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Parkinson's disease is not one, but two diseases

A major study from Aarhus University in Denmark has now identified that there are actually two types of Parkinson's disease.

Although the name may suggest otherwise, Parkinson's disease is not one but two diseases, starting either in the brain or in the intestines. Which explains why patients with Parkinson's describe widely differing symptoms, and points towards personalised medicine as the way forward for people with Parkinson's disease.

This is the conclusion of a study which has just been published in the leading neurology journal *Brain*.

The researchers behind the study are Professor Per Borghammer and Medical Doctor Jacob Horsager from the Department of Clinical Medicine at Aarhus University and Aarhus University Hospital, Denmark.

"With the help of advanced scanning techniques, we've shown that Parkinson's disease can be divided into two variants, which start in different places in the body. For some patients, the disease starts in the intestines and spreads from there to the brain through neural connections. For others, the disease starts in the brain and spreads to the intestines and other organs such as the heart," explains Per Borghammer.

He also points out that the discovery could be very significant for the treatment of Parkinson's disease in the future, as this ought to be based on the individual patient's disease pattern.

Parkinson's disease is characterised by slow deterioration of the brain due to accumulated alpha-synuclein, a protein that damages nerve cells. This leads to the slow, stiff movements which many people associate with the disease.

In the study, the researchers have used advanced PET and MRI imaging techniques to examine people with Parkinson's disease. People who have not yet been diagnosed but have a high risk of developing the disease are also included in the study. People diagnosed with REM sleep behaviour syndrome have an increased risk of developing Parkinson's disease.

The study showed that some patients had damage to the brain's dopamine system before damage in the intestines and heart occurred. In other patients, scans revealed damage to the nervous systems of the intestines and heart before the damage in the brain's dopamine system was visible.

This knowledge is important and it challenges the understanding of Parkinson's disease that has been prevalent until now, says Per Borghammer.

"Until now, many people have viewed the disease as relatively homogeneous and defined it based on the classical movement disorders. But at the same time, we've been puzzled about why there was such a big difference between patient symptoms. With this new knowledge, the different symptoms make more sense and this is also the perspective in which future research should be viewed," he says.

The researchers refer to the two types of Parkinson's disease as body-first and brain-first. In the case of body-first, it may be particularly interesting to study the composition of bacteria in the intestines known as the microbiota.

"It has long since been demonstrated that Parkinson's patients have a different microbiome in the intestines than healthy people, without us truly understanding the significance of this. Now that we're able to identify the two types of Parkinson's disease, we can examine the risk factors and possible genetic factors that may be different for the two types. The next step is to examine whether, for example, body-first Parkinson's disease can be treated by treating the intestines with faeces transplantation or in other ways that affect the microbiome," says Per Borghammer.

"The discovery of brain-first Parkinson's is a bigger challenge. This variant of the disease is probably relatively symptom-free until the movement disorder symptoms appear and the patient is diagnosed with Parkinson's. By then the patient has already lost more than half of the dopamine system, and it will therefore be more difficult to find patients early enough to be able to slow the disease," says Per Borghammer.

The study from Aarhus University is longitudinal, i.e. the participants are called in again after three and six years so that all of the examinations and scans can be repeated. According to Per Borghammer, this makes the study the most comprehensive ever, and it provides researchers with valuable knowledge and clarification about Parkinson's disease - or diseases.

"Previous studies have indicated that there could be more than one type of Parkinson's, but this has not been demonstrated clearly until this study, which was specifically designed to clarify this question. We now have knowledge that offers hope for better and more targeted treatment of people who are affected by Parkinson's disease in the future," says Per Borghammer.

According to the Danish Parkinson's Disease Association, there are 8,000 people with Parkinson's disease in Denmark and up to eight million diagnosed patients worldwide.

This figure is expected to increase to 15 million in 2050 due to the ageing population, as the risk of getting Parkinson's disease increases dramatically the older the population becomes.

https://bit.ly/2EvP2R4

Archaeology uncovers infectious disease spread - 4000 years ago

New bioarchaeology research from a University of Otago PhD candidate has shown how infectious diseases may have spread 4000 years ago, while highlighting the dangers of letting such diseases run rife.

Yaws - from the same bacteria species responsible for syphilis (*Treponema pallidum*) - is a childhood disease causing highly infectious skin lesions. It is spread via touch from person to person and, in advanced cases, can leave sufferers with severe bone disfigurement. While it is easily curable in its early stages, the bone disfigurements are irreversible.

The disease has been eradicated from much of the world but is still prevalent in the Western Pacific, affecting some 30,000 people. A previous global attempt to eradicate this tropical disease failed at the last hurdle in the 1950's and a new attempt was curtailed by the COVID-19 outbreak, University of Otago Department of Anatomy PhD candidate Melandri Vlok says.

Ms Vlok's PhD research uses archaeology to shed light on the spread of diseases when different human populations interact for the first time. Her specific interest is in what she calls the "friction zone", where ancient agricultural people met hunter gatherer people. In 2018 she travelled to Vietnam to study skeletal remains from the Man Bac archaeological site. From the Ninh Bình Province in the north of the country, Man Bac was excavated in 2005 and 2007 and has delivered a treasure trove of information for archaeologists thanks to its role during the transition away from foraging to farming in Mainland Southeast Asia.

Now housed in Hanoi's Institute of Archaeology those remains are well-studied but had not been analysed for evidence of yaws, Ms Vlok says.

Her supervisor at Otago, renowned bioarchaeologist Professor Hallie Buckley, had seen what she thought might be yaws on a photograph of Man Bac remains. Professor Buckley travelled with Ms Vlok and together with a passionate team of experts from Vietnam they confirmed their suspicions, Ms Vlok says. Later, Ms Vlok found a second example of the disease.

This was significant, as the Man Bac site dates back 4000 years. Till now, there was no strong evidence for yaws in prehistoric Asia.

Ms Vlok's research suggests yaws was introduced to hunter-gathers in present-day Vietnam by an agricultural population moving south from modern-day China. These hunter-gathers descended from the first people out of Africa and into Asia who also eventually inhabited New Guinea, the Solomon Islands and Australia.

The farmers had been in China for at least 9000 years but it wasn't until around 4000 years ago farming was introduced to Southeast Asia. It is possible this movement of people brought diseases, including yaws, at the same time.

Ms Vlok says the length of time the disease has existed in the region is relevant when addressing how hard it has been to eradicate.

"This matters, because knowing more about this disease and its evolution, it changes how we understand the relationship people have with it. It helps us understand why it's so difficult to eradicate. If it's been with us thousands of years it has probably developed to fit very well with humans."

This year's COVID-19 pandemic has focused people's attention on infectious diseases, and there are lessons to be learned from the past, Ms Vlok says.

"Archaeology like this is the only way to document how long a disease has been with us and been adapting to us. We understand with COVID-19 today how fantastic that disease is at adapting to humans. And Treponema has been with us for so much longer.

"So, this shows us what happens when we don't take action with these diseases. It's a lesson of what infectious diseases can do to a population if you let them spread widely. It highlights the need to intervene, because sometimes these diseases are so good at adapting to us, at spreading between us."

** Ms Vlok's research paper, published in the journal Bioarchaeology International, can be read here: https://doi.org/10.5744/bi.2020.1000*

https://bit.ly/3i4jekb

Scientists Say Jellyfish Should Become The Next Popular Seafood

We might be eating some threatened species without even realising it.

Jacinta Bowler

According to the IUCN Red List 32,000 species are threatened with extinction – everything from birds and mammals, to reef corals and crustaceans. And that's only the species we know about.

But although we might be working hard to help some species come back from the brink, we might also be eating some threatened species without even realising it. Searching industrial fishing records, researchers identified almost 100 endangered species being sold as seafood, and this is done legally.

"Species that aren't cute like whales or sea turtles often don't end up getting the protection they deserve," University of Queensland (UQ) biologist and first author of the new paper, Leslie Roberson told ScienceAlert. "Despite national and international commitments to protect threatened species, we actively fish for many of these threatened species."

For those of us who enjoy the odd fish and chips this isn't great news, but the researchers have come up with an unconventional way we can help while still enjoying seafood – and it involves eating jellyfish.

Between 2006 and 2014, the team found records of 92 vulnerable or endangered (11 of them critically endangered) species of seafood being caught, recorded, and sold – 13 of them internationally.

When sold, these fish and invertebrate species are not required to be labelled according to species, so consumers have no way of knowing what they're eating.

The team stresses that this is only a snapshot of the real problem, as they only looked at a specific section of records and excluded

groups of fish such as sharks or rays, which are commonly eaten in Australia, Europe, and some Asian countries.

"We looked just at the reported catch and imports, not even digging into illegal and unreported fishing, and found 92 species that are caught or traded despite being listed as globally threatened with extinction," UQ conservation scientist Carissa Klein told ScienceAlert. "A lot of the seafood catch and import records are listed in groups like 'marine fish'. Here we didn't look at those vague records, we only looked at records where the actual species was listed - so we've made a huge underestimate of the actual catch of endangered species."

The seafood industry is a tangled mess of supply chains criss-crossing countries, and very few of us can avoid the blame.

"European countries (e.g. Germany, UK, Spain) and the USA comprise most of the top importers of threatened species by volume and value," the team wrote in their paper. But there are some ways to untangle the mess we're creating in the world's oceans. Including expanding our idea of seafood to include jellyfish.

That might sound a little left of field, but it's not the first time scientists have suggested it as a food source. And with jellyfish being one of a minority of wild animals that scientists think might be actually increasing in numbers around the world, it makes a lot of sense.

Back in 2017, researchers in Denmark made crispy chips out of jellyfish, while people in China have been enjoying jellyfish for over 1,700 years. Depending on the species, it could help us manage jellyfish blooms, and keep other endangered species in the sea.

"It's really just a mild chewy thing without much taste. It's actually quite good with a yummy sauce!" Roberson told ScienceAlert.

"A lot of our tastes for seafood are driven largely by culture and tradition. The obvious example is shark fin soup - shark fins are basically tasteless, and it's all about the seasoning and the sauce (and the status) that makes it a delicacy in China."

Of course, there are other ways to help keep endangered species off the menu. "We need to improve the labelling of seafood so that we are more aware of what we are eating. And if the seafood is not labelled, the consumer should ask what species it is, where it was caught, and how it was caught… so they have all of the information to make an informed choice," said Klein.

And the informed choice, at least in some places, is easier than you might imagine. In Australia, where the researchers are based, there's the Sustainable Seafood Guide, which is able to provide the best choices for seafood. There's also Seafood Watch in the US, which is run by the Monterey Bay Aquarium.

