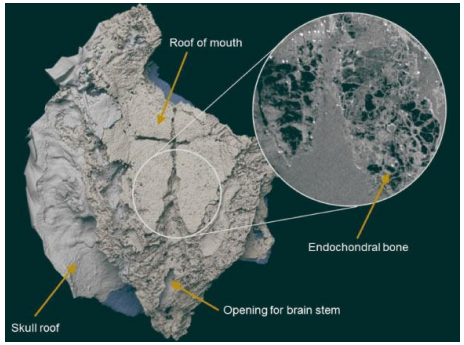
https://bit.ly/35qhHC6

# Devonian Fossil Shows Sharks May Have Evolved from Bony Ancestors

***Discovery suggests the lighter skeletons of sharks may have evolved from bony ancestors, rather than the other way around.***

Paleontologists in Mongolia have found the fossilized remains of *Minjinia turgenensis*, a new genus and species of placoderm fish that lived 410 million years ago (Early Devonian epoch). They've examined a partial braincase and skull roof of *Minjinia turgenensis* and found extensive endochondral bone, the hard bone that makes up our skeleton after birth. This discovery suggests the lighter skeletons of sharks may have evolved from bony ancestors, rather than the other way around.




***Virtual 3D model of the braincase of Minjinia turgenensis generated from CT scan. Inset shows raw scan data showing the spongy endochondral bone inside.*** **Image credit: Brazeau et al, doi: 10.1038/s41559-020-01290-2.**

Sharks have skeletons made of cartilage, which is around half the density of bone. Cartilaginous skeletons are known to evolve before bony ones, but it was thought that sharks split from other animals on the evolutionary tree before this happened, keeping their cartilaginous skeletons while other fish, and eventually us, went on to evolve bone.

*Minjinia turgenensis* belongs to a broad group of fish called placoderms, out of which sharks and all other jawed vertebrates — animals with backbones and mobile jaws — evolved. Previously, no placoderm had been found with endochondral bone, but the skull fragments of the ancient fish species were wall-to-wall endochondral.

This could suggest the ancestors of sharks first evolved bone and then lost it again, rather than keeping their initial cartilaginous state for more than 400 million years.

"It was a very unexpected discovery," said lead author Dr. Martin Brazeau, a researcher in the Department of Life Sciences at Imperial College London and the Department of Earth Sciences at Natural History Museum, London.

"Conventional wisdom says that a bony inner skeleton was a unique innovation of the lineage that split from the ancestor of sharks more than 400 million years ago, but here is clear evidence of bony inner skeleton in a cousin of both sharks and, ultimately, us."

"If sharks had bony skeletons and lost it, it could be an evolutionary adaptation," he added. "Sharks don't have swim bladders, which evolved later in bony fish, but a lighter skeleton would have helped them be more mobile in the water and swim at different depths."

"This may be what helped sharks to be one of the first global fish species, spreading out into oceans around the world 400 million years ago." The study was published online today in the journal *Nature Ecology & Evolution*.

*M.D. Brazeau et al. Endochondral bone in an Early Devonian 'placoderm' from Mongolia. Nat Ecol Evol, published online September 7, 2020; doi: 10.1038/s41559-020-01290-2*

https://bit.ly/2FktBD1

# Producing leather-like materials from fungi

***Biofabrication includes upcycling of low-cost agricultural and forestry by-products***

An international team led by material chemists Alexander Bismarck and Mitchell Jones from the University of Vienna demonstrate the considerable potential of these renewable sustainable fabrics derived from fungi in their latest review article in *Nature Sustainability*.

Traditional leather and its alternatives are typically obtained from animals and synthetic polymers.

Leather can be considered a co-product of meat production with both livestock farming and the leather production process increasingly considered to be ethically questionable and environmentally unfriendly (e.g. deforestation for grazing, greenhouse gas emissions, use of hazardous substances in the tanning process).

The production of synthetic leather materials from plastics such as polyvinyl chloride (PVC) or polyurethane (PU) also depend on chemicals derived from fossil fuels.

"This is where leather-like materials from fungi come into play, which, in general, are CO2 neutral as well as biodegradable at the end of their life span," says Alexander Bismarck from the Faculty of Chemistry at the University of Vienna, who additionally holds a visiting professorship at Imperial College London.

**Growth of fungal mycelium**

Leather substitutes can be produced from fungi by upcycling low-cost agricultural and forestry by-products (e.g. sawdust). These serve as a feedstock for the growth of fungal mycelium, which constitutes a mass of elongated tubular structures and represents the vegetative growth of filamentous fungi.

Within a couple of weeks, the fungal biomass can be harvested and physically and chemically treated (e.g. pressing, cross-linking).

"As a result, these sheets of fungal biomass look like leather and exhibit comparable material and tactile properties," says department head Alexander Bismarck. The first biotech companies are already marketing materials derived from fungi.

Leather substitute materials derived from fungi typically contain completely biodegradable chitin (which acts as a stabiliser in the material) and other polysaccharides such as glucans.

In their own studies, Alexander Bismarck and Mitchell Jones (now affiliated with Vienna University of Technology) already conducted research using fungal species, such as the white button mushroom A. bisporus and bracket fungus D. confragosa, to produce paper and foam-like construction materials for applications, such as insulation.

**Considerable potential as a leather substitute**

In this review article, the scientists examine the sustainability of bovine and synthetic leathers and present an overview of the first developments and commercialisation of leather substitutes derived from fungi.

According to the authors, one of the greatest challenges in the production of fungi-derived leather-like materials is still to achieve homogeneous and consistent mycelium mats, "exhibiting uniform growth and consistent thickness, colour and mechanical properties". To date, the production of these materials has been driven mainly by entrepreneurial spirit.

Fungi as a raw material for leather substitutes provide a cost-effective, socially and environmentally sound alternative to bovine and synthetic leather and are of particular interest to sustainability-conscious consumers and companies as well as to the vegan community, the researchers write.

According to them, "substantial advances in this technology and the growing number of companies that are producing fungi-biomass-based leather alternatives suggests that this new material will play a considerable role in the future of ethically and environmentally responsible fabrics".

*Publication in Nature Sustainability: Leather-like material biofabrication using fungi, Mitchell Jones, Antoni Gandia, Sabu John and Alexander Bismarck, in: Nature Sustainability 2020, DOI: 10.1038/s41893-020-00606-1*

https://bit.ly/35tyPa3

# Psychedelic 'Trips' Really Are Similar to Religious Experiences in Many Ways

***Experiences with psychedelics found that having a mystical or religious experience on drugs might play an important role***

**David Nield**

A growing body of drug research has shown that experiences with psychedelic drugs can be both positive and negative – scary and uncomfortable for some, but leading to improvements in well-being and relationships for others. These substances also show promising early results for treating mental disorders, in controlled doses.

So why the disparity between the good and the bad experiences? A team of researchers questioning 288 individuals on their experiences with psychedelics has found that having a mystical or religious experience on drugs might play an important role.

The study plugs some gaps in our knowledge about how drugs such as LSD and psilocybin induce religious-style experiences, and could tell us more about how to use these substances in treatments.

It also shows that drug highs and spiritual highs can produce the same sort of feelings and moods in people.

"Even when taken for the first time, psychedelics may occasion powerful subjective experiences that share many features with those described by mystics, dedicated meditators, and religious practitioners," psychologist Samuli Kangaslampi from Tampere University in Finland told PsyPost.

"Some research is beginning to demonstrate that undergoing a mystical-type experience may be linked to improved relationships with self, others, and the natural environment later on."

The study made use of a Finnish translation of the 30-question Revised Mystical Experiences Questionnaire (MEQ30), which asks volunteers to try to quantify some of the feelings and sensations they've had while on psychedelics.

The team assessed different ways of translating MEQ30 to find the most reliable method for accurately reflecting volunteers' experiences. They then went on to exploring the link between the psychedelic and the spiritual.

Those people who scored highly on the MEQ30 were more likely to describe their experience as mystical, spiritual, or religious, and more personally significant.

These feelings might include an increased awareness of an inner world, for example, or getting the impression of transcending time and space. This scientific validation opens up more areas for future research, including the lasting effects of these drugs.

"Those with full mystical experiences reported more positive changes in all areas surveyed, as compared with those without such an experience," the researchers write in their paper.

For future studies, the team is interested in looking at how mystical-type experiences brought on by psychedelics might differ between different cultures and contexts, which is why the translation of the MEQ30 is important.

There are some limitations to note: the study participants were self-reporting on their experiences, which can lead to inaccuracies and misremembering. What's more, in some cases the experiences were quite some time ago.

Nevertheless, the researchers suggest that their findings are enough to show links between having a mystical or religious experience on psychedelic drugs, and that experience turning out to be positive in the long term – and that gives medical professionals something to work with in future treatments too.

"Providing a setting conducive to such experiences, whether described as mystical, peak, or emotional breakthrough, is also likely to be of benefit in clinical applications of psychedelics," say the researchers in their published paper. The research has been published in the *Journal of Psychoactive Drugs*.

https://bit.ly/2DRkclN

# Study pinpoints process that might have led to first organic molecules

## *New research could have relevance to search for extraterrestrial life, green chemistry*

New research led by the American Museum of Natural History and funded by NASA identifies a process that might have been key in producing the first organic molecules on Earth about 4 billion years ago, before the origin of life. The process, which is similar to what might have occurred in some ancient underwater hydrothermal vents, may also have relevance to the search for life elsewhere in the universe. Details of the study are published this week in the journal *Proceedings of the National Academy of Sciences*.

All life on Earth is built of organic molecules--compounds made of carbon atoms bound to atoms of other elements such as hydrogen, nitrogen and oxygen. In modern life, most of these organic molecules originate from the reduction of carbon dioxide (CO2) through several "carbon-fixation" pathways (such as photosynthesis in plants). But most of these pathways either require energy from the cell in order to work, or were thought to have evolved relatively late. So how did the first organic molecules arise, before the origin of life?

To tackle this question, Museum Gerstner Scholar Victor Sojo and Reuben Hudson from the College of the Atlantic in Maine devised a novel setup based on microfluidic reactors, tiny self-contained laboratories that allow scientists to study the behavior of fluids--and in this case, gases as well--on the microscale. Previous versions of the reactor attempted to mix bubbles of hydrogen gas and CO2 in liquid but no reduction occurred, possibly because the highly volatile hydrogen gas escaped before it had a chance to react. The solution came in discussions between Sojo and Hudson, who shared a lab bench at the RIKEN Center for Sustainable Resource Science in Saitama, Japan. The final reactor was built in Hudson's laboratory in Maine.

"Instead of bubbling the gases within the fluids before the reaction, the main innovation of the new reactor is that the fluids are driven by the gases themselves, so there is very little chance for them to escape," Hudson said.

The researchers used their design to combine hydrogen with CO2 to produce an organic molecule called formic acid (HCOOH). This synthetic process resembles the only known CO2-fixation pathway that does not require a supply of energy overall, called the Wood-Ljungdahl acetyl-CoA pathway. In turn, this process resembles reactions that might have taken place in ancient oceanic hydrothermal vents.

"The consequences extend far beyond our own biosphere," Sojo said. "Similar hydrothermal systems might exist today elsewhere in the solar system, most noticeably in Enceladus and Europa--moons of Saturn and Jupiter, respectively--and so predictably in other water-rocky worlds throughout the universe."

"Understanding how carbon dioxide can be reduced under mild geological conditions is important for evaluating the possibility of an origin of life on other worlds, which feeds into understanding how common or rare life may be in the universe," added Laurie Barge from NASA's Jet Propulsion Laboratory, an author on the study.

The researchers turned CO2 into organic molecules using relatively mild conditions, which means the findings may also have relevance for environmental chemistry. In the face of the ongoing climate crisis, there is an ongoing search for new methods of CO2 reduction.

"The results of this paper touch on multiple themes: from understanding the origins of metabolism, to the geochemistry that underpins the hydrogen and carbon cycles on Earth, and also to green chemistry applications, where the bio-geo-inspired work can

help promote chemical reactions under mild conditions," added Shawn E. McGlynn, also an author of the study, based at the Tokyo Institute of Technology.

*Other authors on this study include Ruvan de Graaf and Mari Strandoo Rodin from the College of the Atlantic, Aya Ohno from the RIKEN Center for Sustainable Resource Science in Japan, Nick Lane from University College London, Yoichi M.A. Yamada from RIKEN, Ryuhei Nakamura from RIKEN and Tokyo Institute of Technology, and Dieter Braun from Ludwig-Maximilians University in Munich.*

*This work was supported in part by NASA's Maine Space Grant Consortium (SG-19-14 and SG-20-19), the U.S. National Science Foundation (1415189 and 1724300), the Japan Society for the Promotion of Science (FY2016-PE-16047 and FY2016-PE-16721), the National Institutes of Health's National Institute of General Medical Sciences (P20GM103423), the European Molecular Biology Organization (ALTF- 725 1455-2015), the Institute for Advanced Study in Berlin, and the Gerstner Family Foundation.*

*DOI: 10.1073/pnas.2002659117*

***https://bit.ly/2ZuYHP7***

## Skeletal study suggests at least 11 fish species are capable of walking

### *An international team of scientists has identified at least 11 species of fish suspected to have land-walking abilities.*

Gainesville, Fla. - The findings are based on CT scans and a new evolutionary map of the hillstream loach family, which includes the only living fish species caught in the act of walking: a rare, blind cavefish known as Cryptotora thamicola, or the cave angel fish. Pinpointing which species of hillstream loaches have walking capabilities can help scientists piece together how the first land-walking vertebrates might have come to be.

