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Wearable-tech glove translates sign language into speech in real time

The device is inexpensive, flexible and highly durable, UCLA bioengineers say

UCLA bioengineers have designed a glove-like device that can translate American Sign Language into English speech in real time through a smartphone app. Their research is published in the journal *Nature Electronics*.

"Our hope is that this opens up an easy way for people who use sign language to communicate directly with non-signers without needing someone else to translate for them," said Jun Chen, an assistant professor of bioengineering at the UCLA Samueli School of Engineering and the principal investigator on the research. "In addition, we hope it can help more people learn sign language themselves."

The system includes a pair of gloves with thin, stretchable sensors that run the length of each of the five fingers. These sensors, made from electrically conducting yarns, pick up hand motions and finger placements that stand for individual letters, numbers, words and phrases.

The device then turns the finger movements into electrical signals, which are sent to a dollar-coin-sized circuit board worn on the wrist. The board transmits those signals wirelessly to a smartphone that translates them into spoken words at the rate of about a one word per second. The researchers also added adhesive sensors to testers' faces -- in between their eyebrows and on one side of their mouths -- to capture facial expressions that are a part of American Sign Language.

Previous wearable systems that offered translation from American Sign Language were limited by bulky and heavy device designs or were uncomfortable to wear, Chen said.

The device developed by the UCLA team is made from lightweight and inexpensive but long-lasting, stretchable polymers. The electronic sensors are also very flexible and inexpensive.

In testing the device, the researchers worked with four people who are deaf and use American Sign Language. The wearers repeated each hand gesture 15 times. A custom machine-learning algorithm turned these gestures into the letters, numbers and words they represented. The system recognized 660 signs, including each letter of the alphabet and numbers 0 through 9.

In addition to Chen, the study's UCLA authors are co-lead author Zhihao Zhao, Kyle Chen, Songlin Zhang, Yihao Zhou and Weili Deng. All are members of Chen's Wearable Bioelectronics Research Group at UCLA. The other corresponding author is Jin Yang, of China's Chongqing University.

UCLA has filed for a patent on the technology. A commercial model based on this technology would require added vocabulary and an even faster translation time, Chen said.

https://bit.ly/2AmA7GP

Nanotechnology applied to medicine: The first liquid retina prosthesis

Liquid, biocompatible and micro-injectable, the new retinal prosthesis is an aqueous suspension of photoactive nanoparticles that functionally replace the photoreceptors of the retina damaged by degenerative diseases and aging

Genoa (Italy) - Researchers at IIT-Istituto Italiano di Tecnologia (Italian Institute of Technology) has led to the revolutionary development of an artificial liquid retinal prosthesis to counteract the effects of diseases such as retinitis pigmentosa and age-related macular degeneration that cause the progressive degeneration of photoreceptors of the retina, resulting in blindness. The study has been published in *Nature Nanotechnology*: http://www.nature.com/articles/s41565-020-0696-3

The multidisciplinary team is composed by researchers from the IIT's Center for Synaptic Neuroscience and Technology in Genoa

coordinated by Fabio Benfenati and a team from the IIT's Center for Nano Science and Technology in Milan coordinated by Guglielmo Lanzani, and it also involves the IRCCS Ospedale Sacrocuore Don Calabria in Negrar (Verona) with the team lead by Grazia Pertile, the IRCCS Ospedale Policlinico San Martino in Genoa and the CNR in Bologna. The research has been supported by Fondazione 13 Marzo Onlus, Fondazione Ra.Mo., Rare Partners srl and Fondazione Cariplo.

The study represents the state of the art in retinal prosthetics and is an evolution of the planar artificial retinal model developed by the same team in 2017 and based on organic semiconductor materials (Nature Materials 2017, 16: 681-689).

The "second generation" artificial retina is biomimetic, offers high spatial resolution and consists of an aqueous component in which photoactive polymeric nanoparticles (whose size is of 350 nanometres, thus about 1/100 of the diameter of a hair) are suspended, going to replace the damaged photoreceptors.

The experimental results show that the natural light stimulation of nanoparticles, in fact, causes the activation of retinal neurons spared from degeneration, thus mimicking the functioning of photoreceptors in healthy subjects.

Compared to other existing approaches, the new liquid nature of the prosthesis ensures fast and less traumatic surgery that consist of microinjections of nanoparticles directly under the retina, where they remain trapped and replace the degenerated photoreceptors; this method also ensures an increased effectiveness.

The data collected show also that the innovative experimental technique represents a valid alternative to the methods used to date to restore the photoreceptive capacity of retinal neurons while preserving their spatial resolution, laying a solid foundation for future clinical trials in humans. Moreover, the development of these photosensitive nanomaterials opens the way to new future applications in neuroscience and medicine.

"Our experimental results highlight the potential relevance of nanomaterials in the development of second-generation retinal prostheses to treat degenerative retinal blindness, and represents a major step forward" Fabio Benfenati commented. "The creation of a liquid artificial retinal implant has great potential to ensure a wide-field vision and high-resolution vision. Enclosing the photoactive polymers in particles that are smaller than the photoreceptors, increases the active surface of interaction with the retinal neurons, allows to easily cover the entire retinal surface and to scale the photoactivation at the level of a single photoreceptor."

"In this research we have applied nanotechnology to medicine" concludes Guglielmo Lanzani. "In particular in our labs we have realized polymer nanoparticles that behave like tiny photovoltaic cells, based on carbon and hydrogen, fundamental components of the biochemistry of life. Once injected into the retina, these nanoparticles form small aggregates the size of which is comparable to that of neurons, that effectively behave like photoreceptors."

"The surgical procedure for the subretinal injection of photoactive nanoparticles is minimally invasive and potentially replicable over time, unlike planar retinal prostheses" adds Grazia Pertile, Director at Operating Unit of Ophthalmology at IRCCS Ospedale Sacro Cuore Don Calabria. "At the same time maintaining the advantages of polymeric prosthesis, which is naturally sensitive to the light entering the eye and does not require glasses, cameras or external energy sources."

The research study is based on preclinical models and further experimentations will be fundamental to make the technique a clinical treatment for diseases such as retinitis pigmentosa and age-related macular degeneration.

https://bit.ly/38mXCMC

New Zealand's ancient monster penguins had northern hemisphere doppelgangers

New Zealand's monster penguins that lived 62 million years ago had doppelgangers in Japan, the USA and Canada

New Zealand's monster penguins that lived 62 million years ago had doppelgangers in Japan, the USA and Canada, a study published today in the *Journal of Zoological Systematics and Evolutionary Research* has found. Scientists have identified striking similarities between the penguins' fossilised bones and those of a group of much younger Northern Hemisphere birds, the plotopterids.

Plotopterids like these Copepteryx grew to enormous sizes. **Mark Witton**

These similarities suggest plotopterids and ancient penguins looked very similar and might help scientists understand how birds started using their wings to swim instead of fly.

Around 62 million years ago, the earliest known penguins swam in tropical seas that almost submerged the land that is now New Zealand. Palaeontologists have found the fossilised bones of these ancient waddlers at Waipara, North Canterbury. They have identified nine different species, ranging in size from small penguins, the size of today's Yellow-Eyed Penguin, to 1.6 metre-high monsters.