And the obvious - "it should be illegal to eat something that is threatened by extinction, especially species that are critically endangered," Klein said. "If we can better coordinate fisheries and conservation policies, we can prevent it from happening." "We would never consider eating mountain gorillas or elephants, both of which are endangered," Robertson added.

The research has been published in *Nature Communications*.

https://bit.ly/343QiDE

Breathtaking Images Suggest There's Fresh Ice on One of Saturn's Moons

In infrared wavelengths, astronomers have discovered that much of the ice over the entirety of the moon is fresh

Michelle Starr

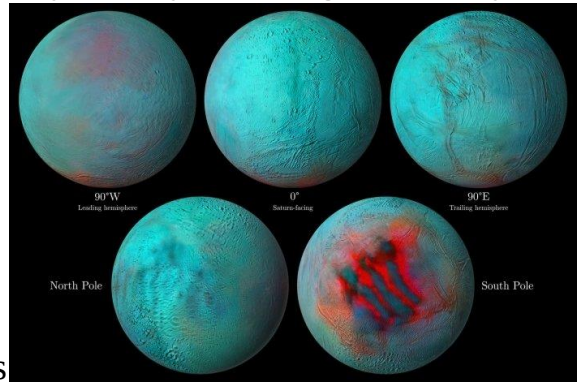
To human eyes, Saturn's moon Enceladus looks relatively plain. Shift the wavelength away from the optical, however, and Enceladus starts to look a lot more interesting, as new images amply demonstrate. Although its surface is scored with deep chasms and gorges, Enceladus seems fairly uniform otherwise, with a glistening white ice shell, like a giant snowball in space.

In infrared wavelengths, astronomers have discovered that much of the ice over the entirety of the moon is fresh, suggesting there might be global internal activity resurfacing the moon.

We've known for a little while now that Enceladus isn't necessarily a quiet place. In 2005, Saturn probe Cassini discovered plumes of salty water shooting out of four huge parallel chasms in the moon's south pole, nicknamed the "tiger stripes". Cassini went on to map over 100 geysers in the tiger stripe fractures.

These fractures are generated by tidal forces on the moon as it makes its eccentric orbit around Saturn. The planet pulls and stretches Enceladus, giving rise to internal heating and geothermal activity, and creating cracks in the surface ice at the south pole. The geysers spew out water from the interior, kept liquid by the internal heating; this water sprays over the surface and freezes, creating a new layer of ice.

So, in infrared images from newly reanalysed data generated by Cassini's Visual and Infrared Mapping Spectrometer (VIMS) - the spacecraft's mission ended in September 2017, but its legacy lives on - it was to be expected you'd find light consistent with fresh ice, reflecting off the region around the tiger stripes



(NASA/JPL-Caltech/University of Arizona/LPG/CNRS/University of Nantes/Space Science Institute)

Sure enough, the highly detailed images, compiled from 23 close flybys, show persistent resurfacing. You can see it in the image above, and you can explore an interactive globe here - the bright red regions around the tiger stripes indicate the spectral signature of crystalline ice, in which the molecules are ordered in a neat, repeating geometric lattice; it reflects infrared light differently from amorphous ice, with disordered higgledy-piggledy molecules.

This matters. Almost all natural ice on Earth is crystalline - but almost all the ice we detect in space is amorphous. This is because temperatures in space tend to be very low, and at very low temperatures, water molecules collide and freeze into place.

Crystalline ice, on the other hand, indicates that the water has been relatively warm, above about 110 Kelvin - even after freezing, the molecules retain enough thermal energy to move into a crystalline configuration. So, when you see crystalline ice in space, you can draw certain inferences about its thermal history.

Most of the ice on the surface of Enceladus is crystalline, but the level of crystallinity is important. If we find ice that is more crystalline than the ice around it, we can assume it formed from warmer water - such as the ice and water freshly spewed out from the interior by way of geysers in the tiger stripes.

But that's not all. What the team led by Rozenn Robidel of the University of Nantes in France did *not* expect to find was a spectral signature of crystalline ice distributed broadly across the globe of Enceladus, including the north pole, which does not have tiger stripes.

This unexpected finding suggests that geological activity has occurred on both hemispheres, and that the northern hemisphere has undergone similar resurfacing to the southern, although the mechanism may be different - a more gradual fracturing of the crust. Since such activity is likely related to seafloor hotspots, and such hotspots are likely to have a lifespan of only a few million years, that allows us to infer the age of the surface in these regions.

"The infrared shows us that the surface of the south pole is young, which is not a surprise because we knew about the jets that blast icy material there," said astronomer Gabriel Tobie of the University of Nantes.

"Now, thanks to these infrared eyes, you can go back in time and say that one large region in the northern hemisphere appears also young and was probably active not that long ago, in geologic timelines."

The team plans to apply their analysis techniques to data obtained in the upcoming Juice and Europa Clipper missions, to see what they can learn about Jupiter's icy moons Ganymede and Europa.

The research has been published in *Icarus*.

https://bit.ly/33ZuCJ8

Genomic adaptations to a rice-based diet mitigate the risk of obesity and diabetes

Some east-Asian populations have evolved genomic adaptations that mitigate the harmful effects of high-glycaemic diets on metabolism

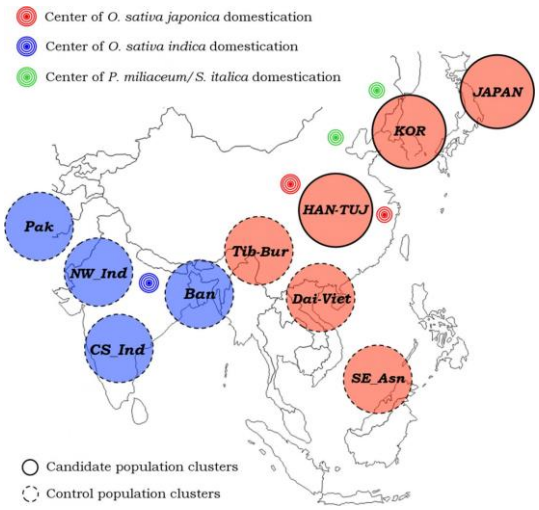
The traditional rice-based diet of some east-Asian population has brought to a number of genomic adaptations that may contribute to mitigating the spread of diabetes and obesity. An international study led by the University of Bologna and published in the journal *Evolutionary Applications* has recently suggested this interesting hypothesis. Researchers analysed and compared the genomes of more than 2,000 subjects from 124 south-east-Asian populations.

"We suggest that it may be possible that some east-Asian populations, whose ancestors started eating rice on a daily basis at least 10,000 years ago, have evolved genomic adaptations that mitigate the harmful effects of high-glycaemic diets on metabolism", confirms Marco Sazzini, study coordinator and professor at the Department of Biology, Geology and Environmental Sciences of the University of Bologna. "Furthermore, these adaptations plausibly continue to play a pivotal role in protecting them from the negative effects that derive from major dietary alterations brought about by the globalisation and westernization of their lifestyles. These alterations dramatically increased their consumption of food rich in processed sugar and with a high glycaemic index".

RICE AND GLYCAEMIC INDEX

Among the so-called domesticated cereals, rice presents a high glycaemic index and is rich in carbohydrates. This means that once ingested and digested, it causes sugar in the blood to increase. If eaten regularly and in large quantities, rice may represent a potential risk factor for developing insulin resistance and related metabolic diseases such as type 2 diabetes.

However, if we compare east-Asian people having used rice as a staple food for over 10,000 years with those in the Indian sub-continent, we soon find out that the latter show higher rates of diabetes and obesity than east-Asians. Why are these two groups different?



Blue clusters showed predominant South Asian ancestry, while red ones are enriched for East and South East Asian ancestry. Red concentric circles indicate archaeological sites along the Yangtze River valley in Eastern China where remains suggesting usual consumption of wild rice have been dated to at least 12,000 years ago. Green concentric circles indicate archaeological sites in the Hebei and Manchuria provinces of Northern China where remains suggesting early cultivation of broomcorn millet and foxtail millet were found. Conversely, all the remaining clusters were used as control groups (i.e., populations not expected to have evolved adaptations to cereal?based diets despite using rice as a staple food). Blue concentric circles indicate archaeological sites across the Indo-Gangetic Plain where evidence for more recent domestication of O. sativa indica was found. **Evolutionary Applications**

A 10,000-YEAR-OLD DIET

Archaeology may provide a hint to answering that question. Archaeobotanical findings in some eastern regions of Asia show that wild rice had been part of the inhabitants' diets in the past starting 12,000 years ago. After rice domestication and the introduction of rice farming techniques, between 7,000 and 6,000 years ago, rice spread rapidly across Korea and Japan. In northern regions of the Indian sub-continent, an independent domestication process had started 4,000 years ago and brought to the selection of rice varieties presenting a lower glycaemic index if compared to east-Asian rice.

"Different rice varieties and a head start of millennia may have put populations in China, Korea, and Japan under a more pressing metabolic stress than that experienced by south Asian populations", explains Arianna Landini, first author of this study and a PhD student at the University of Edinburgh. "This might have allowed them to evolve genomic adaptations that mitigate the risk of becoming ill with metabolic diseases linked with a high-sugar diet".

RICE AND GENOMIC ADAPTATIONS

To test such a hypothesis, researchers analysed the genome of more than 2,000 subjects from 124 east-Asian and south-Asian populations. Then, they compared the adaptive evolution observed in Chinese Han and Tujia ethnic groups, as well as in people of Korean and Japanese ancestry (with a long-standing tradition of rice-based diets) with that of people from regions of Pakistan, Bangladesh, Myanmar, Vietnam, and south-east Asia. Southeast Asian subjects were used as control groups because their adoption of cereal-based diets occurred many thousand years later.

"The genomic adaptations observed in control groups differ greatly from those of east Asian populations and are not related to metabolic stress due to a specific diet", says Claudia Ojeda-Granados, one of the authors and a research fellow at the University of Bologna. "Chinese Han and Tujia ethnic groups, as well as people of Korean and Japanese ancestry show instead similar metabolic genomic adaptations".

Some of the genetic modifications the researchers identified are associated with a lower BMI and a weaker risk of cardiovascular diseases thanks to a reduced conversion of carbohydrates into cholesterol and fatty acids. Some other adaptations favour a reduced insulin resistance as they negatively modulate the glucogenesis in the liver. Finally, some others stimulate the production of retinoic acid, which is a metabolite of vitamin A. Deficiency in this nutritional organic compound often causes health-issues in people eating a rice-based diet.