In a new study, researchers from the Florida Museum of Natural History, the New Jersey Institute of Technology, Louisiana State University and Maejo University in Thailand analyzed the bone structure of nearly 30 hillstream loach species, describing for the first time three categories of pelvic shapes. Based on the shape of the bone that connects some loaches' spines to their pelvic fins, the team found that 10 other species of loach shared the cave angel fish's unusually hefty pelvic girdle.

"Fishes don't usually have any connection between their spine and pelvic fin," said biologist Zachary Randall, manager of the Florida Museum's imaging lab and one of the study's co-authors. "But before the idea was that the cave angel fish was totally unique. What's really cool about this paper is that it shows with high detail that robust pelvic girdles are more common than we thought in the hillstream loach family."

***Thailand's cave angel fish, Cryptotora thamicola, is famous for its ability to walk, using a salamander-like gait. But it may not be alone: At least 10 relatives share its unusual pelvic shape.*** **Zachary Randall/Florida Museum**

But not all loaches are so gifted: Though more than 100 species of hillstream loach are found throughout Southeast Asia, the cave angel fish is the only one whose walking capabilities have been observed and studied. Its salamander-like wiggle, powered by enlarged ribs bolstered with stabilizing muscle attachments, was first described in *Scientific Reports* in 2016 by Brooke Flammang, an assistant professor of biology at NJIT and the study's lead principal investigator.

Randall said the cave angel fish's walk is a key adaptation for surviving fast-flowing cave streams. It can grip rocky streambeds and move between habitats - even up waterfalls - as water levels fluctuate in the dry season. The cave angel fish's increased mobility could help it access well-oxygenated stream regions with few or no occupants. Still, little is known about the species, including what it eats.

"These loaches have converged on a structural requirement to support terrestrial walking not seen in other fishes," said study lead author and NJIT Ph.D. candidate Callie Crawford in a statement.

"The relationships among these fishes suggest that the ability to adapt to fast-flowing rivers may be what was passed on genetically," rather than a set of specific physical characteristics.

The team used CT scanning and DNA analysis to trace the evolutionary history of the hillstream loach family and found that, rather than evolving from a single origin, a robust pelvic region appeared several times across the hillstream loach family.

"Even though the cave angel fish was first described in 1988, this is the first time it's been included in the hillstream loach family tree," Randall said. "With our Thai collaborators and using DNA analysis, we were able to use hundreds of genes to trace how pelvic shapes in these fish have evolved over time. Now, we have a much more accurate tree that adds a framework for studying how many species can walk and the extent to which they're able to."

"This study brought together a team of researchers with interests and levels of expertise that varied from those of us who do fieldwork and study fishes in their natural habitats to geneticists to comparative anatomists," added Lawrence Page, Florida Museum curator of fishes and a co-principal investigator of the study. "The result is a greatly improved understanding of the evolution of an extremely uncommon event - the ability of a fish to walk on land."

Randall and his team most recently observed the cave angel fish on a 2019 cave excursion in northwest Thailand. Given the rarity of spotting a cave angel fish in the field, Randall said the team was surprised to find six of them clinging to the bed of a fast-flowing shallow stream among glittering stalagmites in one of the cave's chambers. He added that the cave angel fish's rarity meant that museum specimens and CT data were key to mapping the family's evolution.

"The beauty of CT scanning is that you can capture different types of high-resolution data without compromising the integrity of the specimen," Randall said. "For rare species like this one, it even allows you to capture things that are hard to observe in the field, even what it eats."

The team published its work in the *Journal of Morphology*.

*Prosanta Chakrabarty, curator of fishes at LSU's Museum of Natural Science, is a co-principal investigator of the study. Pamela Hart of LSU and Apinun Suvarnaraksha of Maejo University are also co-authors.*

*Some CT scans used in the research came from the National Science Foundation-funded oVert project.*

***https://bit.ly/2Relo5G***

## Large-Scale SETI Survey of Vela Region Finds No Signs of Extraterrestrial Intelligence

***In this part of the Milky Way it appears alien civilizations are elusive, if they exist.***

Astronomers using the Murchison Widefield Array (MWA) radio telescope have searched for technosignatures — indicators of advanced extraterrestrial civilizations — in six known exoplanets and over 10 million stellar systems in the Vela region of our Milky Way Galaxy.

But in this part of the Milky Way at least, it appears alien civilizations are elusive, if they exist.

“The MWA is a unique telescope, with an extraordinarily wide field-of-view that allows us to observe millions of stars simultaneously,” said Dr. Chenoa Tremblay, an astronomer at the CSIRO Astronomy and Space Science.

Dr. Tremblay and her colleague, Professor Steven Tingay from the Curtin University node of the International Centre for Radio Astronomy Research, searched for narrow-band signals consistent with radio transmissions from six known exoplanets (HD 75289b, HD 73526b, HD 73526c, HD 70642b, DE0823-49b and KELT-15b) and 10,355,066 stellar systems in the Vela region.

“The telescope was searching for powerful radio emissions at frequencies similar to FM radio frequencies, that could indicate the presence of an intelligent source,” she explained.

"We observed the sky around the constellation of Vela for 17 hours, looking more than 100 times broader and deeper than ever before."
"With this dataset, we found no technosignatures — no sign of intelligent life."

***Dipole antennas of the Murchison Widefield Array in Australia.*** **Image credit: Dragonfly Media.**

"Even though this was the broadest search yet, we were not shocked by the result," Professor Tingay said. "As Douglas Adams noted in *The Hitchhikers Guide to the Galaxy*, 'space is big, really big'." "And even though this was a really big study, the amount of space we looked at was the equivalent of trying to find something in the Earth's oceans but only searching a volume of water equivalent to a large backyard swimming pool."
"Since we can't really assume how possible alien civilizations might utilize technology, we need to search in many different ways." "Using radio telescopes, we can explore an eight-dimensional search space," he said. "Although there is a long way to go in the search for extraterrestrial intelligence, telescopes such as the MWA will continue to push the limits — we have to keep looking." The team's paper appears in the *Publications of the Astronomical Society of Australia*.

*C.D. Tremblay & S.J. Tingay. A SETI survey of the Vela region using the Murchison Widefield Array: Orders of magnitude expansion in search space. Publications of the Astronomical Society of Australia, published online September 7, 2020; doi: 10.1017/pasa.2020.27*

***https://bit.ly/3bLI1ba***

## A lack of oxygen in tumors promotes metastasis

***A research group at the University of Basel has now identified lack of oxygen as the trigger for metastasis***

Metastases are formed by cancer cells that break away from the primary tumor. A research group at the University of Basel has now identified lack of oxygen as the trigger for this process. The results reveal an important relationship between the oxygen supply to tumors and the formation of metastases. This research may open up new treatment strategies for cancer.
The chances of recovery significantly worsen when a tumor metastasizes. Previous research has shown that metastases are formed by clusters of cancer cells that separate from the primary tumor and migrate to new tissue through the bloodstream. However, thus far little has been known about why these clusters of circulating tumor cells (CTCs) leave the tumor in the first place.

**Lack of oxygen leads to more metastases**

Professor Nicola Aceto's research group at the University of Basel's Department of Biomedicine has now shown that a lack of oxygen is responsible for the separation of CTC clusters from the tumor. This is an important starting point for the development of new cancer treatments.
A mouse model for breast cancer formed the basis of the experiments: the researchers analyzed the oxygen supply inside these tumors, which are equivalent to human cancer tissue, the detachment of CTCs and their molecular and cell biological properties.
It turned out that different areas of a tumor are supplied with different levels of oxygen: cancer cells with a lack of oxygen were found wherever the tumor had comparatively fewer blood vessels - in the core of the tumor as well as in clearly defined peripheral areas. Next, the research team investigated the CTC clusters that had separated from these tumors and found that they similarly suffered from a lack of oxygen. This led to the conclusion that cells leave the tumor if they do not receive enough oxygen. "It's as

though too many people are crowded together in a small space. A few will go outside to find some fresh air," says Aceto.

Further experiments showed that these CTC clusters with a lack of oxygen are particularly dangerous: in comparison to clusters with normal oxygen content, they formed metastases faster and shortened the mice's survival time. "If a tumor does not have enough oxygen, these CTC clusters, which have a particularly high potential to develop metastases, will break away," says Aceto.

**Stimulating blood vessel formation as a treatment approach**

This insight led the researchers to take a closer look at the effect of what is called proangiogenic treatment: they stimulated the formation of blood vessels, thus boosting the supply of oxygen to the tumor cells. As expected, the number of separating CTC clusters dropped, the mice formed fewer metastases, and they lived longer - but at the same time, the primary tumor increased in size significantly.

"This is a provocative result," says Aceto. "If we give the tumor enough oxygen, the cancer cells have no reason to leave the tumor and metastasize. On the other hand, this accelerates the growth of the primary tumor."

The next challenge is to transfer these findings to a clinical environment, where the characteristics of tumors vary from patient to patient: "But we speculate that substances that improve oxygen supply to the tumor can inhibit the formation of metastases in breast cancer, alone or in combination with other agents."

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

## How German military scientists likely identified the nerve agent used to attack Alexei Navalny

***Scientists familiar with Novichoks have a good idea how the toxicological sleuths went about it—and are impressed by how fast the culprit was unmasked.***

**By Richard Stone**

On 2 September, German Chancellor Angela Merkel revealed that Alexei Navalny, a Russian opposition politician, had been poisoned with a nerve agent "identified unequivocally in tests" as a Novichok—one of a family of exotic Soviet-era chemical weapons. Merkel, a chemist by training, did not reveal the nature of the tests, conducted in a military lab in Munich. But scientists familiar with Novichoks have a good idea how the toxicological sleuths went about it—and are impressed by how fast the culprit was unmasked.

Navalny fell ill on 20 August after drinking a cup of tea at a Siberian airport. He lapsed into a coma and was flown to Berlin 2 days later; in a statement yesterday, the hospital treating him said he is out of the coma and "responding to verbal stimuli." Navalny's supporters have accused Russian operatives of slipping poison into the tea—a charge that seems credible in light of Russia's recent record of using toxic substances to silence critics.

Novichok A234 was the weapon of choice for settling a score with a former Russian spy, Sergei Skripal, in Salisbury in the United Kingdom in March 2018. In a botched operation, two Russian intelligence officers left a trail of evidence in the attempted assassination of Skripal, whose daughter Yulia also fell ill after exposure to A234. They survived, but a woman who later came across a perfume bottle containing the substance died.

The Salisbury scandal brought Novichoks out of the shadows. After a Russian chemist in 1992 divulged some details about the exquisitely toxic nerve agents—there are at least seven of them—the U.S. government and allies clamped down on open discussion; Novichoks were classified as secret. A234's brazen use in the United Kingdom led to a public reckoning. In October 2019, parties to the Chemical Weapons Convention agreed to add Novichoks to the treaty's list of toxic chemicals, bringing them under the convention's verification regime and paving the way for research

on the mechanism of action of these "fourth generation" nerve agents, as well as on countermeasures and treatments.

The diplomatic progress hardly deterred Navalny's unknown assailants. As doctors in Berlin fought to save him, scientists at the Bundeswehr Institute of Pharmacology and Toxicology in Munich set out to unravel the mysterious cause of his symptoms.

They had clear targets to hunt for. Like other nerve agents, Novichoks bind to acetylcholinesterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine when it is released into synapses. Common symptoms of Novichok poisoning include nausea, trouble breathing, and seizures; without medical intervention, victims can slip into a coma. Red blood cells have AChE anchored to their membranes, so a blood sample could yield a conjugate formed when a Novichok latches onto AChE, which scientists could detect using mass spectrometry, says Palmer Taylor, a pharmacologist at the University of California, San Diego (UCSD).

Another possibility is a Novichok conjugate of serum albumin, the most abundant protein in the blood. Nerve agent conjugates with serum albumin "are very useful markers" that can be detected for at least a couple of weeks after a poisoning, says Stefano Costanzi, a chemist and nonproliferation analyst at American University in Washington, D.C.

A third candidate is a conjugate of butyrylcholinesterase (BChE), an enzyme that scavenges nerve agent molecules in the bloodstream. It would be straightforward to use an anti-BChE antibody to latch onto the conjugate and then digest the protein. Most of the Novichok molecule would remain linked to one of the fragments and would be easy to detect by mass spectrometry, says Oksana Lockridge, a toxicologist at the University of Nebraska Medical Center. "I have no doubt that the Bundeswehr group used this method," she says. "The part of the Novichok that stays attached to the enzyme is way larger than that of any other nerve agent," says UCSD chemist Zoran Radić. Detection of such a conjugate would make identification of a Novichok "100% certain," says Lockridge, who is developing BChE as a prophylactic for exposure to nerve agents.

The Salisbury probe presumably yielded closely held insights into Novichoks. U.K. authorities now "know much more about toxicity, detection, and general behavior of Novichoks," says Kamil Kuča, a toxicologist at the University of Hradec Králové in the Czech Republic. "They could share their results with 'friends'" such as Germany, he says. And chemical detective work undertaken by investigators at the U.K. defense lab Porton Down may have sped up analyses at the Munich lab, Radić says, by "providing a suitable set of protocols to follow."

It may also be possible to directly detect the parent compound—the Novichok itself—in Navalny's body. "One could easily assume that they accumulate in lipids," Radić says. In an article earlier this year in the journal *Heliyon*, a team at the U.S. Army Combat Capabilities and Development Command Chemical Biological Center showed three Novichok compounds are much more stable than other nerve agents, with the most durable, A234, about 1000-fold more stable than the nerve agent sarin.