Plotopterids developed in the Northern Hemisphere much later than penguins, with the first species appearing between 37 and 34 million years ago. Their fossils have been found at a number of sites in North America and Japan. Like penguins, they used their flipper-like wings to swim through the sea. Unlike penguins, which have survived into the modern era, the last plotopterid species became extinct around 25 million years ago.

The scientists - Dr Gerald Mayr of the Senckenberg Research Institute and Natural History Museum, Frankfurt; James Goedert of the Burke Museum of Natural History and Culture and University of Washington, USA; and Canterbury Museum Curators Dr Paul Scofield and Dr Vanesa De Pietri - compared the fossilised bones of plotopterids with fossil specimens of the giant penguin species Waimanu, Muriwaimanu and Sequiwaimanu from Canterbury Museum's collection.

They found plotopterids and the ancient penguins had similar long beaks with slit-like nostrils, similar chest and shoulder bones, and similar wings. These similarities suggest both groups of birds were strong swimmers that used their wings to propel them deep underwater in search of food.

Some species of both groups could grow to huge sizes. The largest known plotopterids were over 2 metres long, while some of the giant penguins were up to 1.6 metres tall.

Despite sharing a number of physical features with penguins both ancient and modern, plotopterids are more closely related to boobies, gannets and cormorants than they are to penguins.

"What's remarkable about all this is that plotopterids and ancient penguins evolved these shared features independently," says Dr De Pietri. "This is an example of what we call convergent evolution, when distantly related organisms develop similar morphological traits under similar environmental conditions."

Dr Scofield says some large plotopterid species would have looked very similar to the ancient penguins. "These birds evolved in different hemispheres, millions of years apart, but from a distance you would be hard pressed to tell them apart," he says. "Plotopterids looked like penguins, they swam like penguins, they probably ate like penguins - but they weren't penguins."

Dr Mayr says the parallels in the evolution of the bird groups hint at an explanation for why birds developed the ability to swim with their wings.

"Wing-propelled diving is quite rare among birds; most swimming birds use their feet. We think both penguins and plotodopterids had flying ancestors that would plunge from the air into the water in search of food. Over time these ancestor species got better at swimming and worse at flying."

Fossils from New Zealand's giant penguins, including Waimanu and Sequiwaimanu are currently on display alongside life-sized models of the birds in Canterbury Museum's exhibition Ancient New Zealand: Squawkzilla and the Giants, extended until 16 August 2020.

Comparative osteology of the penguin-like mid Cenozoic Plotopteridae and the earliest true fossil penguins, with comment on the origins of wing-propelled diving, by Gerald Mayr, James L Goedert, Vanesa De Pietri and R Paul Scofield is published in the Journal of Zoological Systematics and Evolutionary Research. DOI after publication: 10.1111/jzs.12400

This research was partly supported by the Royal Society of New Zealand's Marsden Fund.

https://bit.ly/31CHbKL

Existing drugs can prevent SARS-CoV-2 from hijacking cells

Researchers evaluate how the new coronavirus rewires human proteins for its own replication, and identify several antiviral drugs ready for clinical trials

An international team of researchers has analysed how SARS-CoV-2, the virus that causes COVID-19, hijacks the proteins in its target cells. The research, published in the journal *Cell*, shows how the virus shifts the cell's activity to promote its own replication and to infect nearby cells. The scientists also identified seven clinically approved drugs that could disrupt these mechanisms, and recommend that these drugs are immediately tested in clinical trials.

The collaboration included researchers at EMBL's European Bioinformatics Institute (EMBL-EBI), the Quantitative Biosciences Institute's Coronavirus Research Group in the School of Pharmacy at University of California San Francisco (UCSF), the Howard Hughes Medical Institute, the Institut Pasteur, and the Excellence Cluster CIBSS of the University of Freiburg.

Viruses are unable to replicate and spread on their own: they need an organism - their host - to carry, replicate, and transmit them to further hosts. To facilitate this process, viruses need to take control of their host cell's machinery and manipulate it to produce new viral particles. Sometimes, this hijacking interferes with the activity of the host's enzymes and other proteins.

SARS-CoV-2 viruses visible on a cell with filopodia **Elizabeth Fischer, Miscroscopy Unit NIH/NIAID**

Once a protein is produced, enzymes can change its activity by making chemical modifications to its structure. For example, phosphorylation - the addition of a phosphoryl group to a protein by a type of enzyme called a kinase - plays a pivotal role in the regulation of many cell processes, including cell-to-cell communication, cell growth, and cell death. By altering phosphorylation patterns in the host's proteins, a virus can potentially promote its own transmission to other cells and, eventually, other hosts.

The scientists used mass spectrometry, a tool to analyse the properties of a sample by measuring the mass of its molecules and molecular fragments, to evaluate all host and viral proteins that showed changes in phosphorylation after SARS-CoV-2 infection. They found that 12% of the host proteins that interact with the virus were modified. The researchers also identified the kinases that are

most likely to regulate these modifications. Kinases are potential targets for drugs to stop the activity of the virus and treat COVID-19.

The extraordinary behaviour of infected cells

"The virus prevents human cells from dividing, maintaining them at a particular point in the cell cycle. This provides the virus with a relatively stable and adequate environment to keep replicating," explains Pedro Beltrao, Group Leader at EMBL-EBI.

SARS-CoV-2 not only impacts cell division, but also cell shape. One of the key findings from the study is that infected cells exhibit long, branched, arm-like extensions, or filopodia. These structures may help the virus reach nearby cells in the body and advance the infection, but further study is warranted.

"The distinct visualisation of the extensive branching of the filopodia once again elucidates how understanding the biology of virus-host interaction can illuminate possible points of intervention in the disease," says Nevan Krogan, Director of the Quantitative Biosciences Institute at UCSF and Senior Investigator at Gladstone Institutes.

Old drugs, new treatments

"Kinases possess certain structural features that make them good drug targets. Drugs have already been developed to target some of the kinases we identified, so we urge clinical researchers to test the antiviral effects of these drugs in their trials," says Beltrao.

In some patients, COVID-19 causes an overreaction of the immune system, leading to inflammation. An ideal treatment would relieve these exaggerated inflammatory symptoms while stopping the replication of the virus. Existing drugs targeting the activity of kinases may be the solution to both problems.

The researchers identified dozens of drugs approved by the Food and Drug Administration (FDA) or ongoing clinical trials that target the kinases of interest. Seven of these compounds, primarily anticancer and inflammatory disease compounds, demonstrated potent antiviral activity in laboratory experiments.

"Our data-driven approach for drug discovery has identified a new set of drugs that have great potential to fight COVID-19, either by themselves or in combination with other drugs, and we are excited to see if they will help end this pandemic," says Krogan.

"We expect to build upon this work by testing many other kinase inhibitors while identifying both the underlying pathways and additional potential therapeutics that may intervene in COVID-19 effectively," says Kevan Shokat, Professor in the Department of Cellular and Molecular Pharmacology at UCSF.

