding to germs. Stimulating the mucosal immune system produces two classes of antibodies that identify germs and target them for removal, IgG and IgA. Vaccines that are injected under the skin or into a muscle generally increase only IgG, not IgA, antibodies.

Volunteers who responded to MucoRice-CTB had their highest blood levels of antigen-specific IgG and IgA after eight to 16 weeks. However, 11 of the 30 volunteers who received the vaccine showed low or no measurable immune response. All study volunteers reported never traveling outside of Japan, so it is unlikely that they had any previous exposure or natural immunity to V. cholerae or pathogenic E. coli. "When we saw those data about the 11 low and nonresponders, we thought maybe gut microflora have an influence on the outcome of the immune response," Dr. Kiyono recalled.

The microflora or microbiome is the community of microorganisms that live in our bodies and either benefit us or are harmless. It is well accepted that the microflora of the digestive system influence health and immunity, but scientists are just beginning to understand the precise mechanisms of the relationship.

Extensive genetic analysis of all volunteers' fecal samples identified the thousands of bacterial species living in volunteers' intestines.

"In simplified terms, high responders had more diversified microflora, and in the low-responder group, diversity was much narrower," said Dr. Kiyono.

Researchers cautioned that the small size of the Phase 1 study - giving the vaccine to only 30 healthy Japanese male volunteers - means the relevance and prevalence of nonresponders is still unclear and that the total difference in microflora diversity was subtle. However, the results do hint at the larger role of microflora in vaccine effectiveness.

"It's all speculation right now, but maybe higher microflora diversity creates a better situation for strong immune response against oral vaccine," said Dr. Kiyono.

The link between the gut microbiome and vaccine effectiveness has been previously revealed by the unfortunate fact that most vaccines are developed in industrialized nations and some are then less effective when delivered in developing countries. Mucosal vaccines, including oral vaccines against polio and cholera, seem especially prone to this disparity. Most scientific theories to explain the phenomenon focus on chronic intestinal inflammation linked to poor sanitation. (https://doi.org/10.1186/1741-7007-8-129)

"Probably for every vaccination right now, even injected vaccines, we should think of the immune status of the individual based on the condition of their microflora," said Dr. Kiyono.

It remains to be seen how microflora diversity will impact the global effectiveness of the new MucoRice edible vaccine system compared to other oral vaccines' records.

For now, the researchers plan to work with partners in the pharmaceutical industry to bring MucoRice-CTB into the next phase of clinical trials in Japan and overseas.

Research Publication

Yoshikazu Yuki, Masanori Nojima, Osamu Hosono, Hirotoshi Tanaka, Yasumasa Kimura, Takeshi Satoh, Seiya Imoto, Satoshi Uematsu, Shiho Kurokawa, Koji Kashima, Mio Mejima, Rika Nakahashi-Ouchida, Yohei Uchida, Takanori Marui, Noritada Yoshikawa, Fumitaka Nagamura, Kohtaro Fujihashi, Hiroshi Kiyono. 24 June 2021. Assessment of Oral MucoRice-CTB vaccine for the safety and microbiota-dependent immunogenicity in humans: A Randomized Trial. The Lancet Microbe.

https://bit.ly/3dlbASU

Further hope for BCG vaccine in stemming type 1 diabetes

Researchers presented positive trial updates at the 2021 Annual Scientific Sessions of the American Diabetes Association

Boston - At the recent 2021 Annual Scientific Sessions of the American Diabetes Association, researchers from Massachusetts General Hospital (MGH) presented positive updates on their trials of the bacillus Calmette-Guérin (BCG) vaccine to safely and significantly lower blood sugars.

In type 1 diabetes, an autoimmune disease which currently has no cure, T cells attack the pancreas and destroy its ability to create insulin, a hormone vital in allowing glucose to enter cells to produce energy.

In prior work, Denise Faustman, MD, PhD, director of the MGH Immunobiology Laboratory, and colleagues have found that BCG boosts a substance called TNF, which eliminates the harmful T cells and aids development of beneficial ones called regulatory T cells, or Tregs.

Key findings include new understanding in how response to BCG vaccination differs depending on a patient's age of onset and additional support for the role of BCG vaccination to alter glucose transport and change Tregs.

Currently 143 type 1 diabetics have received at least two doses of BCG, including 25 patients enrolled in a recently launched trial of adults who had pediatric onset. Pending FDA approval, MGH aims to launch a multi-center pediatric trial later this year.

"More data from randomized double-blinded clinical trials will be reported as we move towards additional readout of the Phase II trial," says Faustman, principal investigator of BCG clinical trials at MGH. "We have continued evidence of BCG's ability to reset and restore the immune system."

In 2018 MGH published results of the follow-up of Phase I trial of BCG-treated long-term diabetic participants, showing lasting clinically and statistically significant drops in HbA1c values that persisted with eight years of follow-up. The new data presented at the ADA include:

Type 1 diabetics with age of onset younger than 21 years have a faster response time and greater change in HbA1c than adult onset type 1 diabetics.

Over a period of three years BCG returns gene expression in Tregs in type 1 diabetics to a pattern consistent with non-type 1 control subjects.

The HbA1c response at two years in juvenile onset subjects is consistent with the three-year response seen in the Phase 1 study.