"Our results demonstrate once again how studying evolutionary history may successfully inform biomedical research, eventually leading to the identification of the mechanisms underlying the different susceptibility of human populations to different diseases", concludes Sazzini.

THE AUTHORS OF THE STUDY

The title of this study is "Genomic adaptations to cereal-based diets contribute to mitigating metabolic risk in some human populations of East Asian ancestry" and was published in the journal Evolutionary Applications. The research coordinator is Marco Sazzini, professor at the Molecular Anthropology Lab and Genomic Biology Center of the Department of Biology, Geology and Environmental Sciences of the University of Bologna and of the Alma Mater Research Institute on Global Challenges and Climate Change. Other researchers of the University Bologna participating in the study are Shaobo Yu, Paolo Abondio, Claudia Ojeda?Granados, Stefania Sarno, Sara De Fanti e Davide Pettener (Department of Biology, Geology and Environmental Sciences), together with Eugenio Bortolini and Donata Luiselli (Department of Cultural Heritage), Giovanni Romeo (Unit of Medical Genetics of the Policlinico Sant'Orsola) and Cecilia Prata (Department of Pharmacy and Biotechnology).

Adriana Landini (Centre for Global Health Research at the University of Edinburgh, UK) also took part in the study and was its the first authors alongside Shaobo Yu. Finally, other participants were Guido Alberto Gnecchi Ruscone (Max Planck Institute for the Science of Human History in Jena, Germany), Davide Gentilini and Anna Maria Di Blasio (Istituto Auxologico Italiano) and researchers from universities in South Korea and Vietnam.

https://wb.md/36cjyeu

Study Challenges 'Scoop and Run' Model for Cardiac Arrest

Odds of surviving out-of-hospital cardiac arrest significantly better when resuscitation is continued on scene, as opposed to being performed during transport to the hospital

Megan Brooks

The odds of surviving out-of-hospital cardiac arrest (OHCA) are significantly better when resuscitation efforts are continued on scene, as opposed to being performed while the patient is being transported to the hospital, a large observational study has found.

The process of moving a patient during resuscitation (known as "scoop and run") may impair or delay best practices, including impairing the quality of cardiopulmonary resuscitation (CPR), say investigators with the Resuscitation Outcomes Consortium (ROC).

"Although infrequently there may be individual cases with a specific rationale to pursue hospital transport, overall, these results support a strategy that paramedics dedicate effort and expertise at the scene of the cardiac arrest, rather than prioritizing transport to hospital," first author Brian Grunau, MD, St. Paul's Hospital, Vancouver, British Columbia, Canada, told *theheart.org | Medscape Cardiology*.

Jeffrey M. Goodloe, MD, member of the board of directors of the American College of Emergency Physicians and chief medical officer, Medical Control Board, EMS System for Metropolitan Oklahoma City and Tulsa, agrees. "This study supports and validates what most large urban EMS systems in the US are doing, which is actively resuscitating on scene for a minimum of 20 minutes," he told *theheart.org | Medscape Cardiology*.

"This is absolutely in line with what we have been doing here in metropolitan Oklahoma City and Tulsa for a number of years," said Goodloe, who was not involved in the study.

The study was published online September 15 in *JAMA*.

The findings are based on data from the ROC Cardiac Epidemiologic Registry, which involves 10 study sites and 192 EMS agencies in the United States and Canada.

Among the full cohort of 43,969 adult EMS-treated OHCA patients (median age, 67 years; 37% women), 26% underwent intra-arrest transport. The rate of survival to hospital discharge was 3.8% among these patients, vs 12.6% among those who received on-scene resuscitation.

In a propensity-matched cohort of 27,705 OHCA patients, the probability of survival to hospital discharge was statistically significantly lower with intra-arrest transport than with continued on-scene resuscitation (4.0% vs 8.5%), an absolute difference of 4.6%, with an adjusted risk ratio (RR) of 0.48 (95% CI, 0.43 – 0.54).

Transport during resuscitation was also associated with lower probability of survival to hospital discharge with favorable neurologic outcome (modified Rankin scale, <3; 2.9% vs 7.1%), an absolute difference of 4.2%, with an adjusted RR of 0.60 (95% CI, 0.47 – 0.76).

The findings remained significant in favor of on-scene resuscitation in the subgroups of patients with initial shockable and nonshockable rhythms, as well as with EMS-witnessed and unwitnessed cardiac arrests.

"We attempted to find subgroups of patients for whom intra-arrest transport may be associated with improved outcomes. However, the results for nearly all subgroups tested were consistent with our primary analysis," Grunau told *theheart.org | Medscape Cardiology*.

"We did find, however, that for patients who remained in refractory arrest past 30 minutes and were still undergoing active resuscitation, that intra-arrest transport was associated with improved outcomes," he said.

The caveat to this, however, is that most of the survivors who were transported during resuscitation were successfully resuscitated before they arrived at the hospital, "raising questions about the hospital-based contributions to intra-arrest transport survivors," the authors note in their article.

Strong Clinical Benefit

Goodloe is not surprised by the benefit of continuing resuscitation effort at the scene. "What we have seen in Oklahoma City and Tulsa is that, in the times that we do transport individuals to hospital, it becomes a significant challenge for the EMTs and paramedics that are continuing to provide care in transit to sustain the same quality of CPR," he noted.

In a *JAMA* editorial, Alexander X. Lo, MD, PhD, Department of Emergency Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, says the findings suggest "a strong clinical benefit associated with continuing the resuscitation on scene until a definitive outcome has been achieved."

But Lo argues, "Before embracing this model, and substantially changing the out-of-hospital approach to OHCA, more definitive studies, including high-quality randomized trials, will be needed."

Lo says two contemporary issues lend greater importance to the need to advance the science on OHCA. One is the aging of the US population, which will likely increase the incidence of OHCA and the need for optimal OHCA care.

The other is COVID-19, which has added further risks to the management of OHCA, given that the infection status of patients may be unclear in many cases. CPR and intubation are aerosol-generating procedures and further increase the risk for infection for EMS and hospital workers.

"If continued on-scene resuscitation confers a true benefit in outcome for OHCA, then it must also be accompanied by the necessary policy and logistical considerations to ensure that all EMS personnel have the necessary personal protective equipment to minimize their risk of COVID-19 infection," Lo cautions.

Goodloe thinks this is a "thought-provoking study, not only within EMS and the larger medical community but even more so as we help communities better understand the advanced capabilities that EMS systems have today.

"We often equate rushing to the hospital with it being a good thing. God forbid, if somebody in my family has a sudden cardiac arrest, with a significant on-scene-time committed resuscitation, I'm going to feel a lot better about the outcome, and if that family member dies, I can at least be at peace that they got optimal care if you show me that EMS was on scene for 20-plus minutes as opposed to a handful of minutes," Goodloe commented.

The Resuscitation Outcomes Consortium is supported by the National Heart, Lung, and Blood Institute in partnership with the National Institute of Neurological Disorders and Stroke, the US Army Medical Research and Material Command, the Canadian Institutes of Health Research – Institute of Circulatory and Respiratory Health, Defence Research and Development Canada, the Heart and Stroke Foundation of Canada, and the American Heart Association. Grunau is the principal investigator of a clinical trial investigating the benefit of intra-arrest transport to hospital for extracorporeal CPR initiation and has received speaking honorarium from Stryker Corp. Lo and Goodloe have disclosed no relevant financial relationships.

JAMA. Published September 15, 2020. Abstract, Editorial

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Most people infected with SARS-CoV-2 develop symptoms

Study suggests asymptomatic cases may account for about 20% of infections

While some people who contract SARS-CoV-2 infections never experience any symptoms, there remains disagreement about what proportion of total infections these cases represent. A new study published in the open-access journal *PLOS Medicine* by Diana Buitrago-Garcia at the University of Bern, Switzerland and

colleagues suggests that true asymptomatic cases of SARS-CoV-2 comprise a minority of infections.

The full spectrum and distribution of the severity of COVID-19 symptoms are not well understood. Some infected people may experience severe infections resulting in viral pneumonia, respiratory distress syndrome, and death, while others remain completely asymptomatic or develop mild, nonspecific symptoms. To better understand the proportion of people who become infected with SARS-CoV-2 and never develop any symptoms, as well as the proportion of people who are asymptomatic at the time of diagnosis but develop symptoms later, researchers systematically reviewed literature using a database of SARS-CoV-2 evidence between March and June, 2020. The authors then analysed 79 studies reporting empirical data on 6,616 people, 1,287 of whom were defined as asymptomatic, in order to determine the proportion of infected people who never developed symptoms. While the study was limited by its inability to ascertain the impact of false negatives, the researchers were able to estimate that 20% (95% CI 17-25) of COVID-19 infections remained asymptomatic during follow-up.

Accurate estimations of true asymptomatic and presymptomatic infections are critical to understanding SARS-CoV-2 transmission at the population level and for populations to adopt appropriately tailored public health strategies. Future research should include prospective longitudinal studies that document symptom status. Improved accuracy of serological tests is also needed to reduce the number of false negatives. Since each person infected with SARS-CoV-2 is initially asymptomatic, the proportion that will go on to develop symptoms is estimated to be around 80%, suggesting that presymptomatic transmission may significantly contribute to overall SARS CoV-2 epidemics.

According to the authors, "The findings of this systematic review of publications early in the pandemic suggests that most SARS-CoV-2 infections are not asymptomatic throughout the course of infection. The contribution of presymptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that combination prevention measures, with enhanced hand and respiratory hygiene, testing and tracing, and isolation strategies and social distancing, will continue to be needed.

Research Article

Peer reviewed; Systematic review; People

In your coverage please use this URL to provide access to the freely available paper: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003346

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Competing Interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: GS has participated in two scientific meetings for Merck and Biogen. NL is a member of the PLOS Medicine editorial board.

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https://bit.ly/3kORulh

Is rheumatoid arthritis two different diseases?

Findings add to a growing body of evidence that RA with and without autoantibodies are two distinct conditions

While disease activity improves over time for most rheumatoid arthritis (RA) patients, long-term outcomes only improve in RA patients with autoantibodies, according to a new study published this week in *PLOS Medicine* by Xanthe Matthijssen of Leiden University Medical Center, Netherlands, and colleagues. The

findings add to a growing body of evidence that RA with and without autoantibodies are two distinct conditions.