Authorship and funding: *This work was funded by grants from the National Institute of Mental Health and the National Institute of Allergy and Infectious Diseases, both part of the National Institutes of Health; the Defense Advanced Research Projects Agency; the Center for Research for Influenza Pathogenesis; the Centers of Excellence for Influenza Research and Surveillance of the National Institute of Allergy and Infectious Diseases; the Centers of Excellence for Integrative Biology of Emerging Infectious Diseases of the Agence Nationale de la Recherche (France); F. Hoffmann-LaRoche AG; Vir Biotechnology, Centre for Integrative Biological Signalling Studies (CIBSS), European Research Council (ERC) and the Ron Conway Family. Shokat is a Howard Hughes Medical Institute investigator. A complete list of authors and full funding information is available in the Cell paper.*

https://bit.ly/38lP0pk

At-risk twin pregnancies benefit from an intervention called cerclage

New evidence upturns long-held medical practice, showing the efficacy of an intervention to prevent premature labor and miscarriage for mothers carrying twins.

Philadelphia - Women carrying twins are at higher risk for premature birth and miscarriage - those whose cervix dilates before 24 weeks are at highest risk - and yet one common treatment is not recommended for this population. A new multi-center randomized-controlled trial from Thomas Jefferson University shows that cerclage, an intervention that sutures a dilating cervix closed, can

help prevent preterm birth and miscarriage. The findings could overturn existing guidelines.

The clinical trial was stopped early because of positive results in the intervention group. The researchers showed that perinatal mortality was significantly decreased in women receiving cerclage.

"For women with twin pregnancies and early signs of labor and cervix dilation, there was really very little we could offer," says first author, Amanda Roman, MD, Associate Professor in the Department of Obstetrics and Gynecology at Thomas Jefferson University. "This study provides powerful evidence that there is an effective treatment we can use."

The results were published online in the *American Journal of Obstetrics and Gynecology* (AJOG) on June 24th.

Women who showed signs of preterm labor, as confirmed by a cervical exam that indicates dilation, were enrolled in the study and randomized to either receive cerclage plus antibiotics and indomethacin (an anti-pain medication) , or standard of care. Of the 30 women enrolled, 17 women were randomized to the cerclage group and 13 to non-cerclage. The women in both groups were similar in demographics including age, race, body-mass index and other factors for preterm birth.

The trial enrolled 30 patients across 8 medical centers over the course of four years. "The small number of participants reflects how rare this condition is among all pregnancies," says Dr. Roman. "But because women were randomized to treatment and non-treatment groups, the results are strong, as confirmed by the independent Data Safety Monitoring Board."

The analysis showed that in the group that received cerclage, gestation was prolonged by an average of 5.6 weeks (with a range of 2.0 to 9.3 weeks), and reduced infant mortality by 77%.

"Cerclage is a heroic intervention in this group of women," says Dr. Roman. "The possibility of losing a pregnancy is devastating. So we're very encouraged by these results demonstrating a life-saving intervention for women with twins experiencing early asymptomatic cervical dilation."

"We've already incorporated this cerclage into our practice and have been able to offer this to pregnant mothers with twins with great success," says senior author Vincenzo Berghella, MD, Director of the Division of Maternal Fetal Medicine at Jefferson. "These results have the potential to change practice, and help many more women have healthy twin babies."

Dr. Roman and her collaborators are also exploring whether cerclage might prove effective for another subset of women carrying twins, specifically women whose cervical length has shortened, which is a precursor to cervical dilation, between 16 and 23 weeks. They have a clinical trial currently open. Women participating in the study will be randomized to receiving cerclage or no cerclage (ClinicalTrials.gov # NCT03340688).

No external financial support was received for this study. The authors report no conflicts of interest.

Article Reference: *Amanda Roman, Noelia Zork, Sina Haeri, Corina N. Schoen, Gabriele Saccone, Sarah Colihan, Craig Zelig, Alexis C. Gimovsky, Neil S. Seligman, Fulvio Zullo, Vincenzo Berghella, "Physical Exam Indicated Cerclage in Twin pregnancy: a Randomized Controlled Trial," AJOG, DOI: 10.1016/j.ajog.2020.06.047, 2020.*

https://bit.ly/3grI64H

SARS-CoV-2 Coronavirus Produces Long Tentacles in Infected Cells

Cells hijacked by SARS-CoV-2, a novel coronavirus that causes the COVID-19 disease, grow arm-like extensions, or filopodia, which may explain rapid viral spread throughout the body.

SARS-CoV-2 viruses visible on a cell with filopodia. Image credit: Elizabeth Fischer, Microscopy Unit NIH / NIAID.

“Viruses are unable to replicate and spread on their own: they need an organism to carry, replicate, and transmit them to further hosts,” explained study first author Dr. Mehdi Bouhaddou of Gladstone

Institutes and the University of California San Francisco and colleagues. “To facilitate this process, viruses need to take control of their host cell’s machinery and manipulate it to produce new viral particles. Sometimes, this hijacking interferes with the activity of the host’s enzymes and other proteins.”

“Once a protein is produced, enzymes can change its activity by making chemical modifications to its structure.”

“For example, phosphorylation — the addition of a phosphoryl group to a protein by a type of enzyme called a kinase — plays a pivotal role in the regulation of many cell processes, including cell-to-cell communication, cell growth, and cell death.”

“By altering phosphorylation patterns in the host’s proteins, a virus can potentially promote its own transmission to other cells and, eventually, other hosts.”

The researchers used mass spectrometry to evaluate all host and viral proteins that showed changes in phosphorylation after SARS-CoV-2 infection.

They determined that 40 of the 332 human proteins that interact with SARS-CoV-2 were significantly differentially phosphorylated.

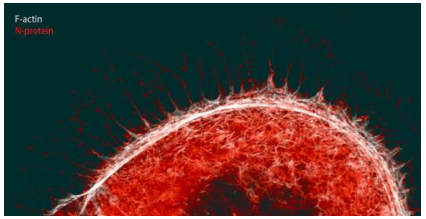
In addition, they identified 49 human kinases, out of a total of 518, that showed changes — either upregulation or downregulation — of phosphorylation activity.

The most strongly hijacked kinases include casein kinase II (CK2), kinases within the p38/MAP kinase (p38/MAPK) pathway, cyclin-dependent kinases (CDKs) and phosphatidylinositol 5-kinase (PIKFYVE), all of which fall within a set of cell signaling pathways.

“The virus prevents human cells from dividing, maintaining them at a particular point in the cell cycle. This provides the virus with a relatively stable and adequate environment to keep replicating,” said co-lead author Dr. Pedro Beltrao, a scientist at the EMBL’s European Bioinformatics Institute.

One of the key findings is that infected cells exhibit long, branched, arm-like extensions, or filopodia.

These structures may help the virus reach nearby cells in the body and advance the infection, but further study is warranted.



SARS-CoV-2 (stained for N-protein in red) was discovered inside finger-like protrusions of cells called filopodia made of actin cytoskeleton filaments (white) as is visible on these microscopic images. **Robert Grosse, CIBSS, University of Freiburg.**

“The distinct visualization of the extensive branching of the filopodia once again elucidates how understanding the biology of virus-host interaction can illuminate possible points of intervention in the disease,” said co-lead author Dr. Nevan Krogan, Director of the Quantitative Biosciences Institute the University of California San Francisco and Senior Investigator at Gladstone Institutes.

“Kinases possess certain structural features that make them good drug targets. Drugs have already been developed to target some of the kinases we identified, so we urge clinical researchers to test the antiviral effects of these drugs in their trials,” Dr. Beltrao said.