That stability may be a big factor in why the handful of known Novichok victims respond so poorly to treatment: It could take weeks for lipids in fat cells to relinquish their Novichok reserves. Another insidious characteristic of Novichoks is their death grip on AChE: They bind to and block not one site in the active center—as other nerve agents do—but two. "Novichok structures are unique. Really different from other nerve agents," Radić says. For that reason oximes, an antidote that pries nerve agents off AChE and leads to reactivation of the enzyme, may be far less effective against Novichoks than against classical nerve agents like sarin.

"There's no declassified information on reactivation" in Novichok victims, Radić says. One researcher says pralidoxime, an antidote carried by U.S. soldiers at risk of nerve agent exposure, helped the Salisbury victims—but not by reactivating AChE.

Regardless of who perpetrated the attack on Navalny, the brazen incident and revelations about the Novichoks's durability heighten concerns about the threat they pose. And while most nerve agents are stockpiled as liquids, some Novichoks are stable as an ultra-fine powder. "They can be hidden and stored much more easily than classical nerve agents," says Radić, who notes that makes them more likely to end up on the black market.

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

## A pain reliever that alters perceptions of risk

***In study, acetaminophen makes risky moves seem less dangerous***

Columbus, Ohio - While acetaminophen is helping you deal with your headache, it may also be making you more willing to take risks, a new study suggests.

People who took acetaminophen rated activities like "bungee jumping off a tall bridge" and "speaking your mind about an unpopular issue in a meeting at work" as less risky than people who took a placebo, researchers found.

Use of the drug also led people to take more risks in an experiment where they could earn rewards by inflating a virtual balloon on a computer: Sometimes they went too far and the balloon popped.

"Acetaminophen seems to make people feel less negative emotion when they consider risky activities - they just don't feel as scared," said Baldwin Way, co-author of the study and associate professor of psychology at The Ohio State University.

"With nearly 25 percent of the population in the U.S. taking acetaminophen each week, reduced risk perceptions and increased risk-taking could have important effects on society."

The study extends a series of studies led by Way that have shown acetaminophen - the main ingredient in the pain-reliever Tylenol and nearly 600 other medicines - has psychological effects that most people don't consider when they take it.

Previous research by Way and his colleagues has shown that acetaminophen reduces positive and negative emotions, including hurt feelings, distress over another's suffering and even your own joy.

Way conducted the current study with Alexis Keaveney, a former doctoral student at Ohio State, and Ellen Peters, a former professor at Ohio State who is now at the University of Oregon. The study was published online in the journal *Social Cognitive and Affective Neuroscience*.

In one study, 189 college students came to a lab and took either 1,000 mg of acetaminophen (the recommended dosage for a headache) or a placebo that looked the same. After waiting for the drug to take effect, the participants rated on a scale of 1 to 7 how risky they thought various activities would be.

Results showed that those under the influence of acetaminophen rated activities like bungee jumping, walking home alone at night in an unsafe area of town, starting a new career in your mid-30s, and taking a skydiving class as less risky than those who took the placebo.

The effects of acetaminophen on risk-taking were also tested in three separate experimental studies.

Across these studies, 545 undergraduate students took part in a task developed in 2002 that is often used by researchers to measure risk-taking behavior. Other researchers have shown that taking more risk on this task predicted risky behaviors outside the laboratory, including alcohol and drug use, driving without a seatbelt and stealing.

In the task, participants click a button on the computer to inflate a balloon on their computer screen. Each time they inflate it they receive virtual money. They can stop at any time and add the money to their "bank," and move on to the next balloon. But there is risk involved.

"As you're pumping the balloon, it is getting bigger and bigger on your computer screen, and you're earning more money with each pump," Way said.

"But as it gets bigger you have this decision to make: Should I keep pumping and see if I can make more money, knowing that if it bursts I lose the money I had made with that balloon?"

For those who took the acetaminophen, the answer was: Keep on pumping. Results showed that those on the drug pumped more times than those on the placebo and had more burst balloons.

"If you're risk-averse, you may pump a few times and then decide to cash out because you don't want the balloon to burst and lose your money," he said. "But for those who are on acetaminophen, as the balloon gets bigger, we believe they have less anxiety and less negative emotion about how big the balloon is getting and the possibility of it bursting."

The results have a variety of real-life implications, Way said.

For example, acetaminophen is the recommended treatment by the CDC for initial COVID-19 symptoms.

"Perhaps someone with mild COVID-19 symptoms may not think it is as risky to leave their house and meet with people if they're taking acetaminophen," Way said.

Even everyday activities like driving presents people with constant decisions involving risk perception and assessment that could be altered by use of the painkiller.

"We really need more research on the effects of acetaminophen and other over-the-counter drugs on the choices and risks we take," he said.

***https://bit.ly/3mq3AWq***

# Kabuki Actor's Forgotten Manuscript Yields Clues About 1855 Quake in Japan

***Researchers analyzed a survivor's account of the disaster to better understand future temblors.***

**By Tim Hornyak**

In 1855, a powerful earthquake struck the Japanese city of Edo (today's Tokyo), killing thousands. The region sits atop multiple tectonic plates that have caused innumerable quakes over the centuries, and because the greater metropolitan area is now home to more than 30 million people, it's critical to mitigate the threat. Japanese scientists have been examining historical records to better understand past quakes and have found that the autobiography of a Kabuki actor can shed light on the 1855 temblor.

## A Time of Turmoil

The 1855 Ansei Edo quake, named for the Ansei imperial era of 1854–1860, came at a time of upheaval in Japan, both literally and figuratively. There were three great Ansei earthquakes: the Tokai and Nankai quakes, both in 1854 and both magnitude 8.4, and the Edo quake the following year, magnitude 7.0. Meanwhile, Japanese society was facing its greatest challenge in centuries. Having been under the hegemony of the Tokugawa shogunate, which implemented a policy of national seclusion for over 230 years, Japan was finally forced to open its doors to ships and trade by American gunboat diplomacy in 1854.

When Edo was hit on 11 November 1855, as many as 10,000 people lost their lives, and over 50,000 structures were destroyed in the temblor and subsequent fires. Some of the devastation can be seen in woodblock prints of the day that depict a giant underground catfish (*Namazu*) that was believed to have caused earthquakes when it thrashed about.

## The Forgotten Manuscript

Fast-forward to 2020, and researchers at the University of Tokyo have found another way to use art to scientifically evaluate the 1855 calamity. Scientists analyzed a manuscript written by Kabuki actor Nakamura Nakazo III to infer the depth of the earthquake.

In a poster presented at a joint conference of the Japan Geoscience Union and AGU (JpGU-AGU Joint Meeting 2020) in July, they noted that later editions of the manuscript had already been the basis for varying estimates of the quake's hypocenter from relatively shallow in the crust to deep in the Philippine Sea plate. However, when the team analyzed Nakamura's original handwritten manuscript of the autobiographical work *Temae Miso* (Self-Praise), recently acquired by Tokyo's National Diet Library, it found a significant difference compared with later editions.

"A strong rumble occurred," Nakamura wrote. "The women and children were surprised and screamed. I said, 'Calm down, it's a big earthquake.' Omitu Bando said to me, 'You should stand up rather than sit.' I stood up. Then the strong shaking started, and I could not walk normally." Instead of the first sentence, one later edition has "a strong upward movement came from the ground," and where the writer describes standing, the later edition reads, "I stood up and walked. Then the strong shaking started…."

Researchers concluded that because the shaking began when Nakamura stood up instead of after he began walking, there was a relatively short period between the arrival of different seismic waves from the quake—in this case, the rumble and the shaking. Longitudinal, or *P*, waves are fastest and correspond to the rumble described by Nakamura. Transverse, or *S*, waves travel about half the speed and correspond to the shaking. Just as the distance to a thunderstorm can be estimated by the lag between a lightning flash and the sound of thunder, the *S*–*P* interval can suggest the distance to an earthquake's epicenter.

The team concluded that the 1855 quake had an *S*–*P* time of 5–10 seconds and, because of the thick sedimentary layers of the Kanto region surrounding Tokyo, a relatively shallow depth of about 20 kilometers, which would place the rupture in the subducting Philippine Sea plate. Many researchers have estimated the depth at over 30 kilometers.

***Courtesans from Edo's Yoshiwara pleasure district attack a mythical giant catfish, which was believed to have caused earthquakes, in this 1855 woodblock print.*** **Earthquake Research Institute Library of the University of Tokyo**

Such details are critical because the Japanese government believes there's a 70% chance of another 1855-type quake in the next 30 years with as many as 23,000 casualties, according to poster coauthor Kenji Satake, director of the University of Tokyo's Earthquake Research Institute.

"Since the typical recurrence interval of large earthquakes is several decades to centuries," Satake added, "we have to use other methods and data to study such large earthquakes in the past and the potential for the future."

"Ground shaking and earthquake damage is larger for shorter hypocentral distances," said coauthor Ryoichi Nakamura, another member of the institute. "Because the 1855 earthquake occurred right beneath Tokyo, the depth strongly affects ground shaking and damage."

## Interdisciplinary Teamwork

William Ellsworth, a professor of geophysics at Stanford University who was not involved in the research, believes the poster agrees with other findings.

"Seismologists have debated [the quake's depth] for more than a century," said Ellsworth. "The plates colliding beneath Tokyo provide a wide range of possibilities, both deep and shallow. The recent paper by Nakamura et al.…makes clever use of reports of the shaking to argue for a relatively shallow depth. Their work supports the conclusion of William Bakun, who used other historical accounts of the earthquake shaking to determine its magnitude, location, and depth."

The poster is part of a greater interdisciplinary effort at the University of Tokyo. Seismologists teamed up with historians from the Historiographical Institute in an effort called the Collaborative Research Organization for Historical Materials on Earthquakes and Volcanoes. Inaugurated years after the catastrophic magnitude 9 Great East Japan Earthquake of 2011, its aim is to improve seismic understanding by compiling a long-term database of events based on historical materials. That means analyzing obscure records like Nakamura's manuscript, written in a highly cursive hand that only experts can decipher.

"Different kinds of materials provide different kinds of information on earthquakes," said poster coauthor Reiko Sugimori, an associate professor in the Historiographical Institute and the only team member who was able to read the Kabuki actor's manuscript. "Earthquake casualties or damage in each village were summarized as reports, which are useful to estimate the distribution of seismic intensity, from which earthquake location and size can be estimated. On the other hand, daily records or personal diaries, written by the same person in the same location, can provide homogeneous daily records of seismicity, including foreshocks or aftershocks. Pictures are also useful because they provide visual records of earthquake damage."

Researchers plan to continue adding details from historical materials to their historical seismic event database, and their work highlights the importance of long-term seismic knowledge. Later this month, *Seismological Research Letters* will publish a focus section coauthored by Satake on historical seismology.

***Citation:*** *Hornyak, T. (2020), Kabuki actor's forgotten manuscript yields clues about 1855 quake in Japan, Eos, 101, https://doi.org/10.1029/2020EO148624. Published on 08 September 2020.*

***https://wb.md/2ZuSa7h***

# Unexpected Results in New COVID-19 'Cytokine Storm' Data

### *Cytokine storm" does not play a major role in more severe COVID-19 outcomes*

**Damian McNamara**

The immune system overactivation known as a "cytokine storm" does not play a major role in more severe COVID-19 outcomes, according to unexpected findings in new research. The findings stand in direct contrast to many previous reports.

"We were indeed surprised by the results of our study," senior study author Peter Pickkers, MD, PhD, told *Medscape Medical News*.

In a unique approach, Pickkers and colleagues compared cytokine levels in critically ill people with COVID-19 to those in patients with bacterial sepsis, trauma, and after cardiac arrest.

"For the first time, we measured the cytokines in different diseases using the same methods. Our results convincingly show that the circulating cytokine concentrations are not higher, but lower, compared to other diseases," said Pickkers, who is affiliated with the Department of Intensive Care Medicine at Radboud University Medical Center in Nijmegen, the Netherlands. The team's research was published online on September 3 in a letter in *JAMA*.

## Cytokines Lower Than Expected

Normally, cytokines trigger inflammation and promote healing after trauma, infection, or other conditions.

Although a cytokine storm remains ill defined, the authors note, many researchers have implicated a hyperinflammatory response involving these small proteins in the pathophysiology of COVID-19. The question remains, however, whether all cytokine storms strike people with different conditions the same way.

Pickkers, lead author Matthijs Kox, PhD, and colleagues studied 46 people with COVID-19 and acute respiratory distress syndrome (ARDS) who were admitted to the ICU at Radboud University Medical Center. All participants underwent mechanical ventilation and were treated between March 11 and April 27, 2020.

The investigators measured plasma levels of cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8). They compared results in this group to those in 51 patients who experienced septic shock and ARDS, 15 patients with septic shock without ARDS, 30 people with out-of-hospital cardiac arrest, and 62 people who experienced multiple traumas. They used historical data for the non-COVID-19 cohorts.

## Conditional Findings

Compared to patients with septic shock and ARDS, the COVID-19 cohort had lower levels of TNF, IL-6, and IL-8. The differences were statistically significant for TNF ($P < .01$), as well as for IL-6 and IL-8 concentrations (for both, $P < .001$).

In addition, the COVID-19 group had significantly lower IL-6 and IL-8 concentrations compared with the patients who had septic shock without ARDS.

The researchers likewise found lower concentrations of IL-8 in patients with COVID-19 compared to the out-of-hospital cardiac arrest patients. IL-8 levels did not differ between the COVID-19 and trauma groups.

Furthermore, the researchers found no differences in IL-6 concentrations between patients with COVID-19 and those who experienced out-of-hospital cardiac arrest or trauma.

However, levels of TNF in people with COVID-19 were higher than in trauma patients.

The small sample sizes and single-center study design are limitations.