"BCG is an old vaccine, but it seems to be presenting new gifts," says Nigel Curtis, MD, PhD, of the Murdoch Children's Research Institute in Melbourne, Australia.

He directs global clinical trials on the beneficial and off-targets effects of the BCG vaccine but was not involved in the current study.

"This new data from MGH adds the growing understanding of how BCG changes the way the body responds to autoimmune and infectious disease."

The MGH team's findings set the stage for the read out of the ongoing five-year phase 2 study currently under way and anticipated to be complete in two years. Additional information about clinical trials is available at http://www.faustmanlab.org or by emailing DiabetesTrial@partners.org.

https://bit.ly/3jibJKv

CRISPR injected into the blood treats a genetic disease for first time

It nearly shut off production of toxic protein by their livers.

By Jocelyn Kaiser

The gene editor CRISPR excels at fixing disease mutations in lab-grown cells. But using CRISPR to treat most people with genetic disorders requires clearing an enormous hurdle: getting the molecular scissors into the body and having it slice DNA in the tissues where it's needed. Now, in a medical first, researchers have injected a CRISPR drug into the blood of people born with a disease that causes fatal nerve and heart disease and shown that in three of them it nearly shut off production of toxic protein by their livers.

Although it's too soon to know whether the CRISPR treatment will ease the symptoms of the disease, known as transthyretin amyloidosis, the preliminary data reported today are generating excitement about what could be a one-time, lifelong treatment. "These are stunning results," says gene editing researcher and cardiologist Kiran Musunuru of the University of Pennsylvania, who was not involved in the trial. "It exceeds all my expectations."

The work also marks a milestone for the race to develop treatments based on messenger RNA (mRNA), the protein-building instructions naturally made by cells. Synthetic mRNAs power two COVID-19 vaccines being given to millions of people to fight the coronavirus pandemic, and many companies are working on other mRNA vaccines and drugs.

The new treatment, which includes an mRNA encoding one of CRISPR's two components, "begins the convergence of the fields of CRISPR and mRNA," says cardiovascular researcher Kenneth Chien of the Karolinska Institute, a co-founder of Moderna, which makes one of the COVID-19 vaccines and is also developing mRNA drugs.

The CRISPR clinical trial aims to deactivate a mutated gene that causes liver cells to churn out misfolded forms of a protein called transthyretin (TTR), which build up on nerves and the heart and lead to pain, numbness, and heart disease. The resulting condition is relatively rare, and an approved drug, patisiran, can stabilize it. But researchers at veteran biotech Regeneron Pharmaceuticals and startup Intellia Therapeutics saw it as a good proof of principle for the injectable CRISPR treatment they were developing.

Last year, researchers used CRISPR to turn on a fetal form of hemoglobin to correct sickle cell disease or a related disease in several people. The treatment required removing a patient's diseased blood stem cells, modifying them with CRISPR in a dish, and then infusing them back into the body. A trial testing a direct injection of a virus encoding CRISPR's components into the eye to treat a condition that causes blindness is also underway.

But treating most other diseases means somehow injecting CRISPR's components, or genetic instructions for them, into the blood and having the therapy target an organ or tissue—a huge challenge, but potentially easier in the liver because it sops up foreign particles.

In the CRISPR trial, four men and two women with transthyretin amyloidosis between ages 46 and 64 were injected with a lipid particle carrying two different RNAs: an mRNA encoding the protein Cas, the CRISPR component that snips DNA, and a guide RNA to direct it to the gene for TTR. After Cas makes its cut, the cell's DNA repair machinery heals the break, but imperfectly, knocking out the activity of the gene.

After 28 days, three men given the higher of two doses of the treatment had an 80% to 96% drop in TTR levels, on par or better than the average of 81% with patisiran, the team reports today in *The New England Journal of Medicine*. "The data are extremely

encouraging," says trial leader Julian Gillmore of University College London, who also presented the study today at the online annual meeting of the Peripheral Nerve Society.

"It could be potentially the first curative treatment for this hereditary disabling and life-threatening disease," says neurologist David Adams of the University of Paris-Saclay, who led trials for patisiran. (That drug is a kind of RNA that silences TTR's production temporarily, meaning it must be injected on a regular basis.)

It may take months for patients receiving the CRISPR treatment to see their symptoms lessen, but they reported few short-term side effects. Problems could surface over time: CRISPR could potentially make cuts in the wrong DNA location (and in nonliver cells), triggering cancer or other problems.

But the lipid-encased mRNA approach is potentially safer than using viruses to ferry genetic instruction for encoding an editing protein and guide RNA into cells, a tried-and-true approach others are pursuing for systemic treatments. Those genes can persist in cells, continuing to make the gene editor long after it has done its job.

In contrast, "The beauty of mRNA is that it is gone afterwards," Chien says.

The study paves the way for treating other liver diseases with CRISPR, either by knocking out a gene or—more challenging—modifying it with the help of a DNA template. The latter approach could also be used to turn the liver into a factory for making an enzyme needed elsewhere in body.

Jennifer Doudna of the University of California, Berkeley, who shared a Nobel Prize last year for discovering CRISPR and co-founded Intellia, sees even bigger prospects. The new work, she says, is "a critical first step in being able to inactivate, repair, or replace any gene that causes disease, anywhere in the body."