In some patients, COVID-19 causes an overreaction of the immune system, leading to inflammation. An ideal treatment would relieve these exaggerated inflammatory symptoms while stopping the replication of the virus. Existing drugs targeting the activity of kinases may be the solution to both problems.

The team identified 87 drugs approved by the Food and Drug Administration (FDA) or ongoing clinical trials that target the kinases of interest.

Seven of these compounds, primarily anticancer and inflammatory disease compounds, demonstrated potent antiviral activity in laboratory experiments.

“Our data-driven approach for drug discovery has identified a new set of drugs that have great potential to fight COVID-19, either by themselves or in combination with other drugs, and we are excited to see if they will help end this pandemic,” Dr. Krogan said

“We expect to build upon this work by testing many other kinase inhibitors while identifying both the underlying pathways and additional potential therapeutics that may intervene in COVID-19 effectively,” said co-lead author Professor Kevan Shokat, a researcher at the University of California San Francisco.

The results appear in the journal *Cell*.

Mehdi Bouhaddou et al. The Global Phosphorylation Landscape of SARS-CoV-2 Infection. Cell, published online June 28, 2020; doi: 10.1016/j.cell.2020.06.034

This article is based on press-releases provided by the European Bioinformatics Institute and the University of Freiburg.

https://wb.md/3eZCz56

Three Stages to COVID-19 Brain Damage, New Review Suggests

A new review recommends hospitalized patients with the virus all undergo MRI to flag potential neurologic damage

Batya Swift Yasgur MA, LSW

A new review outlines a three-stage classification of the impact of COVID-19 on the central nervous system and recommends hospitalized patients with the virus all undergo MRI to flag potential neurologic damage and inform postdischarge monitoring.

In stage 1, viral damage is limited to epithelial cells of the nose and mouth, and in stage 2 blood clots that form in the lungs may travel to the brain, leading to stroke. In stage 3, the virus crosses the blood–brain barrier and invades the brain.

"Our major take-home points are that patients with COVID-19 symptoms, such as shortness of breath, headache, or dizziness, may have neurological symptoms that, at the time of hospitalization, might not be noticed or prioritized, or whose neurological symptoms may become apparent only after they leave the hospital," lead author Majid Fotuhi, MD, PhD, medical director of NeuroGrow Brain Fitness Center, McLean, Virginia, told *Medscape Medical News*.

"Hospitalized patients with COVID-19 should have a neurological evaluation and ideally a brain MRI before leaving the hospital; and, if there are abnormalities, they should follow up with a neurologist in 3 to 4 months," said Fotuhi, who is also affiliate staff at Johns Hopkins Medicine in Baltimore, Maryland. The review was published online June 8 in the *Journal of Alzheimer's Disease*.

Wreaks CNS Havoc

It has become "increasingly evident" that SARS-CoV-2 can cause neurologic manifestations, including anosmia, seizures, stroke, confusion, encephalopathy, and total paralysis, the authors write.

The authors note that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) that facilitates the conversion of angiotensin II to angiotensin. After ACE2 has bound to respiratory epithelial cells, and then to epithelial cells in blood vessels, SARS-CoV-2 triggers the formation of a "cytokine storm."

These cytokines, in turn, increase vascular permeability, edema, and widespread inflammation, as well as triggering "hypercoagulation cascades," which cause small and large blood clots that affect multiple organs.

If SARS-CoV-2 crosses the blood–brain barrier, directly entering the brain, it can contribute to demyelination or neurodegeneration.

"We very thoroughly reviewed the literature published between January 1 and May 1, 2020 about neurological issues [in COVID-19] and what I found interesting is that so many neurological things can happen due to a virus which is so small," said Fotuhi.

"This virus' DNA has such limited information, and yet it can wreak havoc on our nervous system because it kicks off such a potent defense system in our body that damages our nervous system," he said.

Three-Stage Classification

Stage 1

The extent of SARS-CoV-2 binding to the ACE2 receptors is limited to the nasal and gustatory epithelial cells, with the cytokine storm remaining "low and controlled." During this stage, patients may experience smell or taste impairments, but often recover without any interventions.

Stage 2

A "robust immune response" is activated by the virus, leading to inflammation in the blood vessels, increased hypercoagulability factors, and the formation of blood clots in cerebral arteries and veins. The patient may therefore experience either large or small strokes.

Additional stage 2 symptoms include fatigue, hemiplegia, sensory loss, double vision, tetraplegia, aphasia, or ataxia.

Stage 3

The cytokine storm in the blood vessels is so severe that it causes an "explosive inflammatory response" and penetrates the blood–brain barrier, leading to the entry of cytokines, blood components, and viral particles into the brain parenchyma and causing neuronal cell death and encephalitis.

This stage can be characterized by seizures, confusion, delirium, coma, loss of consciousness, or death.

"Patients in stage 3 are more likely to have long-term consequences, because there is evidence that the virus particles have actually penetrated the brain, and we know that SARS-CoV-2 can remain dormant in neurons for many years," said Fotuhi.

"Studies of coronaviruses have shown a link between the viruses and the risk of multiple sclerosis or Parkinson's disease even decades later," he added.

"Based on several reports in recent months, between 36% to 55% of patients with COVID-19 that are hospitalized have some neurological symptoms, but if you don't look for them, you won't see them," Fotuhi noted.

As a result, patients should be monitored over time after discharge, as they may develop cognitive dysfunction down the road.

Additionally, "it is imperative for patients [hospitalized with COVID-19] to get a baseline MRI before leaving the hospital so that we have a starting point for future evaluation and treatment," said Fotuhi.

"The good news is that neurological manifestations of COVID-19 are treatable," and "can improve with intensive training," including lifestyle changes—such as a heart-healthy diet, regular physical activity, stress reduction, improved sleep, biofeedback, and brain rehabilitation," Fotuhi added.

Routine MRI Not Necessary

Kenneth Tyler, MD, chair of the Department of Neurology at the University of Colorado School of Medicine, disagreed that all hospitalized patients with COVID-19 should routinely receive an MRI.

"Whenever you are using a piece of equipment on patients who are COVID-19 infected, you risk introducing the infection to uninfected patients," he told *Medscape Medical News.*

Instead, "the indication is in patients who develop unexplained neurological manifestations — altered mental status or focal seizures, for example —because in those cases, you do need to understand whether there are underlying structural abnormalities," said Tyler, who was not involved in the review.

Also commenting on the review for *Medscape Medical News*, Vanja Douglas, MD, associate professor of clinical neurology, University of California San Francisco, described the review as "thorough" and suggested it may "help us understand how to design observational studies to test whether the associations are due to severe respiratory illness or are specific to SARS-CoV-2 infection."

Douglas, who was not involved in the review, added that it is "helpful in giving us a sense of which neurologic syndromes have been observed in COVID-19 patients, and therefore which patients neurologists may want to screen more carefully during the pandemic."

The study had no specific funding. Fotuhi has disclosed no relevant financial relationships. Coauthor Cyrus Raji reports consulting fees as a member of the scientific advisory board for Brainreader ApS and reports royalties for expert witness consultation in conjunction with Neurevolution LLC. Tyler and Douglas have disclosed no relevant financial relationships.