"The findings of this preliminary analysis suggest COVID-19 may not be characterized by cytokine storm," the researchers note. However, they add, "Whether anticytokine therapies will benefit patients with COVID-19 remains to be determined."

Going forward, Pickkers and colleagues are investigating the effectiveness of different treatments to lower cytokine levels. They are treating people with COVID-19, for example, with the IL-1 cytokine inhibitor anakinra and steroids.

They also plan to assess the long-term effects of COVID-19 on the immune system. "Following an infection, it is known that the immune system may be suppressed for a longer period of time, and we are determining to what extent this is also present in COVID-19 patients," Pickkers said.

## Enough to Cause a Storm?

The study "is quite interesting, and data in this paper are consistent with our data," Tadamitsu Kishimoto, MD, PhD, of the Department of Immune Regulation at the Immunology Frontier Research Center at Osaka University, Osaka, Japan, told *Medscape Medical News* when asked to comment.

His study, published online August 21 in *PNAS*, also revealed lower serum IL-6 levels among people with COVID-19 compared to patients with bacterial ARDS or sepsis.

Kishimoto drew a distinction, however: COVID-19 patients can develop severe respiratory failure, suggesting a distinct immune reaction compared to patients with bacterial sepsis. SARS-CoV-2

directly infects and activates endothelial cells rather than macrophages, as occurs in sepsis.

For this reason, Kishimoto said, "SARS-CoV-2 infection causes critical illness and severe dysfunction in respiratory organs and induces a cytokine storm," even in the setting of lower but still elevated serum IL-6 levels.

*Pickkers and Kishimoto report no relevant financial relationships.*

*JAMA*. Published online September 3, 2020. Abstract

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

## Case study describes unexpected diagnosis of one of the first cases of MIS-C in US

### *Finding of multisystem inflammatory syndrome in children associated with COVID-19 helped create new clinical pathway guidelines to quickly identify and treat cases*

At the height of the COVID-19 pandemic in April, a 14-year-old boy was admitted to the emergency department at Nemours Children's Health System in Delaware with mysterious symptoms in what would later be identified as one of the first cases of multisystem inflammatory syndrome in children (MIS-C) in the U.S.

His care and retrospective diagnosis have been published in *Progress in Pediatric Cardiology* as a timely case study linking COVID-19 to the highly dangerous syndrome which is rare in children and causes inflammation of the heart, lungs and other vital organs.

"There are lessons to be learned from this case, the most critical being to maintain your suspicion if there are several plausible diagnoses," said Deepika Thacker, MD, senior author of the paper and pediatric cardiologist with Nemours Children's Health System. "This allowed us to remain vigilant and adapt treatment as we went, based on the signals and symptoms we were seeing."

Prior to reports from Europe about similar cases in children, the patient presented to the emergency department with a four-day history of fever, fatigue, and abdominal pain. He initially tested negative for COVID-19 and was admitted to the general pediatric ward. But his condition quickly deteriorated, with severe diarrhea, increasingly high fever, and a quickly spreading rash that further escalated to chest pain, fluid in the lungs, and decreasing heart function.

The seemingly unconnected presentation of symptoms made several diagnoses appear possible. While being treated in the cardiac intensive care unit, the patient had to be intubated and placed on mechanical ventilation.

During his 12-day hospital stay, he was treated with penicillin, ceftriaxone, epinephrine, phenylephrine, milrinone, intravenous immune globulins, and high-dose aspirin to cover the wide variety of possible conditions. Only after discharge, an antibody test showed he had had COVID-19.

Based on the team's experience with this patient and others, as well as data from other centers, Nemours' physicians developed a clinical pathway for early recognition and treatment of MIS-C to speed the diagnosis and care of children with this new presentation of COVID-19.

"In the three months since this patient was in critical care, we have learned so much about diagnosing and treating this novel presentation of COVID-19 in children," said Thacker. "This information-sharing has undoubtedly saved lives."

This first patient recovered, as have all 15 patients treated with MIS-C at Nemours Children's Health System in Delaware. Moving forward, the cardiology team will continue to follow up with patients who have experienced MIS-C for at least one year to understand the long-term impact of this acute condition.

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

## COVID-19 Symptoms in Kids Most Often Headache, Fever: App Data

***The COVID Symptom Study app aims to help patients and healthcare providers identify patterns in user-reported data.***

**Lisa Winter**

A symptom-tracking app indicates that children experience different COVID-19 symptoms than adults, *The Guardian* reports. While a persistent cough and a diminished sense of taste and smell are common among adults, the app has found, children with the virus most commonly experience symptoms such as headache, fatigue, and fever, among others.

Since the novel coronavirus emerged in late 2019, scientists have been scrambling to understand its effects on human health. In March, an international group of scientists and institutions announced the COVID Symptom Study to obtain data from patients with COVID-19. According to its website, the app has received self-reported information on more than 4.1 million patients, helping to identify patterns based on demographics.

More than half of the 198 children in their system who tested positive for the virus experienced fatigue and headaches, according to *The Guardian*. Fever occurred in around 50 percent. Around one-third of the kids had sore throats, and a minority of children exhibited a skin rash or experienced diarrhea.

"We need to start to telling people what are the key symptoms at different ages rather than this blanket obsession with fever, cough, and lack of smell," Tim Spector, an epidemiologist at King's College London and co-leader of the project, tells *The Guardia*n. He suggests that children showing these symptoms should be kept home from school, though not necessarily tested.

Sanjay Patel, a pediatric infectious disease doctor at Southampton Children's Hospital in England, cautions that these symptoms are common among many childhood illnesses and could lead parents to unduly quarantine children, which comes with risks. "The harms of that approach are very tangible," Patel tells The Guardian. "Many children would be missing a lot of school, and the majority of children being tested would still be negative."

A recent *New York Times* article, unrelated to the app, comments on how it will be challenging in the coming months for parents to distinguish COVID-19 symptoms from those of the common cold.

"This is not the year to be sending your kid to school sick, even a little bit, even with mild symptoms, which I know is crazy. Because it's really hard for parents," Adam Ratner, the director of pediatric infectious diseases at Hassenfeld Children's Hospital in New York, tells the *Times*. "Sometimes mild symptoms are all we have to go on and kids are really good at shedding the virus, even if they don't have symptoms."

***https://bit.ly/35voACr***

## In Ancient Giant Viruses Lies the Truth Behind Evolution of Nucleus in Eukaryotic Cells

***Giant viruses, like the recently discovered medusavirus, may hold the key to deciphering the evolutionary mystery of the eukaryotic nucleus***

Perhaps as far back as the history of research and philosophy goes, people have attempted to unearth how life on earth came to be. In the recent decades, with exponential advancement in the fields of genomics, molecular biology, and virology, several scientists on this quest have taken to looking into the evolutionary twists and turns that have resulted in eukaryotic cells, the type of cell that makes up most life forms today.

The most widely accepted theories that have emerged state that the eukaryotic cell is the evolutionary product of the intracellular evolution of proto-eukaryotic cells, which were the first complex cells, and symbiotic relationships between proto-eukaryotic cells

and other unicellular and simpler organisms such as bacteria and archaea. But according to Professor Masaharu Takemura of the Tokyo University of Science, Japan, "These hypotheses account for and explain the driving force and evolutionary pressures. But they fail to portray the precise process underlying eukaryotic nucleus evolution."

Prof Takemura cites this as his motivation behind his recent article published in *Frontiers in Microbiology*, where he looks into the recent theories that, in addition to his own body of research, have built up his current hypothesis on the subject.

In a way, Prof Takemura's hypothesis has its roots in 2001 when, along with PJ Bell, he made the revolutionary proposal that large DNA viruses, like the poxvirus, had something to do with the rise of the eukaryotic cell nucleus. Prof Takemura further explains the reasons for his inquiry into the nucleus of the eukaryotic cell as such: "Although the structure, function, and various biological functions of the cell nucleus have been intensively investigated, the evolutionary origin of the cell nucleus, a milestone of eukaryotic evolution, remains unclear."

The origin of the eukaryotic nucleus must indeed be a milestone in the development of the cell itself, considering that it is the defining factor that sets eukaryotic cells apart from the other broad category of cells--the prokaryotic cell. The eukaryotic cell is neatly compartmentalized into membrane-bound organelles that perform various functions. Among them, the nucleus houses the genetic material. The other organelles float in what is called the cytoplasm. Prokaryotic cells do not contain such compartmentalization. Bacteria and archaea are prokaryotic cells.

The 2001 hypothesis by Prof Takemura and PJ Bell is based on striking similarities between the eukaryotic cell nucleus and poxviruses: in particular, the property of keeping the genome separate in a compartment. Further similarities were uncovered after the discovery and characterization of a type of large DNA virus called "giant virus," which can be up to 2.5 μm in diameter and contain DNA "encoding" information for the production of more than 400 proteins. Independent phylogenetic analyses suggested that genes had been transferred between these viruses and eukaryotic cells as they interacted at various points down the evolutionary road, in a process called "lateral gene transfer."

Viruses are "packets" of DNA or RNA and cannot survive on their own. They must enter a "host" cell and use that cell's machinery to replicate its genetic material, and therefore multiply. As evolution progressed, it appears, viral genetic material became integrated with host genetic material and the properties of both altered.

In 2019, Prof Takemura and his colleagues made another breakthrough discovery: the medusavirus. The medusavirus got its name because, like the mythical monster, it causes encystment in its host; that is, it gives its host cell a "hard" covering.

Via experiments involving the infection of an amoeba, Prof Takemura and his colleagues found that the medusavirus harbors a full set of histones, which resemble histones in eukaryotes. Histones are proteins that keep DNA strands curled up and packed into the cell nucleus. It also holds a DNA polymerase gene and major capsid protein gene very similar to those of the amoeba. Further, unlike other viruses, it does not construct its own enclosed "viral factory" in the cytoplasm of the cell within which to replicate its DNA and contains none of the genes required to carry out the replication process. Instead, it occupies the entirety of the host nucleus and uses the host nuclear machinery to replicate.

These features, Prof Takemura argues, indicate that the ancestral medusavirus and its corresponding host proto-eukaryotic cells were involved in lateral gene transfer; the virus acquired DNA synthesis (DNA polymerase) and condensation (histones) genes from its host and the host acquired structural protein (major capsid protein) genes

from the virus. Based on additional research evidence, Prof Takemura extends this new hypothesis to several other giant viruses as well.

Thus, Prof Takemura connects the dots between his findings in 2019 and his original hypothesis in 2001, linking them through his and others' work in the two decades that come in between. All of it taken together, it becomes clear how the medusavirus is prime evidence of the viral origin of the eukaryotic nucleus.

He says: "This new updated hypothesis can profoundly impact the study of eukaryotic cell origins and provide a basis for further discussion on the involvement of viruses in the evolution of the eukaryotic nucleus." Indeed, his work may have unlocked several new possibilities for future research in the field.

***About Professor Masaharu Takemura from Tokyo University of Science***

*Dr Masaharu Takemura is a Professor of molecular biology and giant virus biology at the Faculty of Science, Tokyo University of Science, Japan. A respected and senior researcher, he has more than 95 research publications to his credit. His research focus is virology and cell biology, and his main research aim is to elucidate the evolutionary mechanisms of giant viruses and eukaryotes, and the relationships between them.*

***Funding Information***

*This work was supported by JSPS/KAKENHI (no. 20H03078 to M.T.)*

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

## Study finds botanical effective for chemo-resistant colon cancer

### *Green chiretta given in conjunction with chemotherapy may change the way doctors treat chemotherapy-resistant colorectal cancer*

DUARTE, Calif. -- The natural botanical Andrographis paniculata, when given in conjunction with chemotherapy, may eventually change the way doctors treat chemotherapy-resistant colorectal cancer, reports a new City of Hope study.

Published in the journal *Carcinogenesis*, the study's goal was to use a natural substance that, given as an adjunct treatment along with chemotherapy, would not only be nontoxic but would succeed in killing chemo-resistant cancer cells.

Currently, in an attempt to provide some help for these chemo-resistant patients, other types of chemotherapies are given -- but cancer usually finds a way to outsmart them. What's more, these drugs are highly toxic and can do further harm to the patient.

***Andrographis paniculate (green chiretta)*** *センシンレン（穿心蓮）*

**A Three-Part Study**

Andrographis is commonly used in South Asia and is also available in the U.S. It's known for its anti-inflammatory, antibacterial and antiviral properties, and increasingly, for its ability to fight cancer.

"Many, many scientific articles have been published showing that andrographis kills cancer cells. That's not the news," said Ajay Goel, Ph.D., M.S., founding chair of City of Hope's Department of Molecular Diagnostics and Experimental Therapeutics and corresponding author of the study. "The problem is, how do we kill these 'super cells' that have become chemo-resistant?"

To tackle this challenge, his study tested the efficacy of using a standard chemotherapy for colon cancer, 5-fluorouracil (5FU), alone and combined with andrographis. The study proceeded in three parts.

First, they used cell lines of human colorectal cancer, cultivated in the lab. The combination treatment proved far more effective in killing cancer cells than the chemotherapy alone.

Cell lines do not represent the whole body, so the next step was to look at the effects of using animal tissue. Here too, combining andrographis with 5FU was a more potent cancer killer than 5FU alone.

Knowing that it worked on an animal model, the next step was to further confirm these findings in a 3D-organoid model, grown from human colorectal tumor tissue excised from an actual patient. Again, the combination far outperformed chemotherapy alone in killing cancer cells.