Rheumatoid arthritis is the most common type of autoimmune arthritis, caused when the immune system attacks healthy cells in the linings of joints. Over the last decade it has become clear that there are differences in RA patients with and without RA-associated autoantibodies detectable in their blood. In the new study, researchers followed 1,285 RA patients between 1993 and 2016 through the Leiden Early Arthritis Clinic cohort. Data on patients' symptoms, treatments, autoantibody status, disability and mortality was collected annually.

In total, 823 patients had autoantibody-positive RA and 462 patients had autoantibody-negative RA. In both groups, disease activity decreased significantly over time. Sustained drug-free remission rates increased, as a new treat-to-target treatment strategy became common in 2006 to 2010, in patients with autoantibody-positive, but not autoantibody-negative, RA. Moreover, mortality and functional disability rates decreased with treat-to-target adjustments only in autoantibody-positive patients.

"The disconnection between improvement in disease activity and subsequent improvement in long-term outcomes in RA without autoantibodies suggests that the underlying pathogenesis of RA with and without autoantibodies is different," the authors say. "We propose that it is time to formally divide RA into type 1, with autoantibodies, and type 2, without autoantibodies, in the hope that it leads to stratified treatment in autoantibody-positive and autoantibody-negative RA."

Dr. Matthijssen notes "In the last decennia research in RA has largely focused on the autoantibody-positive subset. More research on autoantibody-negative RA is urgently needed to identify methods to also improve their long-term outcomes."

Research Article

Peer reviewed; Observational study; People

In your coverage please use this URL to provide access to the freely available paper: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003296

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https://bit.ly/3kWhE5L

Living in an anoxic world: Microbes using arsenic are a link to early life

Much of life on planet Earth today relies on oxygen to exist, but before oxygen was present on our blue planet, lifeforms likely used arsenic instead.

These findings are detailed in research published today in *Communications Earth and Environment*.

A key component of the oxygen cycle is where plants and some types of bacteria essentially take sunlight, water and CO2 and convert them to carbohydrates and oxygen which are then cycled and used by other organisms that breathe oxygen. This oxygen serves as a vehicle for electrons, gaining and donating electrons as it powers through the metabolic processes. However, for half of the time life has existed on Earth, there was no oxygen present and for the first 1.5 billion years we really do not know how these systems worked, says lead author of the study and UConn Professor of Marine Sciences and Geosciences Pieter Visscher.

Light-driven, photosynthetic organisms appear in the fossil record as layered carbonate rocks called stromatolites dating to around 3.7 billion years ago, says Visscher. Stromatolite mats are deposited over the eons by microbial ecosystems, with each layer holding clues about life at that time. There are contemporary examples of microbes that photosynthesize in the absence of oxygen using a variety of elements to complete the process, however it is not clear how this happened in the earliest life forms.

Theories as to how life's processes functioned in the absence of oxygen have mostly relied on hydrogen, sulfur, or iron as the elements that ferried electrons around to fulfill the metabolic needs of organisms.

Visscher explains these theories are contested, for example photosynthesis is possible with iron but researchers do not find evidence of that in the fossil record before oxygen appeared some 2.4 billion years ago. Hydrogen is mentioned yet the energetics and competition for hydrogen between different microbes shows it is highly unfeasible.

Arsenic is another theoretical possibility, and evidence for that was found in 2008. Visscher says the link with arsenic was strengthened in 2014 when he and colleagues found evidence of arsenic-based photosynthesis in deep time. To further support their theory, the researchers needed to find a modern analog to study the biogeochemistry and element cycling.

Finding an analog to the conditions on early Earth is a challenge for a number of reasons, besides the fact that oxygen is abundant on modern earth. For instance, the evidence shows early microbes captured atmospheric carbon and produced organic matter at a time when volcanic eruptions were frequent, UV light was intense in the absence of the ozone layer, and oceans were essentially a toxic soup. Another challenging aspect of working within the fossil record, especially those as ancient as some stromatolites, is that there are few left due to the cycling of rock as continents move and time marches on. However, a breakthrough happened when the team discovered an active microbial mat, currently existing in the harsh conditions in Laguna La Brava in the Atacama Desert in Chile.

The mats have not been studied previously but present an otherworldly set of conditions, like those of early Earth. The mats are in a unique environment which leaves them in a permanent oxygen-free state at high altitude where they are exposed to wild, daily temperature swings, and high UV conditions. The mats serve as powerful and informative tools for truly understanding life in the conditions of early Earth.

Visscher explains, "We started working in Chile, where I found a blood red river. The red sediments are made up by anoxogenic photosynthetic bacteria. The water is very high in arsenic as well. The water that flows over the mats contains hydrogen sulfide that is volcanic in origin and it flows very rapidly over these mats. There is absolutely no oxygen."

The team also showed that the mats were making carbonate deposits and creating a new generation of stromatolites. The carbonate materials also showed evidence for arsenic cycling - that arsenic is serving as a vehicle for electrons -- proving that the microbes are actively metabolizing arsenic much like oxygen in modern systems. Visscher says that these findings, along with the fossil evidence gives a strong indication of what was seen on early earth.

"Arsenic-based life has been a question in terms of does it have biological role or is it just a toxic compound?" says Visscher. That question appears to be answered, "I have been working with microbial mats for about 35 years or so. This is the only system on Earth where I could find a microbial mat that worked absolutely in the absence of oxygen."

Visscher points out that an important tool they used to perform this research is similar to one onboard the Mars Perseverance rover, currently en route to Mars.

"In looking for evidence of life on Mars they will be looking at iron and probably they should be looking at arsenic also."

https://bit.ly/3i5UWpR

Study finds lung transplant patients not given antifungal preventive drugs have higher risk of death

Antifungal preventive medications reduce mortality risk by half in the first year following lung transplantation

Rochester, Minn. -- Antifungal preventive medications reduce mortality risk by half in the first year following lung transplantation, according to Mayo Clinic research involving 667 patients who received lung transplants from 2005 to 2018.

The retrospective study, published in the *Annals of the American Thoracic Society*, is the largest ever to evaluate the effectiveness of antifungal preventive drugs in lung transplant recipients who are particularly susceptible to invasive fungal infections. These infections are associated with a nearly threefold increase in mortality for lung transplant recipients.

Mayo Clinic researchers used deidentified administrative claims data from OptumLabs Data Warehouse. The study analyzed data for adult patients who underwent single or double lung transplant, or concurrent heart-lung transplant, in the U.S. between Jan. 1, 2005, and Dec. 31, 2018. Of the 667 patients, 385, or 57.8%, received antifungal treatment and 282, or 42.3%, did not. Sixty-five patients died during the study, and all-cause mortality was significantly lower in those patients who received antifungal medications.

"Use of antifungal preventive medications in lung transplant patients is increasingly common, but no studies have established its efficacy," says Kelly Pennington, M.D., the study's first author. "This is the first study to demonstrate a mortality benefit associated with the use of antifungal prophylaxis in lung transplant patients. We still do not know which lung transplant patients receive the most benefit from these medications, and there are other unanswered questions that will require more research." Dr. Pennington is a Mayo Clinic Scholar in the Division of Pulmonary and Critical Care Medicine.

A 2019 Mayo Clinic study found that 90% of U.S. transplant centers routinely prescribe antifungal preventive medications after lung transplant, but no prospective studies have established the benefits of these medications. "In our retrospective study, the risk of death within the first year posttransplant is about twice as high in patients not receiving antifungal preventive treatment, compared with those receiving treatment," says Dr. Pennington.

Itraconazole and voriconazole were the two most common antifungal preventive medications prescribed in the study. Patients who received antifungal drugs had a lower rate of fungal infections than those who did not, though the difference was not statistically significant.

Protracted use of antifungal drugs can have negative health effects, including cardiomyopathy, skin cancer and liver dysfunction. Also, antifungal medications are expensive and can interact with other medications. Therefore, the health care team must monitor anti-fungal medications closely.

"Given the variation in practice among transplant centers, the potential for medication side effects, medication costs and risk of drug interactions, it was imperative to determine whether antifungal preventive medications are beneficial for lung transplant recipients," says Cassie Kennedy, M.D., senior author. "Our finding of a significant reduction in mortality risk among lung transplant recipients who received antifungal medications is consistent with

several prior studies in hematologic malignancies and bone marrow transplant patients."

Dr. Kennedy is a physician in Mayo Clinic's Division of Pulmonary and Critical Care Medicine. None of the authors has a conflict of interest to disclose. Dr. Kennedy is supported by HNLB1 grant K23 HL128859 from the National Institutes of Health (NIH). Dr. Pennington is supported by Mayo Clinic's Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery. Nilay Shah, Ph.D., is supported by grants from the Centers of Medicare & Medicaid Innovation Center, Food and Drug Administration, Agency for Healthcare Research and Quality, NIH's National Heart, Lung and Blood Institute, Medical Devices Innovation Consortium/National Evaluation System for Health Technology, National Science Foundation, and Patient-Centered Outcomes Research Institute.

https://bit.ly/30dHZEn

Here Are The Detailed And Risky Steps NASA Needs to Take to Land on The Moon by 2024

NASA has released its first full plan for its Artemis missions, which aim to put the first woman on the moon and the first man since 1972.

Susie Neilson & Dave Mosher, Business Insider

The plan calls for a lunar landing in 2024, but before that, NASA intends to launch two other missions to the moon to test its new Orion spacecraft. "Our plan to land the first woman and next man on the moon in 2024 is on track!" Kathy Lueders, chief of NASA's Human Exploration and Operations Mission Directorate, tweeted on Monday.

The plan is ambitious, however a reality NASA Administrator Jim Bridenstine knows well. "2024 is an aggressive timeline," he told reporters during a briefing on Monday. "Is it possible? Yes. Does everything have to go right? Yes."

So far, the agency isn't even sure that it will get enough money to pull off the plan. NASA is asking Congress for nearly US$28 billion. And even if funding does come through and NASA does land astronauts on the moon within four years, the agency's goals get even more challenging after that. NASA hopes to subsequently put people on the lunar surface at least once a year from 2024 on and build a permanent lunar outpost by the early 2030s.

The agency also hopes to construct and install the Gateway, a space station that would orbit the moon and support frequent trips to the surface. That infrastructure might in turn enable trips to Mars after 2030. Here are the latest details on the planned Artemis missions.

Artist's depiction of NASA's Space Launch System. **(NASA/MSFC)**

2 missions must succeed before people can walk on the moon again

The first mission in the Artemis program, Artemis 1, calls for the launch of an Orion space capsule atop NASA's forthcoming mega-rocket, the Space Launch System. The spacecraft wouldn't carry any passengers, but would stay in the moon's orbit for three days as a test of its ability to fly to the moon and back. NASA's timeline suggests that mission would launch in November 2021.