J Alzheimers Dis. Published online June 10, 2020. Full text

https://nyti.ms/2YVmvvJ

Most People With Coronavirus Won't Spread It. Why Do a Few Infect Many?

Growing evidence shows most infected people aren't spreading the virus. But whether you become a superspreader probably depends more on circumstance than biology.

By Carl Zimmer

Following a birthday party in Texas on May 30, one man reportedly infected 17 members of his family with the coronavirus.

Reading reports like these, you might think of the virus as a wildfire, instantly setting off epidemics wherever it goes. But other reports tell another story altogether.

In Italy, for example, scientists looked at stored samples of wastewater for the earliest trace of the virus. Last week they reported that the virus was in Turin and Milan as early as Dec. 18. But two months would pass before northern Italy's hospitals began filling with victims of Covid-19. So those December viruses seem to have petered out.

As strange as it may seem, these reports don't contradict each other. Most infected people don't pass on the coronavirus to someone else. But a small number pass it on to many others in so-called superspreading events.

"You can think about throwing a match at kindling," said Ben Althouse, principal research scientist at the Institute for Disease Modeling in Bellevue, Wash. "You throw one match, it may not light the kindling. You throw another match, it may not light the kindling. But then one match hits in the right spot, and all of a sudden the fire goes up."

Understanding why some matches start fires while many do not will be crucial to curbing the pandemic, scientists say. "Otherwise, you're in the position where you're always one step behind the virus," said Adam Kucharski, an epidemiologist at the London School of Hygiene and Tropical Medicine.

When the virus first emerged in China, epidemiologists scrambled to understand how it spread from person to person. One of their first tasks was to estimate the average number of people each sick person infected, or what epidemiologists call the reproductive number.

The new coronavirus turned out to have a reproductive number somewhere between two and three. It's impossible to pin down an exact figure, since people's behavior can make it easier or harder for the virus to spread. By going into lockdown, for instance, Massachusetts drove its reproductive number down from 2.2 at the beginning of March to 1 by the end of the month; it's now at .74.

This averaged figure can also be misleading because it masks the variability of spread from one person to the next. If nine out of 10 people don't pass on a virus at all, while the 10th passes it to 20 people, the average would still be two.

In some diseases, such as influenza and smallpox, a large fraction of infected people pass on the pathogen to a few more. These diseases tend to grow steadily and slowly. "Flu can really plod along," said Kristin Nelson, an assistant professor at Emory University.

But other diseases, like measles and SARS, are prone to sudden flares, with only a few infected people spreading the disease.

Epidemiologists capture the difference between the flare-ups and the plodding with something known as the dispersion parameter. It is a measure of how much variation there is from person to person in transmitting a pathogen.

But James Lloyd-Smith, a U.C.L.A. disease ecologist who developed the dispersion parameter 15 years ago, cautioned that just because scientists can measure it doesn't mean they understand why some diseases have more superspreading than others. "We just understand the bits of it," he said.

When Covid-19 broke out, Dr. Kucharski and his colleagues tried to calculate that number by comparing cases in different countries.

If Covid-19 was like the flu, you'd expect the outbreaks in different places to be mostly the same size. But Dr. Kucharski and his colleagues found a wide variation. The best way to explain this pattern, they found, was that 10 percent of infected people were responsible for 80 percent of new infections. Which meant that most people passed on the virus to few, if any, others.

Dr. Kucharski and his colleagues published their study in April as a preprint, a report that has not been reviewed by other scientists and published in a scientific journal. Other epidemiologists have calculated the dispersion parameter with other methods, ending up with similar estimates.

In Georgia, for example, Dr. Nelson and her colleagues analyzed over 9,500 Covid-19 cases from March to May. They created a model for the spread of the virus through five counties and estimated how many people each person infected.

In a preprint published last week, the researchers found many superspreading events. Just 2 percent of people were responsible for 20 percent of transmissions.

Now researchers are trying to figure out why so few people spread the virus to so many. They're trying to answer three questions: Who are the superspreaders? When does superspreading take place? And where?

As for the first question, doctors have observed that viruses can multiply to bigger numbers inside some people than others. It's possible that some people become virus chimneys, blasting out clouds of pathogens with each breath.

Some people also have more opportunity to get sick, and to then make other people sick. A bus driver or a nursing home worker may sit at a hub in the social network, while most people are less likely to come into contact with others — especially in a lockdown.

Dr. Nelson suspects the biological differences between people are less significant. "I think the circumstances are a lot more important," she said. Dr. Lloyd-Smith agreed. "I think it's more centered on the events."

A lot of transmission seems to happen in a narrow window of time starting a couple days after infection, even before symptoms emerge. If people aren't around a lot of people during that window, they can't pass it along.

And certain places seem to lend themselves to superspreading. A busy bar, for example, is full of people talking loudly. Any one of them could spew out viruses without ever coughing. And without good ventilation, the viruses can linger in the air for hours.

A study from Japan this month found clusters of coronavirus cases in health care facilities, nursing homes, day care centers, restaurants, bars, workplaces, and musical events such as live concerts and karaoke parties.

This pattern of superspreading could explain the puzzling lag in Italy between the arrival of the virus and the rise of the epidemic. And geneticists have found a similar lag in other countries: The

first viruses to crop up in a given region don't give rise to the epidemics that come weeks later.

Many countries and states have fought outbreaks with lockdowns, which have managed to draw down Covid-19's reproductive number. But as governments move toward reopening, they shouldn't get complacent and forget the virus's potential for superspreading.

"You can really go from thinking you've got things under control to having an out-of-control outbreak in a matter of a week," Dr. Lloyd-Smith said.

Singapore's health authorities earned praise early on for holding down the epidemic by carefully tracing cases of Covid-19. But they didn't appreciate that huge dormitories where migrant workers lived were prime spots for superspreading events. Now they are wrestling with a resurgence of the virus.

On the other hand, knowing that Covid-19 is a superspreading pandemic could be a good thing. "It bodes well for control," Dr. Nelson said.

Since most transmission happens only in a small number of similar situations, it may be possible to come up with smart strategies to stop them from happening. It may be possible to avoid crippling, across-the-board lockdowns by targeting the superspreading events.

"By curbing the activities in quite a small proportion of our life, we could actually reduce most of the risk," said Dr. Kucharski.

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

Scientists Say New Strain of Swine Flu Virus Is Spreading to Humans in China

A new study warns that the strain of H1N1, common on China's pig farms since 2016, should be "urgently" controlled to avoid another pandemic.

By Mike Ives

HONG KONG — A new strain of the H1N1 swine flu virus is spreading silently in workers on pig farms in China and should be "urgently" controlled to avoid another pandemic, a team of scientists says in a new study.

H1N1 is highly transmissible and spread around the world in 2009, killing about 285,000 people and morphing into seasonal flu.

The newer strain, known as G4 EA H1N1, has been common on China's pig farms since 2016 and replicates efficiently in human airways, according to the study published on Monday. So far, it has infected some people without causing disease, but health experts fear that could change without warning.

"G4 viruses have all the essential hallmarks of a candidate pandemic virus," the study said, adding that controlling the spread in pigs and closely monitoring human populations "should be urgently implemented."