**How Andrographis Kills Cancer**

"In cancer there are hundreds of pathways that are malfunctioning, and modern therapies are designed to target a specific gene or molecule or pathway," Goel said. "It can give patients relief in the short term, but sometimes the cancer says, 'No problem. We have 100 different ways to survive.' Unlike many of the targeted therapies we use in cancer patients, natural treatments are unique, as they don't target a specific pathway but work on many pathways."

What this study showed is that two major pathways were altered by the andrographis. One is the ferroptosis pathway, which regulates programmed cell death. Under normal conditions it signals old cells that it's time to die, and they are replaced by new ones. But in cancer, the ferroptosis pathway becomes defective. Old cells don't die; new ones keep coming and a tumor forms.

The other is the β-catenin/Wnt-signaling pathway, which involves cell metabolism, a process that goes haywire in cancer. Cancer cells become hyperactive and channel nutrition away from normal cells.

"After exposure to andrographis, the ferroptosis signals were turned back on, which told the cells, 'Yep, it's time to die,'" Goel said. "And the metabolic process was regulated, taking nutrition away from the cancer cells, allowing them to die."

The next step will be to test 5FU and andrographis in a clinical setting, and Goel will soon submit an application for Food and Drug Administration approval.

This combination of natural botanical and potent pharmaceutical promises to bring new hope to patients who have developed chemo-resistance or suffer a relapse of their colon cancer.

**Nature's Own Medicine**

In addition to the andrographis study, Goel has done several others, including an earlier study in *Carcinogenesis* and another in the journal of the American Association for Cancer Research. This work revealed that two herbs, curcumin (found in turmeric) and boswellic acid, were able to regulate certain microRNAs found in human colorectal cancer, suggesting that these substances would be useful for disease prevention.

In fact, because these substances can be protective, he feels that people should start taking them before cancer has a chance to develop.

***https://bit.ly/35vi7r5***

## Portable MRI brings brain imaging to the patient bedside

***Portable, low-field magnetic resonance imaging (MRI) device can be safely used at bedside in complex clinical care settings***

BOSTON - A portable, low-field magnetic resonance imaging (MRI) device can be safely used at bedside in complex clinical care settings to evaluate critically-ill patients for suspected stroke, traumatic brain injury (TBI), or other neurological problems, results of a proof-of-concept study show.

"How can a portable low-field device that operates on a standard electrical plug change the paradigm? It can bring the MRI to the bedside, and it can do so in a hospital environment where there is metallic material nearby, and can do it safely because the magnetic field strength is lower," says W. Taylor Kimberly, MD, PhD, chief of the division of Neurocritical Care at Massachusetts General Hospital (MGH).

Among 30 patients in a the Yale Neuroscience intensive care unit (ICU), the bedside MRI system produced important neuroimaging findings in 29, and the findings jibed with conventional radiology findings in all but one case, found Kimberly, Matthew S. Rosen, PhD, director of the Low Field MRI and Hyperpolarized Media Lab and co-Director of the Center for Machine Learning at the Athinoula A. Martinos Center for Biomedical Imaging at MGH, and colleagues at Yale University in New Haven, Connecticut.

In addition, the bedside MRI detected abnormal neurologic findings in eight of 20 patients with altered mental status in a COVID-19 ICU. The investigators report their finding online in the journal *JAMA Neurology*.

MRI is unparalleled as an imaging technology for detecting disease or injury to the brain and central nervous system, but traditional MRI units are immobile behemoths containing large, heavy magnets made of super-conducting material that requires super-cooling with liquid nitrogen or helium. In addition, the high magnetic field strengths of standard MRI units - 1.5 to 3 Tesla - require careful screening of patients to ensure that there are no ferrous metals in or on their bodies (such as medical implants, insulin pumps, or shrapnel fragments) that could cause serious injury during imaging, and any medical equipment containing ferromagnetic components must be kept out of the MRI room.

In contrast, the mobile MRI system trades some of the high-resolution imaging quality of a fixed MRI for portability and lower cost. The device contains a 0.064 Tesla permanent magnet that does not require cooling, and can be plugged into a single 110 volt, 15 amp outlet, making it suitable for use in settings such as emergency departments, mobile stroke units, and regions with limited medical resources. The lower strength magnetic field does not interfere with metal-containing equipment in patient care units.

The system grew out of work Rosen began more than a decade ago at the request of the U.S. Department of Defense (DoD). DoD staff were concerned that soldiers with battlefield injuries might have shrapnel in their heads that could cause serious injury or death if they were placed into a high-field scanner.

"This is an enabling technology to bring non-invasive neuroimaging with the soft-tissue contrast and all of those things neurologists have been relying on for years to environments where it otherwise would not be possible," Rosen says.

*Co-authors of the study are Kevin N. Sheth, MD, Mercy H. Mazurek, BS, Matthew M. Yuen, BA, Bradley A. Cahn, BS, Jill T. Shah, BA, Adrienne Ward, RN, Jennifer A. Kim, MD, PhD, Emily J. Gilmore, MD, Guido J. Falcone, MD, ScD, MPH, Nils Petersen, MD, PhD, Kevin T. Gobeske, MD, PhD, MPH, Firas Kaddouh, MD, David Y. Hwang, MD, Joseph Schindler, MD, Lauren Sansing, MD, MS, Charles Matouk, MD, Jonathan Rothberg, PhD, Gordon Sze, MD, Jonathan Siner, MD, and Serena Spudich, MD, MA, all of Yale and/or Yale New Haven Hospital.*

*The study was supported by funding from the American Heart Association. The portable MRI system is made by Hyperfine Research Inc. Rosen and Rothberg co-founded the company, which licenses some technology from MGH.*

***https://bbc.in/3k5bqIW***

## Wildlife in 'catastrophic decline' due to human destruction, scientists warn

***Wildlife populations have fallen by more than two-thirds in less than 50 years, according to a major report by the conservation group WWF.***

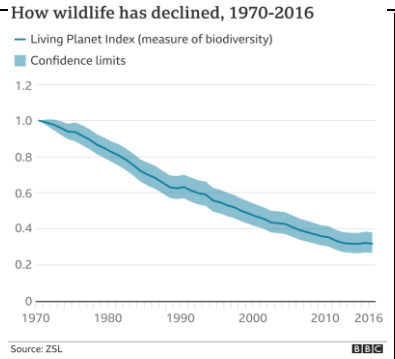
**By Helen Briggs BBC Environment correspondent**

The report says this "catastrophic decline" shows no sign of slowing. And it warns that nature is being destroyed by humans at a rate never seen before.

Wildlife is "in freefall" as we burn forests, over-fish our seas and destroy wild areas, says Tanya Steele, chief executive at WWF.

"We are wrecking our world - the one place we call home - risking our health, security and survival here on Earth. Now nature is sending us a desperate SOS and time is running out."

## What do the numbers mean?




The report looked at thousands of different wildlife species monitored by conservation scientists in habitats across the world. They recorded an average 68% fall in more than 20,000 populations of mammals, birds, amphibians, reptiles and fish since 1970.

The decline was clear evidence of the damage human activity is doing to the natural world, said Dr Andrew Terry, director of conservation at the Zoological Society of London (ZSL), which provides the data. "If nothing changes, populations will undoubtedly continue to fall, driving wildlife to extinction and threatening the integrity of the ecosystems on which we depend," he added. The report says the Covid-19 pandemic is a stark reminder of how nature and humans are intertwined.

Factors believed to lead to the emergence of pandemics - including habitat loss and the use and trade of wildlife - are also some of the drivers behind the decline in wildlife.

New modelling evidence suggests we can halt and even reverse habitat loss and deforestation if we take urgent conservation action and change the way we produce and consume food.

The British TV presenter and naturalist Sir David Attenborough said the Anthropocene, the geological age during which human activity has come to the fore, could be the moment we achieve a balance with the natural world and become stewards of our planet.

"Doing so will require systemic shifts in how we produce food, create energy, manage our oceans and use materials," he said.

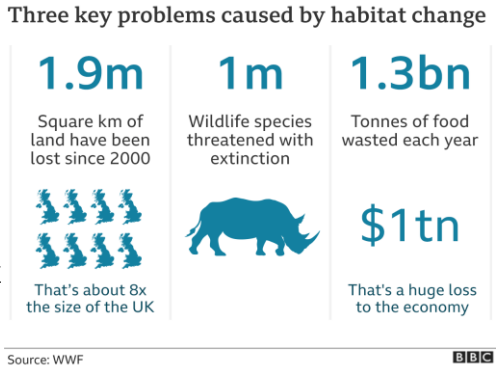
"But above all it will require a change in perspective. A change from viewing nature as something that's optional or 'nice to have' to the single greatest ally we have in restoring balance to our world."

Sir David presents a new documentary on extinction to be aired on BBC One in the UK on Sunday 13 September at 20:00 BST.

## How do we measure the loss of nature?

Measuring the variety of all life on Earth is complex, with a number of different measures. Taken together, they provide evidence that biodiversity is being destroyed at a rate unprecedented in human history.

This particular report uses an index of whether populations of wildlife are going up or down. It does not tell us the number of species lost, or extinctions. The largest declines are in tropical areas. The drop of 94% for Latin America and the Caribbean is the largest anywhere in the world, driven by a cocktail of threats to reptiles, amphibians and birds.




"This report is looking at the global picture and the need to act soon in order to start reversing these trends," said Louise McRae of ZSL. The data has been used for modelling work to look at what might be needed to reverse the decline.

Research published in the journal Naturesuggests that to turn the tide we must transform the way we produce and consume food, including reducing food waste and eating food with a lower environmental impact.

Prof Dame Georgina Mace of UCL said conservation actions alone wouldn't be sufficient to "bend the curve on biodiversity loss".

"It will require actions from other sectors, and here we show that the food system will be particularly important, both from the agricultural sector on the supply side, and consumers on the demand side," she said.

## What do other measures tell us about the loss of nature?

Extinction data is compiled by the International Union for Conservation of Nature (IUCN), which has evaluated more than 100,000 species of plants and animals, with more than 32,000 species threatened with extinction.

In 2019, an intergovernmental panel of scientists concluded that one million species (500,000 animals and plants, and 500,000 insects) are threatened with extinction, some within decades.

The WWF report is one of many assessments of the state of nature being published in the coming weeks and months in the build-up to a major summit next year. The UN will reveal next Tuesday its latest assessment of the state of nature worldwide.

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

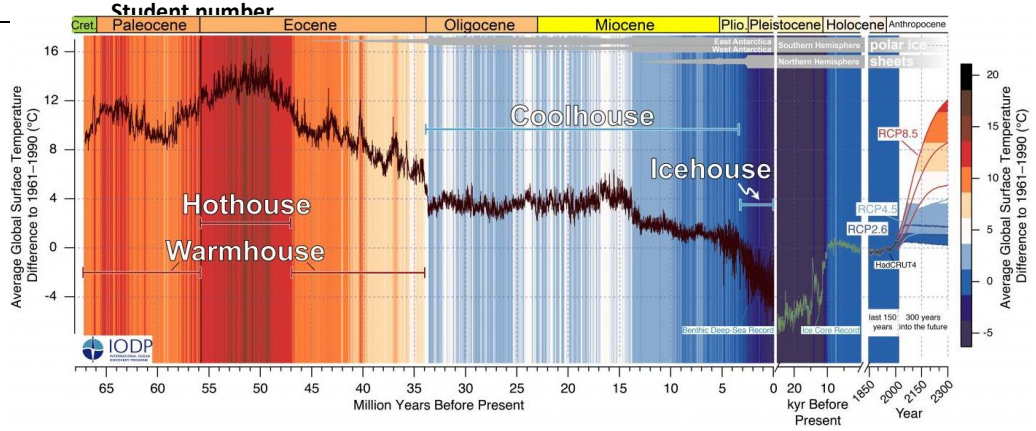
## 66 million years of Earth's climate uncovered from ocean sediments

***Changes in the Earth's climate over the last 66 million years have been revealed in unprecedented detail by a team involving UCL researchers, highlighting four distinctive climatic states***

Changes in the Earth's climate over the last 66 million years have been revealed in unprecedented detail by a team involving UCL researchers, highlighting four distinctive climatic states and the natural million- and thousand-year variability that Earth's climate has experienced.

Published today in *Science*, the new global "climate reference curve" created by the team is the first record to continually and accurately trace how the Earth's climate has changed since the great extinction of the dinosaurs 66 million years ago.

It was achieved by bringing together research from 12 international laboratories using sample material from the ocean floor collected over more than five decades of international scientific drilling expeditions by the International Ocean Discovery Program (IODP) and its predecessors.




***The CENOGRID shows Earth has experience four distinct climate states over the last 66 million years. The detailed climatic changes of the past can be studied like a colourful barcode and provide context for ongoing anthropogenic change and how exceptional it is. Earth's climate has gradually cooled for the last 50 million years, but unmitigated anthropogenic changes reverse this cooling trend and far exceed the warmest climates of the last 66 million years.*** **Credit: Thomas Westerhold**

Led by researchers from MARUM - Center for Marine Environmental Sciences at the University of Bremen, the Potsdam Institute for Climate Impact Research (PIK) and UCL, the authors used advanced mathematical analysis of this highly accurate climate reference curve to identify four climatic states, classified as "Hothouse", "Warmhouse", "Coolhouse" and "Icehouse". These states are recognised by the characteristic pattern of their climate variability. The distinctive climatic "beat' of each state is driven by greenhouse gas concentrations and polar ice volume, with higher CO2 and little-to-no global ice volume during the Hothouse and Warmhouse compared to the Coolhouse and Icehouse.

To generate the climate reference curve, called CENOGRID (CENOzoic Global Reference benthic foraminifer carbon and oxygen Isotope Dataset), the team analysed and compiled the oxygen and carbon isotopes from tiny microfossils found in deep-sea sediments. For the first time, this period of Earth's history was

accurately dated by identifying the imprint of semi-periodical changes in Earth's orbit around the sun in CENOGRID.