After that, Artemis 2 would be the first crewed test of Orion and the SLS rocket. In a lunar flyby, the Orion capsule would carry four astronauts around the moon's far side, which is almost a quarter of a million miles from Earth. That crew would go farther into deep space than any humans before them.

Once Orion gets that far away, gravity from the moon and Earth would slingshot the spacecraft back home. The entire mission is expected take about 10 days, serving as a test of Orion's capacity to ferry humans safely to and from the moon.

The mission is currently slated to launch in August 2023.

Artemis 3 would land astronauts on the moon's South Pole

For the Artemis 3 mission in 2024, NASA would launch an Orion spacecraft, fly it into lunar orbit, land astronauts on the lunar surface, then safely return everyone to Earth.

The mission is expected to send people to the moon's South Pole (despite recent rumours suggesting the missions might land at a site previously visited by Apollo astronauts). Landing at the South Pole is more technically difficult than landing at other sites; no human or robotic mission has ever pulled off the feat.

To accomplish this goal, NASA needs a human landing system: a spacecraft to take astronauts from orbit to the moon's surface. The Artemis plan calls for the system to provide life support for about a week once the astronauts have landed, then get them back to lunar orbit. The agency is already working with three commercial space companies â€" Blue Origin, Dynetics, and SpaceX â€" to develop prototypes for this system.

New spacesuits are in in the works, too. While they look fairly similar to the ones the Apollo astronauts wore (and they still contain diapers), the suits are more flexible, which should make it easier for astronauts to do complex tasks on spacewalks. The designs also include better in-helmet communications systems and other technological upgrades.

NASA is betting that the moon's South Pole will offer the most value to human travellers, since it likely contains lots of frozen water hidden in the bottoms of craters never touched by sunlight. Astronauts (or robots) could ostensibly mine that ice, melt it, store it, and use electricity to split the water into liquid oxygen and hydrogen a key oxidizer and fuel, respectively, for many types of rockets.

NASA scientists hope that fuel mined and produced on the moon could then be used for trips back home or deeper into space.

Harvesting such resources on the moon, Bridenstine said, would allow space explorers to start "living off the land."

After its first mission, NASA hopes to put humans on the moon every year

Artemis 3 is only the beginning of NASA's ambitions. After that, the agency hopes to install the Gateway, an orbiting station similar to the International Space Station, in the moon's orbit.

Like the ISS, the Gateway is expected to be an international effort: Many other space agencies have agreed to help build it, including the Russia's Roscomos, the Japan Aerospace Exploration Agency, and the Canadian Space Agency.

These agencies are also on board to collaborate on a lunar base camp at the moon's South Pole that could house four people. The base would be equipped with two lunar-terrain vehicles, one of which could enable long, exploratory drives away from the camp.

Artist's rendering of a Human Landing System. **(NASA)**

But the budget still hasn't been worked out

Most immediately, NASA says it needs US$3.2 billion in funding to develop a human landing system. So far, the agency has spent about US$1 billion on that effort.

The rest of the funds are far from a sure bet, however. NASA is pinning its hopes on an omnibus appropriations bill at the end of the year, but the House of Representatives has so far only approved about US$630 million in additional funds.

Bridenstine said on Monday that he hopes to get a new budget in place to fund Artemis after the November election.

"If we can have that done before Christmas, we're still on track for a 2024 moon landing," he said.

Bridenstine is expected to appear before a Senate subcommittee on Wednesday to explain NASA's budget request, which has come about six months earlier than usual, Space News reported.

Without full funding from Congress, Bridenstine said, the agency would not get to the moon in 2024, though it may still try to get there "at the earliest possible opportunity."

Commercial enterprises like SpaceX could also potentially travel to the moon on their own dime, he added.

"The companies themselves could step up to the plate in a bigger way," Bridenstine said. "If the money doesn't materialise, could they do it with their own resources? I'll leave it to them to make their own determination."

https://lat.ms/3cBGV2f

Young adults are now the largest group of Americans getting COVID-19, CDC says

The longer the COVID-19 pandemic goes on, the younger its victims get.

By Karen Kaplan Science and Medicine Editor

A new study from the Centers for Disease Control and Prevention reports that the median age of people with COVID-19 in the U.S. has declined over the spring and summer, with Americans in their 20s now accounting for more cases than people in any other age group. The findings suggest that if the U.S. wants to get its coronavirus outbreak under control, it will need more cooperation from young adults.

In May, the median age of U.S. residents with COVID-19 was 46. By July, it had dropped to 37, then rose slightly to 38 in August.

Likewise, in May, people in their 20s made up 15.5% of confirmed COVID-19 cases nationwide. At the time, they trailed people in their 30s (who accounted for 16.9% of total cases) as well as people in their 40s and 50s (both of those age groups accounted for another 16.4% of cases).

But by June, 20-somethings had taken over the top spot, making up 20.2% of all cases. That figure rose to 23.2% in July, then dropped back to 21% in August.

The proportion of cases among Americans in their 30s also increased in June and July. But by August, it had fallen slightly below the level seen in May.

Meanwhile, the share of cases among adults 40 and older decreased steadily through the end of July, according to the study.

The trend toward younger COVID-19 patients came as the total number of new cases increased. In May, 604,570 Americans of all ages were diagnosed with COVID-19. By July, that figure exceeded 1 million — a 71% increase.

The CDC researchers who produced the report drew on three kinds of data: They tallied confirmed cases of COVID-19 in reports from state health departments, examined data from the National Syndromic Surveillance Program to identify patients who went to hospital emergency rooms with COVID-19 symptoms, and analyzed coronavirus test results from 37 states.

The trend toward younger patients was evident in all three data sources, the researchers said.

The increase in COVID-19 cases among people in their 20s was striking. In May, 93,741 Americans between the ages of 20 and 29 were newly diagnosed with the disease. That figure swelled to 149,761 in June, 240,105 in July and 189,366 in August.

Americans in their 30s made up the second-largest group of new COVID-19 cases. Among people ages 30 to 39, 101,917 cases were confirmed in May, 130,415 were identified in June, 183,487 were diagnosed in July, and 148,500 were added in August.

Over time, these infections in younger adults appeared to spread to older, more vulnerable adults in certain parts of the country, the researchers wrote.

In the Southeastern U.S., an increase in the test positivity rate for people in their 20s and 30s was followed nine days later by an increase in the positivity rate for people in their 40s and 50s. Six

days after that, people ages 60 and up had a higher positivity rate as well.

In the Southwestern U.S., an increase in the positivity rate for people under 60 was followed about four days later by an increase in the positivity rate for people ages 60 and up. The same pattern was seen in the south-central states, though the lag there was seven days.

This sequence of events offers "preliminary evidence that younger adults contributed to community transmission of COVID-19 to older adults," the researchers wrote. "Similar observations have been reported by the World Health Organization," they added.

There are several plausible explanations for why this might be the case, the CDC team wrote. Younger adults are more likely to work in restaurants, stores, childcare centers and other places that put them at greater risk of exposure to the coronavirus. At the same time, they may be more cavalier about social gatherings and more lax about the need for physical distancing.

Also, the fact that younger adults are more likely to have mild COVID-19 symptoms or even asymptomatic infections means they're more apt to spread the virus without even realizing they're sick.

The median age of people with positive coronavirus test results began falling before there was a drop in the median age of all people who got tested. That essentially rules out the possibility that the observed drop in patients' ages can be chalked up to more testing by younger people, the CDC team wrote.

The findings underscore the need for health officials to target younger adults with "age-appropriate prevention messages" about the importance of preventing COVID-19 spread, the study authors wrote. (Paul Rudd, are you listening?)

The study was published Wednesday in the CDC's Morbidity and Mortality Weekly Report.

https://bit.ly/334Ez8P

Hidden immune weakness found in 14% of gravely ill COVID-19 patients

In a significant minority of patients with serious COVID-19, the interferon response has been crippled by genetic flaws or by rogue antibodies that attack interferon itself

By Meredith Wadman

From the first months of the COVID-19 pandemic, scientists baffled by the disease's ferocity have wondered whether the body's vanguard virus fighter, a molecular messenger called type I interferon, is missing in action in some severe cases. Two papers published online in *Science* this week confirm that suspicion. They reveal that in a significant minority of patients with serious COVID-19, the interferon response has been crippled by genetic flaws or by rogue antibodies that attack interferon itself.

"Together these two papers explain nearly 14% of severe COVID-19 cases. That is quite amazing," says Qiang Pan- Hammarström, an immunologist at the Karolinska Institute.

Tadatsugu Taniguchi, a pioneering interferon scientist and emeritus professor at the University of Tokyo, calls the discoveries "remarkable." He says they highlight the "critical" role of type I interferons in SARS-CoV-2 infection and the development of potentially lethal COVID-19.

Co-author Isabelle Meyts, a pediatric immunologist at the University Hospitals Leuven, was struck by one paper's finding that rogue antibodies underlie COVID-19 in 10% of gravely ill patients: "There has never been any infectious disease explained at this level by a factor in the human body. And it's not an isolated cohort of Europeans. Patients are from all over the world, all ethnicities." Another finding, that 94% of the patients with interferon-attacking antibodies were male, also helps explain why men face higher risk of severe disease.

The paired studies have immediate practical implications. Synthetic interferons, long used to treat other diseases, might help some at-risk patients, as might other therapies aimed at removing the damaging antibodies. A common kind of antibody test could be readily developed and return answers in hours. Those found to be at high risk of developing severe COVID- 19 could take precautions to avoid exposure or be prioritized for vaccination, says Elina Zuniga, an immunologist who studies interferons at the University of California, San Diego.

The findings also raise a red flag for plasma donations from recovered patients. Because it may be rich in antibodies to the virus, "convalescent plasma" is already given to some patients to fight the infection. But some donations could harbor the interferon-neutralizing antibodies. "You should eliminate these patients from the pool of donors," Zuniga says. "You definitely don't want to be transferring these autoantibodies into another person."

Type I interferons are made by every cell in the body and are vital leaders of the antiviral battle early in infection. They launch an immediate, intense local response when a virus invades a cell, triggering infected cells to produce proteins that attack the virus. They also summon immune cells to the site and alert uninfected neighboring cells to prepare their own defenses.