The study, published online in the journal Proceedings of the National Academy of Sciences, is based on the surveillance of pigs in 10 Chinese provinces from 2011 to 2018. In the last three years of the study, researchers collected 338 blood samples from workers on 15 pig farms and 230 from people in nearby households.

The study found that 10.4 percent of the workers and 4.4 percent of the others tested positive for antibodies to G4 EA H1N1, and that workers between the ages of 18 and 35 tested positive at a higher rate: 20.5 percent.

Predicting risk is not a precise science, but close attention to the virus would be advisable, said Ian H. Brown, the head of the virology department at Britain's Animal and Plant Health Agency and one of two scientists who reviewed the paper before it was published. "It may be that with further change in the virus it could become more aggressive in people much as SARS-CoV-2 has done," Dr. Brown said in an email on Tuesday, referring to the new coronavirus.

The study was sent for review in early December, weeks before the coronavirus outbreak in the Chinese city of Wuhan began making global headlines.

Li-Min Huang, director of the Division of Pediatric Infectious Diseases at National Taiwan University Hospital, said that a crucial next step would be finding out whether any of the infected workers at the pig farms had contracted the virus from humans, as well as whether any had spread the virus to their families.

"It's a very important study, and the virus looks quite dangerous," Dr. Huang said. "We need to be worried about any disease with the potential to spread human to human."

Eurasian variations of H1N1 have been circulating in pigs in Europe and Asia for decades, the study said, but the incidence of G4 viruses in farmed Chinese pigs with respiratory symptoms began rising sharply after 2014.

Recent evidence "indicates that G4 EA H1N1 virus is a growing problem in pig farms, and the widespread circulation of G4 viruses in pigs inevitably increases their exposure to humans," it said.

Asked about the new strain at a U.S. Senate hearing on Tuesday, Dr. Anthony Fauci, the nation's top infectious disease expert, said that it was not an "immediate threat" but "something we need to keep our eye on just the way we did with in 2009 with the emergence of the swine flu."

The study was a collaboration among government agencies in China, including the Center for Disease Control and Prevention, as well as the World Health Organization, scientists from several universities in China and the University of Nottingham in Britain. Dr. Brown teaches at the University of Nottingham but was not involved in the research.

The H1N1 virus that caused a pandemic in 2009 had a relatively low fatality rate, estimated at 0.02 percent. By contrast, the fatality rate of the 1918 flu pandemic was about 2.5 percent of its victims. But that virus killed an estimated 50 million, perhaps more, because it infected so many people and spread at a time when medical care was cruder.

Determining the fatality rate of the new coronavirus is a key question for epidemiologists, but one they may not be able to answer until the pandemic has ended.

Cao Li contributed reporting.

https://bit.ly/3eXSQHY

Study finds the minimum number of Martian settlers for survival is 110

How many people are needed to make it work? A new study pegs the minimum number of settlers at 110.

by Evan Gough, Universe Today

So you want to colonize Mars. Well, Mars is a long ways away, and in order for a colony to function that far from Earthly support, things have to be thought out very carefully. Including how many people are needed to make it work.

A new study pegs the minimum number of settlers at 110.

The study is titled "Minimum Number of Settlers for Survival on Another Planet." The author is Jean-Marc Salotti, a professor at Bordeaux Institut National Polytechnique. His paper is published in *Scientific Reports*.

Obviously, there's a lot to think about when it comes to establishing any kind of sustained presence on another planet. How will people organize themselves? What equipment will they bring? How will they extract in-situ resources? What kind of skills are needed?

These questions have been addressed before, of course, and in this report, Salotti says that "the use of in situ resources and different social organizations have been proposed, but there is still a poor understanding of the problem's variables."

This study mostly focuses on one question: How many people will it take? Salotti writes: "I show here that a mathematical model can

be used to determine the minimum number of settlers and the way of life for survival on another planet, using Mars as the example."

A lot of thought has gone into colonizing Mars. SpaceX says their proposed interplanetary spacecraft could carry 100 people to Mars. Musk has talked about building a fleet of them, so that there's a constant flow of resources to Mars.

"However," Salotti writes, "this is an optimistic estimate of the capability, the feasibility of the reusability remains uncertain and the qualification of the vehicle for landing on Mars and relaunch from Mars could be very difficult and take several decades."

Artist's impression of SpaceX's proposed Mars Base Alpha. **Credit: SpaceX**

A similar dynamic hovers over other parts of the Mars colony discussion. Many researchers have thought about in-situ resource utilization, for instance. Gasses could be extracted from the atmosphere, and minerals from the soil. In-situ resource extraction could provide organic compounds, iron and even glass. Even if we grant the feasibility of these ideas, "the complexity of the implementation is poorly understood and the number of items that would remain to be sent each year would still represent a tremendous challenge," writes Salotti.

The problem of a colony is bewilderingly complex.

Salotti worked on a mathematical model that he thinks could serve as a good starting point for thinking about a self-sustaining colony. Central to his idea is what he calls the sharing factor, "which allows some reduction of time requirements per individual if, for example, the activity concerns the construction of an object that can be shared by several individuals."

The starting point of the settlement is critical to the rest of the work. What resources will be in place? If there's a large amount of resources and technological tools in the beginning, that will affect the rest of the calculations. But in some ways, the starting point might not be as critical, for two factors.

The complexity, expense and feasibility of interplanetary travel is one. And the lifetime of the equipment that settlers start with is another. Every piece of equipment has a lifetime.

"For the sake of simplicity," Salotti writes, "it is assumed here that the initial amount of resources and tools sent from Earth will be rather limited, and as a consequence, will not have much impact on survival." In essence, building a model that relies on easy re-supply from Earth wouldn't be that helpful.

So granting that the initial state of the colony is viable, Salotti moves on to two variables which will have a huge effect on survival:

- ***The availability of local resources. Basically, this means water, oxygen and chemical elements. Those resources have to be easy to exploit.***
- ***Production capacity. Think of it as a list of things that have to be produced, like tools, and if enough of them can be produced in the appropriate time frame.***

What Salotti is working up to here is an equation. Things like resource availability and production capacity are variables in that equation. But Salotti's idea always circles back to the concept of the "sharing factor."

Imagine an isolated individual in a colonizing situation on Mars. They would have to perform all tasks themselves. They would need to build and or maintain their own systems to acquire drinking water, oxygen, and to generate power. There wouldn't be enough time in each day. The burden on a single person would be enormous.

But in a larger colony, their technology for things like getting drinking water, oxygen and for generating power is used by more people. That creates more demand, but it also spreads out the burden. The effort it takes to build and maintain all those systems is now spread out among more people. That, in essence, is Salotti's sharing factor. It gets better.

As the number of people increases, there's room for more specialization. Imagine a colony of only 10 people. How many of them would need to be able to repair and maintain the drinking water system? Or the oxygen system? Those systems cannot be allowed to fail, so there would be pressure for a large percent of those people to be able to operate and understand those systems.

Salotti writes, "If each settler was completely isolated and no sharing was possible, each individual would have to perform all activities and the total time requirement would be obtained by a multiplication by the number of individuals."

But if there are 100 people, how many people need to understand those systems? Not everyone. So that allows others to specialize in something else.

"…a greater number of individuals makes it possible to be more efficient through specialization and to implement other industries, allowing the use of more efficient tools."