The CENOGRID is the clearest and most accurate view of past climate conditions to date, providing information about past deep-sea temperatures, global ice volumes and the carbon cycle. These detailed climatic changes can be studied like a colourful barcode and used to draw comparisons between the past, present and future.

Co-author Dr Anna Joy Drury (UCL Earth Sciences), said: "We use CENOGRID to understand what Earth's normal range of natural climate change and variability is and how quickly Earth recovered from past events. While we show that the Earth previously experienced warm climate states, these were characterised by extreme climate events and were radically different from our modern world. Since the peak warmth of the Hothouse, Earth's climate has gradually cooled over the last 50 million years, but the present and predicted rapid anthropogenic changes reverse this trend and, if unabated, far exceed the natural variability of the last 66 million years. CENOGRID's window into the past provides context for the ongoing anthropogenic change and how exceptional it is."

While the rough framework of a global climate reference curve has existed since 2001, climate records from many new sediment cores greatly improved in recent years. Over the last two decades, scientific drilling specifically targeted older geological strata, especially older than 34 million years, giving researchers access to better material for reconstructing global climate in much greater detail than ever before.

*Lead author, Dr Thomas Westerhold (MARUM, University of Bremen), said: "We now know more accurately when it was warmer or colder on the planet and have a better understanding of the underlying dynamics and the processes that drive them. The time from 66 to 34 million years ago, when the planet was significantly warmer than it is today, is of particular interest, as it represents a parallel in the past to what future anthropogenic change could lead to."*

*CENOGRID is a lasting international legacy of 50 years of scientific ocean drilling now led by IODP. The authors see CENOGRID as a basis for researchers worldwide to correlate their data to and place it within the context of Earth's climate history. With more data, it is now possible to not only further refine the picture of the climatic past, but also to identify regional intricacies. The authors emphasize that this is fundamental for testing the reliability of climate models for the future.*

*The UCL contribution was funded by a Horizon 2020 Marie Skłodowska-Curie Action Fellowship to Anna Joy Drury.*

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

## Think 2020's disasters are wild? Experts see worse in future

***Experts say we'll probably look back and say those were the good old days, when disasters weren't so wild.***

**by Seth Borenstein**

A record amount of California is burning, spurred by a nearly 20-year mega-drought. To the north, parts of Oregon that don't usually catch fire are in flames.

Meanwhile, the Atlantic's 16th and 17th named tropical storms are swirling, a record number for this time of year. Powerful Typhoon Haishen lashed Japan and the Korean Peninsula this week. Last month it hit 130 degrees in Death Valley, the hottest Earth has been in nearly a century.

Phoenix keeps setting triple-digit heat records, while Colorado went through a weather whiplash of 90-degree heat to snow this week. Siberia, famous for its icy climate, hit 100 degrees earlier this year, accompanied by wildfires. Before that Australia and the Amazon were in flames.

Amid all that, Iowa's derecho—bizarre straight-line winds that got as powerful as a major hurricane, causing billions of dollars in damages—barely went noticed.

Freak natural disasters—most with what scientists say likely have a climate change connection—seem to be everywhere in the crazy year 2020. But experts say we'll probably look back and say those were the good old days, when disasters weren't so wild.

"It's going to get A LOT worse," Georgia Tech climate scientist Kim Cobb said Wednesday. "I say that with emphasis because it does challenge the imagination. And that's the scary thing to know as a climate scientist in 2020."

Colorado University environmental sciences chief Waleed Abdalati, NASA's former chief scientist, said the trajectory of worsening disasters and climate change from the burning of coal, oil and gas is clear, and basic physics.

"I strongly believe we're going to look back in 10 years, certainly 20 and definitely 50 and say, 'Wow, 2020 was a crazy year, but I miss it,'" Abdalati said.

That's because what's happening now is just the type of crazy climate scientists anticipated 10 or 20 years ago.

"It seems like this is what we always were talking about a decade ago," said North Carolina State climatologist Kathie Dello.

Even so, Cobb said the sheer magnitude of what's happening now was hard to fathom back then. Just as the future of climate disasters is hard to fathom now.

"A year like 2020 could have been the subject of a marvelous science fiction film in 2000," Cobb said. "Now we have to watch and digest real-time disaster after disaster after disaster, on top of a pandemic. The outlook could not be any more grim. It's just a horrifying prospect." "The 2030s are going to be noticeably worse than the 2020s," she said.

University of Michigan environment dean Jonathan Overpeck, a climate scientist, said that in 30 years because of the climate change already baked into the atmosphere "we're pretty much guaranteed that we'll have double what we have now."

Expect stronger winds, more drought, more heavy downpours and floods, Abdalati said. "The kind of things we're seeing are no surprise to the (scientific) community that understands the rules and the laws of physics," Abdalati said.

"A lot of people want to blame it on 2020, but 2020 didn't do this," Dello said. "We know the behavior that caused climate change."

Consider the world's environment like an engine: "We have injected more energy into the system because we have trapped more heat into the atmosphere," said World Meteorological Organization Secretary-General Petteri Taalas.

That means more energy for tropical storms as well as changes to rainfall patterns that bring drought to some places and heavy rainfall to others, Taalas said.

In California, where more than 2.3 million acres have burned, the fires are spurred by climate change drying plants and trees that then go up in flames, said University of Colorado fire scientist Jennifer Balch. California is in the midst of a nearly 20-year mega-drought, the first of its kind in the United States since Europeans arrived, Overpeck said.

Scientists also make direct connections between heat waves and climate change.

Some disasters at the moment can't be directly linked to man-made warming, such as the derecho, Overpeck said. But looking at the big picture over time shows the problem, and it's one that comes down to the basic physics of trapped heat energy.

"I am not an alarmist. I don't want to scare people," Abdalati said. "It's a problem with tremendous consequences and it's too important not to get right."

And so even though the climate will likely get worse, Overpeck is also optimistic about what future generations will think when they look back at the wild and dangerous weather of 2020.

"I think we'll look back and we'll see a whole bunch of increasingly crazy years," Overpeck said. "And that this year, in 2020, I hope we look back and say it got crazy enough that it motivated us to act on climate change in the United States."

https://bit.ly/3iq3NUt

# Levodopa may improve vision in patients with macular degeneration

***The widely used and well-tolerated drug commonly used to treat Parkinson's disease may help significantly reduce the need for more costly, more invasive treatments, report investigators***

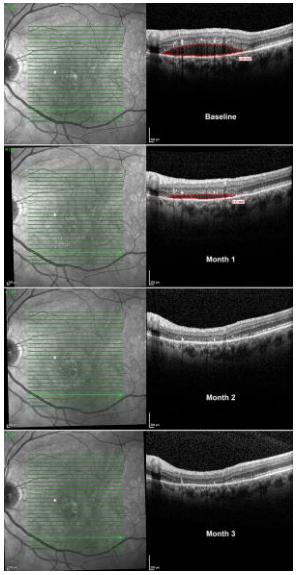
Philadelphia - Investigators have determined that treating patients with an advanced form of age-related macular degeneration (AMD) with levodopa, a safe and readily available drug commonly used to treat Parkinson's disease, stabilized and improved their vision. It reduced the number of treatments necessary to maintain vision, and as such, will potentially reduce the burden of treating the disease, financially and otherwise. Their findings appear in the *American Journal of Medicine*, published by Elsevier.

More than 15 percent of the US population over the age of 70 has AMD, a common cause of blindness in developed nations. Neovascular AMD (nAMD) is characterized by the abnormal growth of new blood vessels, triggered by vascular endothelial growth factor (VEGF), which can cause fluid and blood to leak in the subretinal space of the eye. While nAMD represents only 10-15 percent of all AMD cases, it is responsible for 90 percent of the vision loss attributed to the disease. The standard treatment requires frequent injections of agents to block VEGF. While effective, the injections are expensive and painful.

Earlier research found that patients being treated with levodopa for movement disorders such as Parkinson's disease were significantly less likely to develop any type of AMD. Lead investigator Robert W. Snyder, MD, PhD, Department of Biomedical Engineering, The University of Arizona, Tucson, and Snyder Biomedical Corporation, Tucson, AZ, USA, explained, "Levodopa has a receptor (GPR143) selectively expressed on pigmented cells. This receptor can be supportive of retinal health and survival, which led to the development of our hypothesis that it may prevent or treat AMD."

The investigators developed two proof-of-concept studies to test whether levodopa improves visual acuity and the anatomical changes caused by nAMD. They also evaluated the safety and tolerability of the drug in treating nAMD and whether treatment reduced or delayed the need for anti-VEGF therapy.

In the first study, 20 patients newly diagnosed with nAMD who had never had VEGF treatment were given a small daily dose of levodopa for one month and were evaluated weekly by their referring retina specialist, who determined whether anti-VEGF treatment was needed. In the second part of the study, the patients who completed the first study and a second group of 14 patients who had received anti-VEGF treatment for at least three months before the study received escalating doses of levodopa to test the tolerance and efficacy of the drug. The patients continued to be evaluated monthly by their referring retina specialist.




***Spectral domain optical coherence tomography images of the same macular segmentation line at baseline and monthly follow-up visits in a patient naïve to intravitreal anti-vascular endothelial growth factor (VEGF) therapy. There was a 59 percent reduction in retinal fluid at one month; retinal fluid completely resolved at the same macular segmentation line at month 2, and fluid remained stable up to month 3 without anti-VEGF injections. Collectively, all macular segmentation lines revealed a 92 percent total retinal fluid decrease at 3 months.*** **The American Journal of Medicine**

This trial demonstrated for the first time that levodopa is safe, well-tolerated, and delayed anti-VEGF injection therapy while improving visual outcomes. In the first month, retinal fluid decreased by 29 percent. After six months the decrease in retinal

fluid was sustained and mean visual acuity improved enabling patients in the first and second group to read an additional line on the eye chart. This is the equivalent of improvement from 20/40 to 20/32. Side effects were limited.

The investigators noted that levodopa may be unlikely as a standalone treatment in patients with newly diagnosed nAMD since 11 of the patients did require anti-VEGF injections. However, they required fewer than the standard monthly treatments, and in the second group, monthly injections of anti-VEGF decreased by 52 percent.

According to Dr. Snyder, although this limited proof-of-concept study included a small sample size and limited patient diversity, its findings suggest efficacy and support the targeting of the GPR13 receptor with levodopa for the treatment of nAMD in future studies. The concept had its genesis 20 years ago when Dr. Snyder began working with co-investigator Brian S. McKay, who had developed techniques to culture and examine retinal endothelial pigment cells. "We had a strong desire to make an impact in AMD, and I had a strong hunch that Dr. McKay could make a significant contribution," Dr. Snyder said. "Although this is nowhere near completed, I am happy to say, 20 years later, we have all persevered, and I believe the GPR143/levodopa story will make a significant impact on our treatment and prevention of AMD."

***https://bit.ly/33uAtpk***

## Middle-aged individuals may be in a perpetual state of H3N2 flu virus susceptibility

### *Individuals' immunological imprint from early childhood infection likely lessens severity but does not prevent infection*

PHILADELPHIA -- Penn Medicine researchers have found that middle-aged individuals -- those born in the late 1960s and the 1970s -- may be in a perpetual state of H3N2 influenza virus susceptibility because their antibodies bind to H3N2 viruses but fail to prevent infections, according to a new study led by Scott Hensley, PhD, an associate professor of Microbiology at the Perelman School of Medicine at the University of Pennsylvania. The paper was published today in *Nature Communications*.

"We found that different aged individuals have different H3N2 flu virus antibody specificities," Hensley said. "Our studies show that early childhood infections can leave lifelong immunological imprints that affect how individuals respond to antigenically distinct viral strains later in life."

Most humans are infected with influenza viruses by three to four years of age, and these initial childhood infections can elicit strong, long lasting memory immune responses. H3N2 influenza viruses began circulating in humans in 1968 and have evolved substantially over the past 51 years. Therefore, an individual's birth year largely predicts which specific type of H3N2 virus they first encountered in childhood.

Researchers completed a serological survey -- a blood test that measures antibody levels -- using serum samples collected in the summer months prior to the 2017-2018 season from 140 children (ages one to 17) and 212 adults (ages 18 to 90). They first measured the differences in antibody reactivity to various strains of H3N2, and then measured for neutralizing and non-neutralizing antibodies. Neutralizing antibodies can prevent viral infections, whereas non-neutralizing antibodies can only help after an infection takes place. Samples from children aged three to ten years old had the highest levels of neutralizing antibodies against contemporary H3N2 viruses, while most middle-aged samples had antibodies that could bind to these viruses but these antibodies could not prevent viral infections.

Hensley said his team's findings are consistent with a concept known as "original antigenic sin" (OAS), originally proposed by Tom Francis, Jr. in 1960. "Most individuals born in the late 1960s

and 1970s were immunologically imprinted with H3N2 viruses that are very different compared to contemporary H3N2 viruses. Upon infection with recent H3N2 viruses, these individuals tend to produce antibodies against regions that are conserved with older H3N2 strains and these types of antibodies typically do not prevent viral infections."

According to the research team, it is possible that the presence of high levels of non-neutralizing antibodies in middle-aged adults has contributed to the continued persistence of H3N2 viruses in the human population. Their findings might also relate to the unusual age distribution of H3N2 infections during the 2017-2018 season, in which H3N2 activity in middle-aged and older adults peaked earlier compared to children and young adults.