In one study, Jean-Laurent Casanova, an infectious disease geneticist at Rockefeller University, and his team examined blood samples from 987 gravely ill patients from around the world. In 10.2% of the patients, the researchers identified antibodies that attacked and neutralized the patients' own type I interferon. A subgroup of affected patients had extremely low or undetectable blood levels of this interferon. Lab studies confirmed the antibodies knocked the interferon out of action and cells exposed to the patients' plasma failed to fend off invasion by the new coronavirus.

At least 10% of critical COVID-19 is an autoimmune attack.

Jean-Laurent Casanova, Rockefeller University

None of the 663 people in a control group with mild or asymptomatic SARS-CoV-2 infection had those damaging antibodies. The antibodies were also scarce in the general population, showing up in only 0.33% of more than 1200 healthy people tested. "What this means is that at least 10% of critical COVID-19 is an autoimmune attack against the immune system itself," Casanova says.

The preponderance of male patients was a surprise, because women have higher rates of autoimmune disease. "Our favorite hypothesis is that it is an X-linked recessive trait," Casanova says. "Women with two X chromosomes are protected and men, with one, are not." Supporting that suspicion, one woman with a rare condition that silences one X chromosome was among the severely ill patients with autoantibodies.

If these striking results hold up, they might also help explain the increased vulnerability of older people to severe COVID-19: Half the gravely ill patients with autoantibodies were older than 65.

The second paper found genetic flaws in patients that led to the same end result: a grossly inadequate interferon response to SARS-CoV-2 infection. The team sequenced DNA from 659 critically ill COVID-19 patients and from 534 controls with mild or asymptomatic disease. They examined 13 genes, chosen because flaws in them impair the body's production or use of type I interferon; mutations in the genes underlie life-threatening influenza or other viral illnesses. The researchers found that 3.5% of the critically ill patients harbored rare mutations in eight of those genes. In patients for whom blood samples were available, interferon levels were vanishingly small. No members of the control group carried any of the mutations. "This is the first paper to pin down indisputably disease-causing mutations underlying severe COVID-19," Pan-Hammarström says.

But it's "probably the tip of the iceberg," says Paul Hertzog, an interferon expert at the Hudson Institute of Medical Research. Many other damaging mutations, interferon related and not, may influence the development of severe COVID-19, he says.

Zuniga notes that none of the patients who made antibodies against interferon or had the mutations had a history of life-threatening viral illnesses requiring hospitalization. "This suggests that we are more reliant on type I interferons to protect ourselves against SARS-CoV-2 versus other viral infections," she says. "That makes it important to try therapies aimed at boosting type I interferon responses."

Dozens of randomized clinical trials are now deploying interferons against SARS-CoV-2. One, led by Tom Wilkinson at the University of Southampton, reported promising findings in a small group of hospitalized COVID-19 patients. But synthetic interferons won't help patients who harbor mutations that prevent interferons from working, or those with antibodies that attack them.

Some researchers caution that the interferon-neutralizing antibodies could be a consequence, rather than a cause, of severe COVID-19. "It's possible that they develop during the disease," says Miriam Merad, an immunologist at the Icahn School of Medicine at Mount Sinai. That would explain why the patients hadn't faced life-threatening viral infections before, she says.

But Casanova, who has made a career of discovering mutations that confer susceptibility to infectious diseases, says there is a strong case for causality. He points out that preexisting blood samples from a handful of patients showed they had the antibodies in their blood before contracting SARS-CoV-2. He argues that, in response to infection, it's unlikely that the body could quickly generate the high levels of anti-interferon antibodies his team saw.

Yanick Crow, a clinical geneticist at the University of Edinburgh who studies interferon signaling, calls the antibody paper "shocking," in part because men were so much more likely than women to carry the rogue antibodies. Tests screening for the antibodies can and should be rapidly developed, he says, and will quickly reveal whether the new findings hold up. Given tens of millions of cases worldwide, he says, "10% is such a high figure and the implications are very important."

***Correction, 25 September, 11 a.m.:** A previous version of this story mistakenly reversed the words "cause" and "consequence" when introducing a quote from Miriam Merad. This has been corrected.*

https://bit.ly/30dGeqD

Newfound brain structure explains why some birds are so smart—and maybe even self-aware

Previously unknown arrangement of microcircuits in the avian brain that may be analogous to the mammalian neocortex

By Virginia Morell

Never before has "bird brain" been such a compliment: In recent years, birds have been found to make tools, understand abstract concepts, and even recognize paintings by Monet and Picasso. But their lack of a neocortex—the area of the mammalian brain where working memory, planning, and problem solving happen—has long puzzled scientists.

Now, researchers have found a previously unknown arrangement of microcircuits in the avian brain that may be analogous to the mammalian neocortex. And in a separate study, other researchers have linked this same region to conscious thought.

The two papers are already being hailed as groundbreaking. "It's often assumed that birds' alien brain architecture limits thought, consciousness, and most advanced cognition," says John Marzluff, a wildlife biologist and specialist on crows at the University of Washington, Seattle, who was not involved with either study. Researchers who have "demonstrated the cognitive abilities of birds

won't be surprised by these results," he adds, "but they will be relieved."

Indeed, it was because of birds' and mammals' similar cognitive abilities that Martin Stacho, a neuroanatomist at Ruhr-University Bochum, decided to investigate the avian forebrain, which controls perception. A gross comparison of mammalian and avian brains suggests "they have nothing in common," he says. "Yet birds and mammals have many of the same cognitive skills."

To find out how bird brains support these mental talents, Stacho and his colleagues examined microscopic slices of three homing pigeon brains using 3D polarized light imaging. This high-resolution technique let them analyze the circuitry of a forebrain region called the pallium, considered most similar to the mammalian neocortex. Although the pallium lacks the cortex's six layers, it has distinctive structures connected by long fibers.

The scientists compared the images of the birds' pallia with those of rat, monkey, and human cortices. Their analysis revealed the fibers in the birds' pallia are organized in a manner strikingly similar to those of fibers in mammal cortexes.

Researchers also visualized the connections among neurons in the brains of two distantly related avian species: pigeons and owls. After removing the brains of deeply anesthetized birds, scientists injected crystals into the dissected brains and discovered circuits in the sensory regions that were similar to those found in the mammalian neocortex. It is this neuroarchitecture—the connections between structures, rather than the structures themselves—that explains why birds are as cognitively talented as mammals, they report today in *Science*.

"This research confirms the old adage that looks can be deceiving," Marzluff says. Although bird and mammalian brains "look very different, this study shows us they are actually wired in very complementary ways."

But do birds have conscious experiences? Are they aware of what they see and do? To find out, Andreas Nieder, a neurophysiologist at the University of Tübingen, observed the brains of carrion crows (*Corvus corrone*) as they responded to cues. Known as "feathered apes" for their intelligence, these crows and their cousins have even been shown to reason causally. But inferring consciousness from such experiments is challenging, Nieder says.

So, he and colleagues used a test similar to one that probes primates for signs of consciousness—a state of mind thought to arise with the sudden activation of certain neurons. They trained two lab-raised, 1-year-old carrion crows to move or stay still in response to a faint cue displayed on a monitor. When correct, the birds were rewarded.

The scientists then implanted electrodes in the crows' brains to record their neuronal signals as they responded. When the crows reacted, their neurons fired, suggesting they had consciously perceived the cue; but when they didn't, their neurons were silent. The neurons that fired in agreement with the crows' action were located in the pallia, the researchers report today, also in *Science*. Nieder calls this "an empirical marker of sensory consciousness in birds' brains," similar to that seen in primates.

That's certain to stir debate, as "some researchers argue that consciousness is uniquely human," says Irene Pepperberg, a comparative psychologist at Harvard University known for her work with Alex, an African gray parrot who communicated in English about abstract concepts. Pepperberg was not involved in these new studies but finds them "really exciting."

Stacho and Nieder add that the building blocks for mammalian and avian cognition may have been present in their last common ancestor, some 320 million years ago. "Of course, mammal and bird brains evolved differently," Stacho says. "What is surprising is how similar they still are in their perceptual and cognitive abilities."

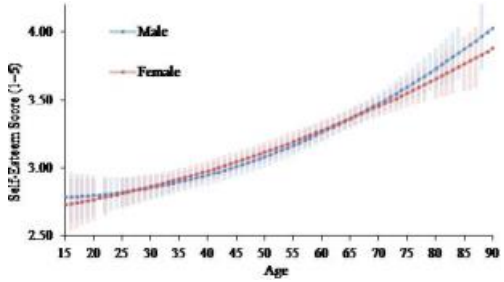
https://bit.ly/36cGJFl

Older the person, higher the self-esteem: age differences in self-esteem in Japan

Japanese people aged 50 and older do not tend to have lower self-esteem, suggesting that trajectory of self-esteem may differ across cultures

Self-esteem does not remain constant through life, but changes as a person develops. A large number of studies conducted on this topic, mainly in the United States, have shown that self-esteem is high in childhood, declines in adolescence, but then continues to increase throughout adulthood, peaking in the 50s and 60s, and declining thereafter. Studies in Japan have also reported that self-liking, which is an aspect of self-esteem, follows a similar trajectory across different ages.

However, previous Japanese studies had two main limitations. First, they focused on self-liking, one element of self-esteem. Self-esteem is composed of self-liking (the affective judgment of oneself) and self-competence (the overall sense of oneself as capable and effective). It is important to comprehensively examine self-esteem, including simultaneous investigation of both the aspects of self-liking and self-competence, to clarify the developmental trajectory of self-esteem. Second, the studies did not sufficiently investigate age differences in self-esteem in elderly people aged 70 years and older.



Predicted self-esteem scores across ages in Japan (2017 survey; Error bars represent 95% confidence intervals) **Tokyo University of Science**

Research has indicated that self-esteem does not decline in Japan up to 69 years of age, but it may decline thereafter. Furthermore, a decline in self-esteem itself may be absent in Japan. Reports have consistently demonstrated that levels of self-esteem vary across different cultures, but the differing tendencies of developmental trajectories have not been adequately reported. Thus, it is also necessary to examine the self-esteem of elderly people aged 70 years and older, to elucidate the developmental trajectory of self-esteem in Japan.

To address this gap, Assistant professor Yuji Ogihara, from the Faculty of Science Division II, Tokyo University of Science and Professor Takashi Kusumi, from the Graduate School of Education, Kyoto University, conducted a large-scale study comprehensively examining age differences in self-esteem from adolescence to old age, including both self-liking and self-competence, across a wider sample of people, including respondents aged 70 and older.