Salotti argues that this sharing factor can be calculated and estimated with mathematical functions. Math-interested people can check out that part of the paper for themselves.

There are some constraints and starting points for the sharing factor, of course. "The sharing factor depends on the needs, the processes, the resources and environmental conditions, which may be different depending on the planet," Salotti writes.

This leads us to Salotti's description of "survival domains." Salotti outlines five domains that need to be considered in these calculations:

- ***ecosystem management***
- ***energy production***
- ***industry***
- ***buildings***
- ***human factors/social activities***

These are mostly self-explanatory, but human factors refers to things like raising and education children, and some amount of cultural activities like sports, games and perhaps music.

Now Salotti turns to Mars, the primary planet when it comes to this kind of futuristic figuring, and the planet that Salotti addresses in his paper.

Salotti doesn't start from scratch when it comes to Mars. There's already been a lot of scientific thinking into building a sustained human presence on that planet. "The specific utilization of Martian resources for life support, agriculture and industrial production has been studied in different workshops and published in reports and books," Salotti explains.

Obviously, this is a complex problem, and some assumptions have to be made in order to think about it. For any solution to have merit, those assumptions have to be honest. No place for science fiction here.

The basic assumption Salotti uses is that for whatever reason, the flow of supplies from Earth has been interrupted, and the colony must sustain itself. He borrows a scenario from a contest organized by the Mars Society, where participants were asked to define a realistic scenario for settling Mars.

Basically, Salotti's equation comes down to time. How much time is required for survival vs. how much time is available. For Salotti, the effective number of people required to balance the time equation is 110 on Mars. "It is based on the comparison between the required working time to fulfill all the needs for survival and the

working time capacity of the individuals," he writes in the conclusion.

Naturally, work of this nature makes some assumptions, which are spelled out in the paper. "This is obviously a rough estimate with numerous assumptions and uncertainties," he writes. But that doesn't diminish its usefulness.

If there's ever going to be a human colony on Mars at some point in the future, then we need to develop working models to guide our thinking and our planning. We have a lot of sci-fi talk and flowery announcements from people with large Twitter followings, but that's not real work. "To our knowledge, it is nevertheless the first quantitative assessment of the minimum number of individuals for survival based on engineering constraints," Salotti says.

"Our method allows simple comparisons, opening the debate for the best strategy for survival and the best place to succeed," he concludes.

Let the debate begin.

More information: *Jean-Marc Salotti. Minimum Number of Settlers for Survival on Another Planet, Scientific Reports (2020).* *DOI: 10.1038/s41598-020-66740-0*
Journal information: *Scientific Reports*
Provided by Universe Today

https://bit.ly/3qlqlLq

Malaria's secret to surviving in the blood uncovered

New research from the Francis Crick Institute has found how the malaria parasite protects itself from toxic compounds in red blood cells.

Malaria causes around 400,000 deaths globally each year. It is caused by Plasmodium parasites which are transmitted by mosquitoes and grow in a person's blood stream.

In their study, published in *Proceedings of the National Academy of Sciences USA*, Crick researchers together with colleagues from Germany and Switzerland identified a protein used by the malaria parasite to protect itself from a toxic compound in red blood cells. They hope this could lead to the development of drugs that block this process.

When the malaria parasite enters a red blood cell it digests haemoglobin, leading to the release of a compound called haem, which is toxic to the parasite if it is left loose inside the cell.

The researchers found that to overcome this, the parasite uses a protein, called PV5, to control a process where free haem molecules are joined together into insoluble crystals which are not harmful. This is vital to the survival of the malaria parasite.

When the researchers blocked this protein in the lab, they found that the human-infecting malaria parasite made fewer and highly misshapen crystals. When the protein was blocked in mice that had been infected with a rodent strain of malaria, the parasite became more sensitive to several antimalarial drugs.

Joachim Matz, lead author and postdoctoral research fellow in the Malaria Biochemistry Laboratory at the Crick says: "The importance of haem crystallisation to malaria has been understood for a while, but what has been missing is knowledge about how this process is controlled by the parasite. By identifying a protein that is key to this process, we've opened the door to potential new treatments which can stop malaria in its tracks".

Mike Blackman, author and group leader of the Malaria Biochemistry Laboratory at the Crick says: "The issue of malaria developing resistance to antimalarial drugs is of grave concern. The parasite is already resistant to many drugs and this underpins the need to find new treatments."

"We hope that an improved understanding of the mechanisms at play during this haem crystallisation process will provide valuable insights for the development of future drugs."

The researchers will continue to study the role of PV5 during haem crystallisation, with a view to identify the exact mechanism behind this process.

https://wb.md/2D3yxut

Colchicine Promising in COVID-19 Treatment?

Colchicine, an anti-inflammatory drug used to treat gout and rheumatic disease, may be a promising treatment for COVID-19, a randomized, open-label trial suggests.

Batya Swift Yasgur, MA, LSW

In the Greek Study in the Effects of Colchicine in COVID-19 Complications Prevention (GRECCO-19), investigators randomly assigned 105 patients who had COVID-19 to receive either the standard of care or the standard of care plus colchicine for 3 weeks. They found that for patients in the colchicine group, the time to clinical deterioration improved, although there were no significant differences between the groups in cardiac and inflammatory biomarkers.

"Colchicine is an old drug utilized for its anti-inflammatory and antimitotic effects," lead author Spyridon Deftereos, MD, PhD, professor of cardiology, Second Department of Cardiology, "Attikon" University Hospital National and Kapodistrian University of Athens, told *theheart.org | Medscape Cardiology*.

"While our study did not directly evaluate the mechanisms of action, we believe the key lies on its anti-inflammatory properties combined with an antithrombogenic effect that was indeed observed in our cohort and has also been reported in the literature," he said.

The study was published online June 24 in *JAMA Network Open.*

Inflammatory Response

Deftereos and colleagues have studied the effects of colchicine in a variety of clinical settings for the past decade. Being familiar with its safety profile, potential pathophysiologic mechanisms, and clinical actions, Deftereos said, "It was inevitable for us not to wonder whether it could be of benefit in a disease in which inflammatory response plays a crucial role."

To address the question, the researchers conducted an open-label, prospective study that spanned roughly 3 weeks (April 3 to April 27, 2020).

They randomly assigned 105 patients who had COVID-19 (58.1% men; median age, 64 years; interquartile range [IQR], 54 – 76 years) to receive either low-dose colchicine (1.5-mg loading dose, followed by 0.5 mg after 60 min and then maintenance doses of 0.5 mg/day twice daily) plus standard medical treatment (n = 50 patients) or standard treatment only (n = 55 patients).

The treatment groups were "largely similar" in demographic characteristics, clinical status at presentation, baseline laboratory evaluation, and baseline clinical score (4 in both groups). Most patients were being treated with chloroquine or hydroxychloroquine and azithromycin (98.1% and 92.4%, respectively).

The researchers established three primary endpoints and three secondary endpoints. Primary endpoints included maximum high-sensitivity cardiac troponin level; time for C-reactive protein (CRP) to reach >3 times the upper reference limit; and time to deterioration by 2 points on a 7-point clinical status scale. Secondary endpoints included percentage of participants who required mechanical ventilation; all-cause mortality; and the number, type, severity, and seriousness of adverse events.