The researchers say that it will be important to continually complete large serological surveys in different aged individuals, including donors from populations with different vaccination rates. A better understanding of immunity within the population and within individuals will likely lead to improved models that are better able to predict the evolutionary trajectories of different influenza virus strains.

"Large serological studies can shed light on why the effectiveness of flu vaccines varies in individuals with different immune histories, while also identifying barriers that need to be overcome in order to design better vaccines that are able to elicit protective responses in all age groups," said Sigrid Gouma, PhD, a postdoctoral researcher of Microbiology and first author on the paper.

*Other Penn authors include Madison Weirick and Megan E. Gumina. Additional authors include Angela Branche, David J. Topham, Emily T. Martin, Arnold S. Monto, and Sarah Cobey.*

*This work was supported by the National Institute of Allergy and Infectious Diseases (1R01AI113047, S.E.H.; 1R01AI108686, S.E.H.; 1R01AI097150, A.S.M.; CEIRS HHSN272201400005C, S.E.H., S.C., E.T.M., A.S.M. A.B., D.J.T.) and Center for Disease Control (U01IP000474, A.S.M.). Scott E. Hensley holds an Investigators in the Pathogenesis of Infectious Disease Awards from the Burroughs Wellcome Fund.*

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

## COVID ventilator patients can have permanent nerve damage

### *Prone positioning saves lives, but nerve pressure injuries impair arms and legs*

CHICAGO --- Severely ill COVID-19 patients on ventilators are placed in a prone (face down) position because it's easier for them to breathe and reduces mortality. But that life-saving position can also cause permanent nerve damage in these vulnerable patients, reports a newly accepted study from Shirley Ryan AbilityLab and Northwestern University Feinberg School of Medicine.

Scientists believe the nerve damage is the result of reduced blood flow and inflammation. Other non-COVID-19 patients on ventilators in this position rarely experience any nerve damage.

The study has been accepted by the *British Journal of Anaesthesia*. It can be viewed as a preprint.

"It's shocking how big a problem it is," said lead investigator Dr. Colin Franz, a physician-scientist at Shirley Ryan AbilityLab and an assistant professor of physical medicine and rehabilitation and neurology at Northwestern's Feinberg School of Medicine. "This is a much higher percentage of patients with nerve damage than we've ever seen in any other critically ill population. Ordinarily, very sick people can tolerate the position that helps their breathing. But COVID patients' nerves can't tolerate the forces other people can generally bear."

Based on this study and another that came out after Franz's, 12% to 15% percent of the most severely ill COVID-19 patients have permanent nerve damage. Based on the number of COVID patients worldwide, Franz estimated thousands of patients have been impacted.

"It's underappreciated, if you take our numbers and extrapolate them," Franz said. So far, he and colleagues have seen 20 patients from seven different hospitals with these injuries.

The injury has been missed because people who have been critically ill are expected to wake up with some generalized, symmetric weakness because they have been bedridden, Franz said. But the pattern of weakness in the COVID-19 patients caught the researchers' attention during rehabilitation since quite often an important joint such as the wrist, ankle or shoulder would be completely paralyzed on one side of the body.

As a result of the findings, physicians are modifying the prone position protocol for COVID-19 patients at Northwestern Memorial Hospital in order to prevent nerve damage.

"We noticed patients are getting a lot of pressure at the elbow or at the neck, so we've made some adjustments to the way we position the joints as well as putting extra padding under the elbow and the knee where there is the most pressure," Franz said.

The most common injuries are wrist drops, foot drops, loss of hand function and frozen shoulder. Some patients had as many as four distinct nerve injury sites. Some people who are dragging a foot need assistance with walking such as a wheelchair, brace or cane.

Franz and colleagues have been doing some therapeutic nerve stimulation, which has shown in other work to help regrow nerves. Franz collaborates on this line of research with John Rogers, biomedical engineer at Northwestern's McCormick School of Engineering, and Dr. Sumanas Jordan, an assistant professor of surgery at Feinberg and a Northwestern Medicine plastic surgeon.

But many patients have pre-existing conditions that interfere with nerve regeneration, such as diabetes mellitus, so they are less likely to recover full function.

"This could mean permanent difficulties with walking or critical hand functions like writing or operating a computer or cell phone," Franz said.

The multidisciplinary team of scientists at Northwestern and Shirley Ryan AbilityLab are working on a pressure map of hot spots for nerve sensitivity, radiology imaging to document the injury and skin sensors to help identify better "prone" position strategies.

***https://bit.ly/3bX3fD0***

## Electroconvulsive therapy shown to significantly reduce suicide risk in Bipolar patients

***ECT was able to reduce suicide risk by 84% in high-risk patients, as well as giving effective treatment to around 72%***

One of the largest ever studies of patients with untreatable bipolar disorder has shown that ECT (Electroconvulsive Therapy) was able to reduce suicide risk by 84% in high-risk patients, as well as giving effective treatment to around 72% of sufferers.

Bipolar disorder, where patients exhibit emotional instability and may experience very severe mood swings, is amongst the most common mental health disorders. It affects around 1% of Europeans, meaning that approximately 5 million Europeans suffer. Bipolar disorder can cause mixed states of mania and depression; this mix can lead to an increased risk of suicide, since sufferers may simultaneously experience both the symptoms of depression (such as the sense of guilt and worthlessness) and symptoms of mania (such as increased activity and tendency to act without thinking twice). Most patients can control the condition via prescription drugs, but almost a third of patients are resistant to treatment.

Now the largest-ever study to follow bipolar patients and treatment from a single centre has confirmed that ECT can reduce suicide risk, and allow a majority of patients affected by treatment-resistant bipolar disease to return to a more normal life. This work is

presented at the ECNP conference, after part-publication in the peer-reviewed journal The World Journal of Biological Psychiatry*. Between January 2006 and July 2019, 670 patients were referred to the University of Pisa psychiatry clinic for ECT treatment for bipolar disorder. Dr Giulio Emilio Brancati, of the Department of Clinical and Experimental Medicine at the University of Pisa, said "ECT was invented in Italy, but despite this there are very few clinics in Italy which offer the treatment nowadays. A lot of patients who have failed with other treatments are referred to the Pisa clinic, which is why we were able to gather so much data from a single clinic".

The treatment showed great success in treating bipolar sufferers, with remission rates of over 60% for symptoms characteristic of bipolar "mixed states", such as emotional overreactivity, motor hyperactivity, aggressiveness and persecutory delusions, uncooperativeness, catatonia and associated movement disturbances.

"Most importantly, 77 of our patients were classified as being at severe risk of suicide. After treatment only 2 remained at severe risk, while 65 showed no risk at all. This is an 84% drop in suicidality after ECT treatment. We have not found this level of acute improvement with any other treatment", said Giulio Brancati. He continued:

"This is a real-life study, not a clinical trial. A formal trial would have been difficult and probably unethical in these patients, many of who were severely ill. They were generally referred to us only after multiple treatment failures, so most of these patients were running out of treatment options. When we sampled the patients who came to us we found that around 93% had tried and failed with pharmacological treatment, 88% had failed on 2 different drugs. In fact, on average each patient who came to us had tried 5 different drugs, without success".

The public tends to have a negative view of ECT, largely based on media representation of the very different psychiatric world of the 1950s, but patients and psychiatrists are generally positive about the effects of ECT on otherwise untreatable or difficult to treat mental health conditions. Modern ECT is given under general anaesthetic, and can lead to rapid recovery from Major Depression (the main side effect is a possible transitory loss of recent memory). It's normally given 2 to 3 times per week, with between 6 and 16 treatments needed to show a positive effect. The use of ECT in general has recently dropped by around a third in the USA. This is despite the success of the treatment and the willingness of famous sufferers, such as Carrie Fisher, to come forward and talk about their treatment. Despite ECT being invented in Italy, the use of the technique is extremely restricted, leading to Italy having fewer centres specialising in ECT than most other countries of comparable size.

"ECT is used for major depression, but much less so for the other phases of Bipolar Disorder, especially for so-called mixed states, which have a lower visibility. We find that many patients with treatment resistant bipolar catatonic and mixed states are misdiagnosed as having schizophrenia. These patients need to be given a chance via receiving the right treatment", said Giulio Brancati.

Commenting, Dr Henricus Ruhe, psychiatrist at Radboudumc Netherlands, and Chair of the ECNP Abstract and Poster Committee, said:

"This study again shows that ECT can be a life-saving treatment and should not be withheld to patients suffering from difficult to treat mood disorders such as bipolar disorder. Although we should acknowledge adverse effects like (mostly temporary) memory impairments, these results show how well, and often how fast the response to ECT can be.

This effectiveness generally outweighs the adverse effects in these severely ill patients, who otherwise might suffer for much longer or not have effective treatment at all. Unfortunately, despite the long-term evidence, ECT is still viewed as a controversial treatment by the general public and the media, but also by many patients and relatives. This is also the case in Italy where very few centres can offer ECT nowadays.This prejudice against modern ECT unjustly stigmatizes both patients and psychiatry, and denies treatment to seriously-ill patients". This is an independent comment, Dr Ruhe was not involved in this work.

**See https://www.tandfonline.com/doi/full/10.1080/15622975.2020.1770860*

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

## Should mother's milk be produced in the lab?

***Human milk grown from mammary cells could liberate breastfeeding women – but it's a controversial sell***

**Zoë Corbyn**

One of the saddest things about being diagnosed with breast cancer a few years ago (it was fortunately treatable) was having to stop breastfeeding my 10-month-old baby. Unceremoniously she was shunted on to an early diet of pure solid food, which I reasoned was probably just as nutritious as infant formula and the best solution in the absence of donor milk from a breast-milk bank, which is reserved for premature and ill babies, and dispensed by prescription. Baby Agnes thrived, but what if there were another option? What if we could make human breast milk in the lab? Enter startups Biomilq and TurtleTree Labs, founded in 2019 and based in the US (North Carolina) and Singapore respectively. The companies believe they can provide a more nutritious alternative to infant formula by inducing human mammary cells in a bioreactor to lactate, then harvesting the product. "The end goal is a product that is as close to breast milk as we can produce," says Michelle Egger, Biomilq's co-founder and CEO.

Lab-made milk has similarities with lab-grown meat. While the cultivated meat companies are trying to grow animal cells that can then be harvested and eaten, milk companies aim to keep human mammary cells healthy and fed so they will secrete milk.

This June, Biomilq secured $3.5m and TurtleTree Labs $3.2m in early investment. Bill Gates's venture firm is among Biomilq's funders, while backers of TurtleTree Labs include the venture firm of the Saudi prince Khaled bin Alwaleed bin Talal. TurtleTree Labs says its methods could also be applied to producing the milk of other mammals; cow milk is a second area of work.

Both companies acknowledge that their products can't replicate everything in breast milk. They won't, for example, include the antibodies a mother's milk contains, which help a baby fight infection and protect against allergies, or the microbes known to help infant gut health. But they believe that they can trigger the cells to produce thousands of the components found in breast milk. These include proteins, fats and the entire spectrum of human milk oligosaccharides (HMOs), complex sugars that nourish young immune systems. Nothing is yet on the market and the work is still at an experimental stage.

"Visually you can see that milk has been produced," says Fengru Lin, TurtleTree Labs co-founder and CEO, adding that the colour is whitish and the nutritional quality is similar to human breast milk.

Tests so far, Egger says, have confirmed that the cells are producing lactose, the sugar found naturally in most mammals' milk, and human casein. She expects further testing to reveal other components. If proven, the technology would leapfrog the best efforts to improve cow-based infant formula: adding one or two key HMOs made by bio-engineering microbes.

If lab milk reduces the chances of women breastfeeding it is likely to rile some doctors and breastfeeding groups

The concept of inducing mammary cells in a dish to lactate is not new. Over the past couple of decades, scientists have had success plying 3D clusters of animal and human mammary epithelial cells with lactogenic hormones. But that was to study mammary-gland biology – not to make milk in an industrial sense.

"No one was thinking of using this as a production system," says Bruce German, director of the Foods for Health Institute at the University of California, Davis, who studies breast milk and has provided unpaid advice to Biomilq. Experiments published to date have shown the production of some milk proteins – casein and whey protein – and lactose. "[But] the full spectrum of what I would define as milk definitely hasn't been achieved," notes Alecia-Jane Twigger, a lactation and mammary gland biologist at the University of Cambridge. It isn't even known how the mammary gland makes all the thousands of different components it does, she adds.

Biomilq begins with adult mammary cells, which it says are predominantly epithelial cells, found in the ducts and lobules of the breast. TurtleTree Labs starts with stem cells, which it induces to grow into mammary cells. Both say their secret is in their culture media – the fluid containing nutrients, vitamins, and lactation hormones they feed their cells. They also say they have their own unique bioreactor systems, which allow their milk to be harvested free of cells, media and waste.

TurtleTree Labs' vision is to license its technology to infant formula manufacturers. Biomilq has been considering whether it could extract mammary cells from women before their babies are born, and then produce milk from those mammary cells to create a personalised milk – though individualisation would be lost too: maternal diet, for example, influences breast milk.

Both say their goal is an affordable product, though cell-culture media can be expensive, notes Twigger. Egger aims to be on par with top-end infant formula. Max Rye, TurtleTree Labs co-founder and chief strategist, says the company was producing a litre for around $170 (£127) but has managed to lower the cost to $35 (£26) by synthesising components of the lactation media in-house. The price of a litre of ready-to-drink infant formula is about $8 in the US and £4 in the UK.

The companies are yet to present any scientific data to support their claims. "They have gone after one of the most difficult biological challenges there is," says German. To show that they are producing something that "even vaguely resembles milk", Twigger says she would like, as a start, to see proof of different species of HMOs and fats.