They analyzed six web-based surveys administered to a large and diverse sample of people in Japan from 2009 to 2018. The responses were obtained from 6113 persons (2996 males and 3117 females) between the ages of 16 and 88. Each study used the most commonly used self-esteem scale (10 items) to measure self-esteem. The scale includes items for measuring self-liking, such as "On the whole, I am satisfied with myself", and items for measuring self-competence, such as "I feel that I have a number of good qualities". The participants scored each item on a scale of one to five, from "1: Not applicable" to "5: Applicable".

The results showed that self-esteem is low in adolescence but increases gradually from adulthood to old age (see Figure 1). The changes from adolescence to middle age were consistent with findings from previous research in Europe and the United States, but unlike observed in previous studies, there was no decline in self-esteem from the 50s onwards. Therefore, the findings in this research suggest that the developmental trajectory of self-esteem may differ in different cultures.

"Previous research has insisted that one of the causes of the decline in self-esteem after middle age in Europe and the United States is that elderly people come to accept their limitations and faults, leading them to have a more humble, modest, and balanced view of themselves. On the other hand, reports have shown that people in Japan have a humbler view of themselves even before middle age. This may be the reason for the lack of decline in self-esteem in this study," suggests Dr Ogihara. Other factors that may generate cultural differences, including the seniority system and the culture of respect for the aged, require further detailed examination.

Generational effects may obscure the low self-esteem in Japan after middle age. Therefore, further investigation is needed to separate these developmental changes from generational differences, such as conducting a longitudinal survey that tracks people of the same generation. Further work is required owing to the small sample size of participants in their 80s--collecting and analyzing more data and verifying that similar results can be obtained.

"Examining the age differences and developmental trajectories of self-esteem is not only academically and theoretically significant, as described above, it also has practical and social significance," explains Dr. Ogihara. "For example, understanding when self-esteem tends to be low can help determine when the adoption of effective preventive measures is more necessary, and allow for timely intervention and response."

This study has elucidated the age differences in self-esteem--one of the most basic psychological tendencies. Thus, Ogihara and Kusumi hope that these findings can contribute not only to related academic research in various fields, but also more broadly to clinical and general practice, including prevention and intervention.

Funding information

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https://wb.md/3kO12wI

Once-Weekly 'Centennial Insulin': Will It Live Up to the Promise?

What would you say to a basal insulin that doesn't need to be injected daily but just once a week?

Harpreet S. Bajaj, MD, MPH

We are approaching a new frontier in diabetes management that can be considered one of the greatest leaps in innovation since the discovery of insulin in 1921. A once-weekly "centennial insulin" seems an apt way to mark the 100th anniversary of the life-saving protein.

The 2020 European Association for the Study of Diabetes (EASD) virtual congress presented results from three phase 2 trials on icodec, a novel insulin analog in clinical development that has a half-life of 196 hours.

The pivotal trial of icodec randomized 247 insulin-naive participants with type 2 diabetes to weekly icodec vs daily glargine U100 in a double-blind, double-dummy, treat-to-target study design. Participants who received icodec had a statistically comparable A1c reduction (from a baseline mean of 8.1% to 6.7% at 26 weeks), along with a similar incidence of combined level 2 (clinically significant hypoglycemia defined as < 54 mg/dL) and level 3 (severe) hypoglycemia compared with the glargine U100 arm. Level 1 hypoglycemia (alert level hypoglycemia, between 54 and 70 mg/dL) was slightly higher with icodec.

Results of a second trial with icodec seem to suggest that a less intensive titration algorithm (ie, slower weekly increments titrated to a less stringent target of 80-130 mg/dL) may reduce the risk for hypoglycemia while maintaining adequate glycemic control. In addition, adopting a slightly relaxed titration regimen for these new insulin analogs that have a half-life of more than a week may be necessary in real-life scenarios to reduce the potential for over-

insulinization with acute changes in diet (eg, fasting), exercise, illness, or in preparation for surgery.

Transitioning to this weekly insulin from a daily insulin requires a loading dose that is double the first calculated weekly dose, according to results of a third phase 2 trial presented at EASD. The group receiving icodec without a loading dose experienced an initial transient, mild worsening of fasting self-monitored blood glucose values compared with those who received the loading dose or who were on glargine U100. This may relate to the 3-4 weeks required to reach steady state for icodec because of its long half-life.

What Are the Next Steps?

To further bolster its clinical utility, we will need to see at least comparable glycemic efficacy and safety in larger and longer phase 3 trials that include participants with a wide variety of background antihyperglycemic regimens, and compare the novel once-weekly insulin analogs against the currently available "ultra-long-acting" once-daily options.

For people with type 2 diabetes, there is also the exciting possibility of combining a weekly GLP-1 receptor agonist with the weekly insulin in the same injection. This has the potential to further reduce injection burden while improving acceptability, tolerability, and adherence.

For people with type 1 diabetes, latent autoimmune diabetes of adults, or type 2 diabetes who are currently dependent on a basal-bolus insulin regimen, this may reduce injection frequency to once per week (from 28 per week) if an inhaled or oral bolus insulin were to become available for widespread use in the future.

Issues around day-to-day and week-to-week glucose variability with a weekly basal insulin will need to be carefully examined, as these problems are especially relevant to those with insulin sensitivity (eg, the majority of people with type 1 diabetes).

Another once-weekly insulin in development, code-named LY3209590, recently completed at least one phase 1 and phase 2 study, with results expected imminently.

The results we've seen so far from the first phase 2 trials with a once-weekly insulin are encouraging. Let's hope that the remaining phase 2 and 3 studies — planned for both type 1 and type 2 diabetes — continue to live up to that promise.

Harpreet S. Bajaj, MD, MPH, is a community endocrinologist in Brampton, Ontario, Canada, and vice chair of the Diabetes Canada Guidelines. His clinical and research interests are the prevention and management of diabetes and its related complications. He is the founder of STOP Diabetes Foundation and volunteers with numerous community public health organizations to raise awareness of diabetes prevention and treatment.

https://wb.md/30c5YDQ

NIH 'Very Concerned' About Serious Side Effect in Coronavirus Vaccine Trial

Everyone's hopes are on a vaccine, and if you have a major complication the whole thing could get derailed

Arthur Allen and Liz Szabo

The Food and Drug Administration is weighing whether to follow British regulators in resuming a coronavirus vaccine trial that was halted when a participant suffered spinal cord damage, even as the National Institutes of Health has launched an investigation of the case.

"The highest levels of NIH are very concerned," said Dr. Avindra Nath, intramural clinical director and a leader of viral research at the National Institute for Neurological Disorders and Stroke, an NIH division. "Everyone's hopes are on a vaccine, and if you have a major complication the whole thing could get derailed."

A great deal of uncertainty remains about what happened to the unnamed patient, to the frustration of those avidly following the progress of vaccine testing. AstraZeneca, which is running the global trial of the vaccine it produced with Oxford University, said

the trial volunteer recovered from a severe inflammation of the spinal cord and is no longer hospitalized.

AstraZeneca has not confirmed that the patient was afflicted with transverse myelitis, but Nath and another neurologist said they understood this to be the case. Transverse myelitis produces a set of symptoms involving inflammation along the spinal cord that can cause pain, muscle weakness and paralysis. Britain's regulatory body, the Medicines and Healthcare Products Regulatory Agency, reviewed the case and has allowed the trial to resume in the United Kingdom.

AstraZeneca "need[s] to be more forthcoming with a potential complication of a vaccine which will eventually be given to millions of people," said Nath. "We would like to see how we can help, but the lack of information makes it difficult to do so."

Any decision about whether to continue the trial is complex because it's difficult to assess the cause of a rare injury that occurs during a vaccine trial — and because scientists and authorities have to weigh the risk of uncommon side effects against a vaccine that might curb the pandemic. "So many factors go into these decisions," Nath said. "I'm sure everything is on the table. The last thing you want to do is hurt healthy people."

The NIH has yet to get tissue or blood samples from the British patient, and its investigation is "in the planning stages," Nath said. U.S. scientists could look at samples from other vaccinated patients to see whether any of the antibodies they generated in response to the coronavirus also attack brain or spinal cord tissue.

Such studies might take a month or two, he said. The FDA declined to comment on how long it would take before it decides whether to move forward.

Dr. Jesse Goodman, a Georgetown University professor and physician who was chief scientist and lead vaccine regulator at the FDA during the Obama administration, said the agency will review the data and possibly consult with British regulators before allowing resumption of the U.S. study, which had just begun when the injury was reported. Two other coronavirus vaccines are also in late-stage trials in the U.S.

If it determines the injury in the British trial was caused by the vaccine, the FDA could pause the trial. If it allows it to resume, regulators and scientists surely will be on the watch for similar symptoms in other trial participants.

A volunteer in an earlier phase of the AstraZeneca trial experienced a similar side effect, but investigators discovered she had multiple sclerosis that was unrelated to the vaccination, according to Dr. Elliot Frohman, director of the Multiple Sclerosis & Neuroimmunology Center at the University of Texas.

Neurologists who study illnesses like transverse myelitis say they are rare — occurring at a rate of perhaps 1 in 250,000 people — and strike most often as a result of the body's immune response to a virus. Less frequently, such episodes have also been linked to vaccines.

The precise cause of the disease is key to the decision by authorities whether to resume the trial. Sometimes an underlying medical condition is "unmasked" by a person's immune response to the vaccine, leading to illness, as happened with the MS patient. In that case, the trial might be continued without fear, because the illness was not specific to the vaccine.

More worrisome is a phenomenon called "molecular mimicry." In such cases, some small piece of the vaccine may be similar to tissue in the brain or spinal cord, resulting in an immune attack on that tissue in response to a vaccine component. Should that be the case, another occurrence of transverse myelitis would be likely if the trial resumed, said Dr. William Schaffner, an infectious disease specialist at the Vanderbilt University School of Medicine. A second case would shut down the trial, he said.

In 1976, a massive swine flu vaccination program was halted when doctors began diagnosing a similar disorder, Guillain-Barré syndrome, in people who received the vaccine. At the time no one knew how common GBS was, so it was difficult to tell whether the episodes were related to the vaccine.

Eventually, scientists found that the vaccine increased the risk of the disorderby an additional one case among every 100,000 vaccinated patients. Typical seasonal flu vaccination raises the risk of GBS in about one additional case in every 1 million people.

"It's very, very hard" to determine if one rare event was caused by a vaccine, Schaffner said. "How do you attribute an increased risk for something that occurs in one in a million people?"

Before allowing U.S. trials to restart, the FDA will want to see why the company and an independent data and safety monitoring board (DSMB) in the U.K. felt it was safe to continue, Goodman said. The AstraZeneca trial in the United States has a separate safety board.

FDA officials will need to review full details of the case and may request more information about the affected study volunteer before deciding whether to allow the U.S. trial to continue, Goodman said. They may also require AstraZeneca to update the safety information it provides to study participants.

It's possible that the volunteer's health problem was a coincidence unrelated to the vaccine, said Dr. Amesh Adalja, a senior scholar at the Johns Hopkins Center for Health Security. Studies aren't usually stopped over a single health problem, even if it's serious.

Yet many health leaders have expressed frustration that AstraZeneca hasn't released more information about the health problem that led it to halt its U.K. trial.

"There is just so little information about this that it's impossible to understand what the diagnosis was or why the DSMB and sponsor were reassured" that it was safe to continue, Goodman said.

AstraZeneca has said it's unable to provide more information about the health problem, saying this would violate patient privacy, although it didn't say how.

But there's an exceptional need for transparency in a political climate rife with vaccine hesitancy and mistrust of the Trump administration's handling of the COVID-19 response, leading scientists say.

"While I respect the critical need for patient confidentiality, I think it would be really helpful to know what their assessment of these issues was," Goodman said. "What was the diagnosis? If there wasn't a clear diagnosis, what is it that led them to feel the trial could be restarted? There is so much interest and potential concern about a COVID-19 vaccine that the more information that can be provided, the more reassuring that would be."

The FDA will need to balance any possible risks from an experimental vaccine with the danger posed by COVID-19, which has killed nearly 200,000 Americans.

"There are also potential consequences if you stop a study," Goodman said.

If the AstraZeneca vaccine fails, the U.S. government is supporting six other COVID vaccines in the hope at least one will succeed. The potential problems with the AstraZeneca vaccine show this to be a wise investment, Adalja said. "This is part of the idea of not having just one vaccine candidate going forward," he said. "It gives you a little more insurance."

Schaffner said researchers need to remember that vaccine research is unpredictable. "The investigators have inadvisedly been hyping their own vaccine," Schaffner said. "The Oxford investigators were out there this summer saying, 'We're going to get there first.' But this is exactly the sort of reason … Dr. [Anthony] Fauci and the rest of us have been saying, 'You never know what will happen once you get into large-scale human trials.'"

This KHN story first published on California Healthline, a service of the California Health Care Foundation.

https://bit.ly/30aSqID

As if 2020 Wasn't Enough, Climate Change Is Now Raising 'Zombie Storms' From The Dead

Wildfires are burning the West Coast, hurricanes are flooding the Southeast — and some of those storms are rising from the dead.

Yasemin Saplakoglu, Live Science

"Zombie storms", which regain strength after initially petering out, are the newest addition to the year 2020. And these undead weather anomalies are becoming more common thanks to climate change.

"Because 2020, we now have Zombie Tropical Storms. Welcome back to the land of the living, Tropical Storm #Paulette," the National Weather Service wrote on Twitter on Tuesday (September 22).

Earlier this month, Tropical storm Paulette formed in the Atlantic Ocean and made landfall in Bermuda as a Category 1 hurricane, according to CNN.

It then strengthened over land into a Category 2 hurricane, before weakening and dying off five and half days later.

But then, Paulette opened her frightening eye once again. She wasn't gone.

Paulette regained strength and became a tropical storm once more about 300 miles (480 kilometers) away from the Azores Islands on Monday (September 21), according to CNN.

The term "zombie storm" is new, and though the phenomenon has been recorded before, it is thought to be rare.

But zombie storms are going to happen more often, said Donald Wuebbles, a professor of atmospheric sciences at the University of Illinois at Urbana-Champaign.

And as with other natural disasters that have been intensifying in recent years, such as wildfires and hurricanes, climate change and rapid global warming are to blame.

There has been an "extreme amount of heating of the Gulf (of Mexico), particularly in some of the ocean areas off of the Carribean," Wuebbles told Live Science.

The Gulf of Mexico, where many hurricanes gain strength before hitting the US, is particularly vulnerable to global warming because the gulf waters are very shallow — and thus heat up easily, Wuebbles said.

Atlantic Ocean storms typically form in warmer parts of the ocean near Africa, due to a combination of atmospheric and ocean conditions. They then "race across" the ocean toward the Americas, Wuebbles said.

Hurricanes need warm water and moist air to form, according to the University Corporation for Atmospheric Research. Storms grow if there's a continuous supply of energy from warm water and air, and they weaken when they move over cooler waters or over land.

"If they're not so strong, in the past, they would just die out," over the Atlantic, Wuebbles said. But now, they reach warm water in the Caribbean region and pick up energy again, he added.

This is also true for storms that haven't died out yet. For instance, about a month ago, Hurricane Laura strengthened overnight from a Category 1 storm to a Category 4 storm because it picked up energy from warm water in the Gulf, Wuebbles said.

With a warming globe, "storms are likely to become more intense," he added. That means the idea of "zombie storms" may be here to stay.

Thankfully Paulette seems to have become a post-tropical cyclone once more and will die out soon, according to the National Hurricane Center.

https://bit.ly/2GkBOXR

SARS-CoV-2 Seems to Block Some Pain Signals. Here's Why This Is Important

Imagine being infected with a deadly virus that makes you impervious to pain. By the time you realize you are infected, it's already too late. You have spread it far and wide.

Rajesh Khanna, The Conversation

Recent findings in my lab suggest that this scenario may be one reason that people infected with SARS-CoV-2, the virus causing COVID-19, may be spreading the disease without knowing it.

Most accounts to date have focused on how the virus invades cells via the ACE2 protein on the surface of many cells.

But recent studies, which have not yet been peer-reviewed, suggest there is another route to infecting the cell that enables it to infect the nervous system. This led my research group to uncover a link between a particular cellular protein and pain – an interaction that is disrupted by the coronavirus. Our research has now been peer-reviewed and will be published in the journal *PAIN*.

I am a scientist who studies how proteins on cells trigger pain signals that are transmitted through the body to the brain.

When these proteins are active, the nerve cells are talking to each other. This conversation occurs at deafening levels in chronic pain.

So by studying what causes the excitability of nerve cells to change, we can begin to unravel how chronic pain becomes established. This also allows us to design ways to mute this conversation to blunt or stop chronic pain.

My laboratory has a longstanding interest in designing nonopioid-based alternatives for pain management.

Linking SARS-CoV-2 and pain

You might be wondering how my lab began to probe the connection between SARS-CoV-2 and pain.

We were inspired by two preliminary reports that appeared on the preprint server BioRxiv that showed that the infamous spike proteins on the surface of the SARS-CoV-2 virus bound to a protein called neuropilin-1. This means that the virus can also use this protein to invade nerve cells as well as through the ACE2 protein.

For the past year, some six months before the pandemic took hold, my colleagues and I had been studying the role of neuropilin-1 in the context of pain perception.

Because neuropilin-1, like the ACE2 receptor, allowed spike to enter the cells, we wondered if this alternate gateway could also be related to pain. Under normal circumstances, the neuropilin-1 protein controls the growth of blood vessels, and as well as the growth and survival of neurons.

However, when neuropilin-1 binds to a naturally occurring protein called called Vascular endothelial growth factor A (VEGF-A), this triggers pain signals. This signal is transmitted via the spinal cord into higher brain centers to cause the sensation we all know as pain.

Staring at this jigsaw puzzle – neuropilin-1 and VEGF-A and neuropilin and spike – we wondered if there was a link between spike and pain.

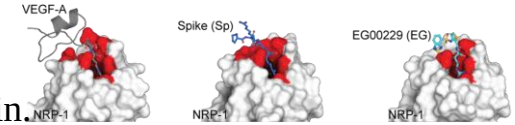
Previous research has shown a link between VEGF-A and pain. For people with osteoarthritis, for instance, studies have shown that increased activity of the VEGF gene in fluids lubricating joints, like the knee, is associated with higher pain scores.

Although activity of the neuropilin-1 gene is higher in biological samples from COVID-19 patients compared to healthy controls and activity of the neuropilin-1 gene is increased in pain-sensing neurons in an animal model of chronic pain, the role of neuropilin-1 in pain has never been explored until now.

In in vitro studies done in my lab using nerve cells, we showed that when spike binds to neuropilin-1 it decreases pain signaling, which

suggests that in a living animal it would also have a pain-dulling effect. When the spike protein binds to the neuropilin-1 protein, it blocks the VEGF-A protein from binding and thus hijack's a cell's pain circuitry.

This binding suppresses the excitability of pain neurons, leading to lower sensitivity to pain.



Above: Crystal structure of neuropilin-1 b1 domain (white surface with binding site in red) showing binding of VEGF-A (left), spike protein (middle), and the neuropilin-1 inhibitor EG00229 (right). **(Dr Samantha Perez-Miller, CC BY-SA)**

From the COVID-19 fog a new pain target emerges

If our finding that the new coronavirus is attacking cells through a protein associated with pain and disabling the protein can be confirmed in humans, it may provide a new pathway for drug development to treat COVID-19.

A small molecule, called EG00229, targeting neuropilin-1 had been reported in a 2018 study. This molecule binds to the same region of the neuropilin-1 protein as the viral spike protein and VEGF-A.

So I and my colleagues asked if this molecule was able to block pain. It did, during pain simulations in rats. Our data reaffirmed the notion of neuropilin-1 as a new player in pain signaling.

There is precedence for targeting the neuropilin-1 protein for cancer treatment: for example, a Phase 1a clinical trial of an antibody called MNRP1685A (known under the product name Vesencumab) that recognizes and binds to neuropilin-1 and blocks VEGF-binding. This was mostly well tolerated in cancer patients, but it caused pain rather than blocking it.

Our studies identify a different approach because we targeted blocking the pain-triggering VEGF-A protein, which then resulted in pain relief. So our preclinical work described here provides a rationale for targeting the VEGF-A/NRP-1 pro-pain signaling system in future clinical trials.

Analysis of the structure of the neuropilin-1 receptor protein may allow design of drugs targeting this critical site which also controls axon growth, cell survival – in addition to pain relief.

For instance, these neuropilin-1 receptor targeted drugs could potentially block viral infection. The testing of several candidate compounds, some of them on the FDA's generally regarded as safe list, is currently underway by my group.

Sneaky virus, fooling people into believing that they do not have COVID-19. But, ironically, it may be gifting us with the knowledge of a new protein, critical for pain.

Two roads emerge in the forest ahead: (1) block neuropilin-1 to limit SARS-CoV-2 entry, and (2) block neuropilin-1 to block pain.

Rajesh Khanna, Professor of Pharmacology, University of Arizona.