Even if the companies can get that far, there will still be much absent from a bulk milk tank. And that extends beyond breast milk's immunological properties. The production of breast milk is a dynamic process. It changes not only over the course of a breastfeeding term but also over an individual feeding, and even with the time of day. Biotechnology is no match for the human breast. "Mothers should feel special," says German, adding that breastfeeding is also associated with health benefits for mothers.

Achieving industrial-scale production is also unlikely to be easy. The scientific research has seen only microlitres produced, says Twigger, and she hasn't seen evidence that mammary cells in the lab can sustain production for more than a few weeks. The companies will also face hurdles in gaining approval for their products.

Egger says Biomilq is focused on testing and isn't looking to launch anything yet. Rye says TurtleTree Labs is continuing to iterate and is planning to sign its first licensing agreement by mid-2021. Neither seems fazed by the task of scaling up, and both are looking into the path to regulation. "That we don't have antibodies and microbes turns out to be a huge advantage," says Rye.

The technology could be controversial. On one hand many women struggle to breastfeed. The infant formula they have to fall back on is "basically the barest essentials," says German. On the other, if lab milk reduces the chances of women breastfeeding it is likely to rile some doctors and breastfeeding groups.

"There is a need for a high-quality breast-milk substitute for those infants who are not breastfed," said the breastfeeding support charity, La Leche League Great Britain. But the charity also asked whether similar investments to those being ploughed into the technology shouldn't be put towards supporting women who want to breastfeed. La Leche also emphasised the "artificial" nature of the proposed products. "The benefits of breastfeeding cannot be replicated in a laboratory," it said.

For their part, the companies emphasise that their aim isn't to replace breast milk, breastfeeding or breast-milk banks, but simply to be the next best thing if that isn't possible. "Babies deserve whatever we can do to get them the best nutrition," says Egger. "Technology has changed and it is time we started to apply some of that in honour of babies, mums and families."

***https://bit.ly/32ufR1r***

## A supercomputer found a promising theory about why COVID-19 cases go downhill fast

***It even explains the bizarre range of symptoms.***

**Aria Bendix**

- ***Tennessee researchers used a supercomputer to analyze lung fluid from coronavirus patients.***
- ***They found that patients with severe cases may produce too much bradykinin, a chemical that regulates blood pressure.***
- ***This could set off a chain reaction that leads to COVID-19's bizarre range of symptoms — including cardiac, gastrointestinal, and neurological problems.***

Imagine trying to drive a car with a leaky engine. Now imagine there are no brakes, either. Eventually, you're going to run out of fuel or crash. Some passengers might survive — others won't.

The human body may endure a similar experience in response to a coronavirus infection, according to a study from researchers at the Oak Ridge National Laboratory in Tennessee. The lab's supercomputers — one of which is the second-fastest in the world — analyzed lung fluid samples from nine coronavirus patients with severe cases in Wuhan, China.

The computers detected major differences in way these patients expressed certain genes relative to the way healthy people do.

Based on those abnormalities, the researchers came up with a new theory: Patients with severe COVID-19 may experience what's known as a "bradykinin storm."

Bradykinin is a chemical that regulates blood pressure. The researchers found that some people with the coronavirus may produce it in extreme excess. That storm throws major systems — including respiratory, gastrointestinal, and neurological pathways — off balance.

The theory aligns with researchers' growing view of the coronavirus as a vascular disease instead of a respiratory one. Research has shown that COVID-19 can lead to blood clots, leaky capillaries, and inflamed blood vessels — which is why some patients may experience heart damage or stroke.

"We were really scratching our heads for a while, how does this disease have this darn broad set of symptoms across lots of different organ systems?" Dr. Daniel Jacobson, the lead researcher behind the supercomputer study, told Business Insider. "As we looked at the effects of bradykinin, our model was that this virus can affect several different types of tissues, several different organs."

**Too much bradykinin can send the body spiraling out of control**

Scientists already know that the coronavirus binds to cell receptors called ACE2. That's how the virus sneaks into the body's upper respiratory tract, then infects organs like the lungs, heart, kidneys, or intestines.

But the supercomputers found that coronavirus patients had a 200-fold increase in the expression of ACE2 relative to a healthy person. This suggests the virus is actively influencing our bodies to make them even easier to infiltrate. At the same time, the computers found, coronavirus patients also had an eight-fold decrease in the expression of ACE, a protein that normally works with ACE2 to keep blood pressure in check.

"This system that is normally very carefully balanced — COVID-19 really throws it out of whack," Jacobson said.

This imbalance, the researchers think, is what leads to the over-production of bradykinin, which swoops in to keep blood pressure from getting too high. In severe cases, the cycle seems to go into overdrive: The body can't stop producing bradykinin. This is what researchers call a "bradykinin storm."

An excess of the chemical widens the gaps in blood vessels, which allows fluid to leak out. That fluid, in turn, starts to fill up the alveoli: tiny air sacs in the lungs — hence why patients have trouble breathing.

The supercomputers also found that coronavirus patients may over-produce a highly absorbent substance called hyaluronic acid. When the acid mixes with the fluid in the lungs, patients can feel like they're trying to breathe out of "a balloon full of Jell-O," Jacobson said.

"There may be a tipping point where enough of this hyaluronic acid builds up, then all of a sudden they have respiratory distress," he added. "That explains why some people seem to be doing fine and then they crash and all of a sudden need hospitalization or worse."

**An explanation for the wide range of COVID-19 symptoms**

The bradykinin theory offers a surprisingly cohesive explanation for why COVID-19 infections can result in a broad spectrum of symptoms. Though the disease has certain hallmarks — a fever, dry cough, and shortness of breath — patients have reported a range of cardiac, gastrointestinal, and neurological problems.

"Everywhere we go in the body and look at the symptoms being reported, they map pretty well to exactly what you'd expect to see from bradykinin," Jacobson said.

A bradykinin storm could cause fluid to leak from the blood vessels in the brain, which would explain neurological symptoms like dizziness, headaches, fogginess, and confusion that some patients experience. It can also trigger swelling, pain, and inflammation in the body — which can result in muscle soreness and body aches, now known to be common COVID-19 symptoms. That could even lead to purple, swollen toes.

What's more, Jacobson said, a loss of taste or smell is a classic response to decreased levels of ACE receptors. Lower levels of ACE have also been linked to a dry cough and fatigue.

Furthermore, the increased production of hyaluronic acid may explain why some asymptomatic patients have abnormal lung scans, Jacobson added.

"There's probably damage being done in people who feel fine otherwise," he said.

**Implications for future treatments**

Scientists still need to perform more clinical studies to know whether bradykinin storms are driving COVID-19 symptoms. But Jacobson's team isn't the first to suggest the theory.

In May, Michigan researchers hypothesized that a bradykinin response could lead to life-threatening respiratory complications in some COVID-19 patients. A study published the month prior also proposed that the body's bradykinin response was to blame for leaky blood vessels observed in the lungs of COVID-19 patients.

The researchers behind that work suggested that a drug called icatibant, which blocks the body's signal to produce bradykinin, could help treat infected patients. A follow-up study showed that four of nine patients who received the drug no longer needed oxygen support after 10 to 35 hours. The drug also had no severe adverse effects. But the study was too small to yield any significant conclusions.

Jacobson's study, meanwhile, found evidence that vitamin D might hinder a bradykinin storm from developing in the first place. Studies have already shown that Vitamin D could help reduce the severity of COVID-19 infections.

His study also supports the idea that corticosteroids can improve survival rates for COVID-19 patients. Bradykinin receptors activate an enzyme called phospholipase A2, which is inhibited by steroids. The World Health Organization issued a "strong recommendation" for the use of steroids among seriously ill patients last week.

**A competing hypothesis: the cytokine storm**

Previously, some scientists suggested that a different internal "storm" could be behind people's severe reactions to the coronavirus: a cytokine storm. That release of chemical signals, when it goes into overdrive, can instruct the body to attack its own cells. This response was also observed in patients who died of H1N1, SARS, MERS, and the 1918 Spanish flu.

Jacobson said a cytokine response could produce some COVID-19 symptoms, but it's probably not as "stormy" as researchers once thought.

"That hypothesis is losing a little bit of traction," he said. "We're not saying they're not linked. I think they are. It just doesn't look like the full-blown cytokine storm is completely supported by data."

So far, the medical community has approached the bradykinin theory with cautious optimism.

"To be honest, I'm worried that this proposal is almost too neat and form-fitting," Derek Lowe, a medicinal chemist, wrote in Science Magazine. "Rarely do you get something that falls together this well."

Still, he added, the findings are "pretty plausible."

Jacobson said his team hopes to do more follow-up studies to test the theory, including studies involving long-haul coronavirus patients who have been sick for several months. "I have a couple of long haulers on my team, so this is really near and dear to our hearts, and we're seeing it play out in real time," he said.

The bradykinin theory might play in there, too: Jacobson's team thinks that once that storm takes off, it could continue until the body figures out how to reset it. But it's still unclear whether any available treatments would make a difference for long-haul patients.

"That's part of the joy of science," Jacobson said. "For every answer you have, it raises 10 more questions."

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

## Turns Out There's Another Ocean Creature That Scares The Hell Out of Great White Sharks

***Orcas have toppled the great white shark off their 'apex predator' throne***

**Michelle Starr**

Just when you think orcas couldn't possible be any more awesome, they get even better. A study in 2019 showed these whales are really good at scaring off the most feared beast in the sea. Yep. Orcas have toppled the great white shark off their 'apex predator' throne.

A team of marine scientists found that great white sharks (*Carcharodon carcharias*) will make themselves extremely scarce whenever they detect the presence of orcas (*Orcinus orca*).

"When confronted by orcas, white sharks will immediately vacate their preferred hunting ground and will not return for up to a year,

even though the orcas are only passing through," said marine ecologist Salvador Jorgensen of Monterey Bay Aquarium.

The team collected data from two sources: the comings and goings of 165 great white sharks GPS tagged between 2006 and 2013; and 27 years of population data of orcas, sharks and seals collected by Point Blue Conservation Science at Southeast Farallon Island off the coast of San Francisco.

The team also documented four encounters between great white sharks and orcas in the Greater Farallones National Marine Sanctuary, which they could then analyse against the other data.

The data revealed that whenever orcas showed up in the region - as in, every single time - the sharks made a swift exit, stage left, and stayed away until the next season. They would choof off within minutes, even when the orcas only hung around for less than an hour.

And there was a surprising beneficiary: the elephant seals (*Mirounga angustirostrous*) that inhabit the coastline and are preyed upon by the great white sharks. "On average we document around 40 elephant seal predation events by white sharks at Southeast Farallon Island each season," said marine biologist Scot Anderson of the Monterey Bay Aquarium. "After orcas show up, we don't see a single shark and there are no more kills."

Transient orcas have also been known to eat the elephant seals, but these visiting whales only show up infrequently. Resident killer whales feed on fish.

The sharks didn't always go far. Sometimes they would only move a safe distance along the coast, where they were close to different elephant seal colonies. Sometimes, though, they would head out to the middle of the Pacific Ocean, the region dubbed the White Shark Café.

These are not tiny sharks, either. Some of them measure over 5.5 metres (18 feet) from nose to tail, and are probably pretty used to getting their own way wherever they go. But 5.5 metres is on the small side for orcas, which can prey on whales much larger than that, so they're unlikely to be pushed around easily.

In addition, orcas have been observed preying on great white sharks around the world, including near the Farallon Islands. It's still a little unclear why, but the orca-killed sharks that wash ashore (one is pictured at the top of the page) are missing their livers - their delicious, oil-rich, full-of-vitamins livers.

Whether the sharks are instinctively avoiding the predators that can so handily eviscerate them, however, or whether transients in the past have bullied the sharks away from the elephant seal food source is still an unknown.

"I think this demonstrates how food chains are not always linear," Jorgensen said. "So-called lateral interactions between top predators are fairly well known on land but are much harder to document in the ocean. And because this one happens so infrequently, it may take us a while longer to fully understand the dynamics."

The research was published in the journal *Scientific Reports*.

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

## Latest Results on Peanut Allergy Treatment Are In, And They're Super Promising

***A pioneering new study is offering new hope to peanut allergy sufferers.***

**Rachel Hosie**

It may be possible to reduce the severity of allergic reactions to peanuts, research published in *The Lancet Child & Adolescent Health* suggests.

Peanut allergy is the leading cause of food-related anaphylaxis, the report states, with 6.1 million people suffering from the allergy in the US. The number of sufferers has soared in recent decades, too, with a 2017 study suggesting prevalence in children had risen 21 percent since 2010.

The new study involved a trial, called the Artemis trial, undertaken at hospitals across Europe. 175 children with peanut allergies aged 4 to 17 took part in the research, which saw them given either increasing amounts of peanut allergen protein or a placebo every day. Those who took the peanut protein were given a slightly higher dose every two weeks for six months, after which point the same dose was maintained for three months.

The researchers found that 58 percent of children who'd taken the peanut protein could tolerate at least three to four peanuts by the end of the trial. It compared to just 2 percent of those given the placebo. The researchers concluded that the treatment "led to rapid desensitization to peanut protein."

The research does not suggest peanut allergy sufferers will soon be able to eat peanut butter by the spoonful, however the researchers hope it could mean less severe reactions from accidental exposure to the nuts.

One participant, James Redman, 12, told *The Times* that he can now tolerate up to seven peanuts after previously suffering severe reactions to any peanut traces. "Taking part in the study was the greatest opportunity of my life," he said.

"The nurses and doctors were really caring and great fun. I didn't mind the taste of the peanut protein as I got to mix it with chocolate pudding which was great. "I really hope the study leads to a treatment so that other children with a peanut allergy can benefit."