Results showed that hospital duration was 1 day longer in the control group compared to the colchicine group (median duration, 12 days [IQR, 9 – 22] vs 13 days [IQR, 9 – 18]; P = .91).

No significant differences were found between the groups in the first two primary outcomes. The median peak high-sensitivity cardiac troponin values were 0.0112 (0.0043 – 0.0093) ng/mL in the control group and 0.008 (0.004 – 0.0135) ng/mL in the colchicine group (P = .34). The median maximum CRP levels were 4.5 (1.4 – 8.9) mg/dL in the control group and 3.1 (0.8 – 9.8) mg/dL in the colchicine group (P = .73).

However, the clinical primary endpoint rate was 14.0% in the control group vs 1.8% in the colchicine group (odds ratio, 0.11; 95% confidence interval, .01 – .96; *P* = .02).

The mean event-free survival time was 18.6 (.83) days in the control group vs 20.7 (.31) days in the colchicine group (log rank *P* = .03). Most adverse events were similar in the two groups; however, diarrhea was more frequent in the colchicine group than in the control group.

There was an attenuation of the maximum D-dimer levels in the colchicine group vs the control group, "suggesting an anti-inflammatory and antithrombogenic effect," the authors note.

Improved time to clinical deterioration "was our prespecified clinical endpoint, as per protocol design, [and] indeed, the clinical endpoint occurred only in 1 of 55 patients in the colchicine group and in 7 of 50 patients in the control group," Deftereos said.

Of the eight patients who met the clinical endpoint, one required noninvasive mechanical ventilation, six required invasive mechanical ventilation, and one suffered sudden cardiorespiratory arrest.

"Therefore, we may consider that colchicine treatment is of benefit for treatment of such patients," Deftereos said. Still, they call the results hypothesis-generating and conclude they should be "interpreted with caution."

Encouraging Data

Commenting on the study for *theheart.org | Medscape Cardiology*, Amir B. Rabbani, MD, assistant clinical professor, UCLA David Geffen School of Medicine, Los Angeles, called colchicine "an attractive therapeutic target for the treatment of COVID-19 patients because it works on multiple different pathways, rather than inhibiting one factor."

If future studies, such as the COLCORONA study and his own group's COLHEART-19 study, now ongoing, show similar results, "colchicine may become a standard tool in the COVID-19 therapeutic toolbox," suggested Rabbani, who is the author of an accompanying editorial and was not involved with the study.

Although more data are needed "to understand where colchicine will fall in the treatment spectrum, initial data are encouraging that there will be benefit as possibly an important adjunct to antiviral therapy," Rabbani suggested, adding, "It remains to be seen if long-term treatment with colchicine may prevent some of the debilitating post-COVID symptoms."

Urgent Situation

Deftereos called COVID-19 an "urgent situation" that "literally changed the way clinicians and researchers take decisions."

During the first COVID-19 wave, therapeutic algorithms included treatments for which no randomized trial data were available, and "inclusion of a drug in the suggested therapeutic algorithm remains in the responsibility of local authorities, after evaluation of the data that slowly but steadily accumulated," he pointed out.

He noted that multiple trials of colchicine are recruiting patients, and some plan to recruit larger populations and patients with mild COVID-19 who do not require hospitalization.

"Evidence-based medicine process is rather like a marathon rather than a sprint. We tried to contribute in this procedure with our study," Deftereos concluded.

The study was funded by ELPEN Pharmaceuticals, Acarpia Pharmaceuticals, and Karian Pharmaceuticals. Deftereos reports no relevant financial relationships. The other authors' disclosures are listed on the original article. Rabbani reports no relevant financial relationships. JAMA Netw Open. Published online June 24, 2020. Full text, Editorial

https://nyti.ms/2VL5IJX

In Early February, the Coronavirus Was Moving Through New York

Antibodies appeared in blood samples taken later in the month, a new study finds.

By Apoorva Mandavilli

A new study offers the first physical evidence that the coronavirus was circulating at low levels in New York City as early as the first week of February.

The city confirmed its first infection on March 1. Mathematical models have predicted that the virus was making its way through the city weeks before then, but the new report is the first to back the conjecture with testing data.

The study found that some New Yorkers had antibodies to the virus as early as the week ending Feb. 23. Given the time needed to produce antibodies, those people were most likely infected with the virus about two weeks earlier.

"You're probably talking about very early in February," said Florian Krammer, an immunologist at the Icahn School of Medicine at Mount Sinai, who led the study. "It looks like there was at least low-level circulation."

The findings were posted online Tuesday and have not yet been vetted by other scientists in a formal review, but several experts said the work was rigorous and credible, if not entirely surprising.

Genetic analyses have suggested that the virus entered the city several times early in the year, but most of those introductions died out and did not initiate the city's epidemic.

"If I had to put a single date on it, based on current models, we had it as Feb. 19 as the arrival that fueled things," said Trevor Bedford, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle. Dr. Krammer's date is only slightly earlier, he noted.

The study also confirms estimates by epidemiologists working for New York State that roughly one in five New Yorkers had been exposed to the virus by late April, a figure broadly consistent with data released on Friday by the Centers for Disease Control and Prevention.

"I think it's cool that we all have similar numbers," Dr. Krammer said.

The similarity is even more striking, experts said, because the three studies all arrived at their estimates differently.

Dr. Krammer and his colleagues analyzed plasma samples from nearly 5,500 patients who went to Mount Sinai for routine medical appointments, were seen in its emergency department or were hospitalized from the week ending Feb. 9 through the week ending April 19.

The C.D.C. looked at blood samples from people who went in for routine medical exams, but only the week ending April 1 for New York City. The New York State study recruited people at supermarkets from April 19 to April 28.

"When we have three sources all giving you consistent results, that lends strength to all the findings," said Eli Rosenberg, an epidemiologist at the State University of New York at Albany and lead author of the state study.

The numbers from all three studies also agree on a crucial point: The vast majority of infections in New York City and elsewhere in the country went undiagnosed. Even in places with large outbreaks, the number of people exposed to the virus is still far from what is needed for herd immunity.

The Mount Sinai researchers grouped their samples in different ways and analyzed them using a lab-based antibody test that is highly accurate and specific to the new coronavirus.

Among people admitted to the emergency room or the hospital during the study period, the prevalence of antibodies rose to nearly 60 percent from 3.2 percent, the researchers found. These numbers are high because they include people who were severely ill with the coronavirus.

But among people who gave blood for routine appointments, or were admitted to the hospitals for reasons unrelated to the

coronavirus — a group that represents the general population — fewer than 2 percent of people had antibodies until the week ending March 29. The rate rose exponentially after that, ending at 19.3 percent among patients seen in the week ending April 19.

The team broke this latter group down further by the reason for their appointment, and found the increase in prevalence was mostly driven by pregnant women. Nearly one in 10 pregnant women had antibodies to the virus by the week of March 29, and the number rose steadily to nearly 27 percent by the week ending April 19.

By comparison, people who came in for appointments related to surgery, cancer or cardiology plateaued at about 9 percent.

Subgroup analyses tend not to be reliable because of the smaller sample sizes, but this is a large study and the trends are intriguing, said Taia Wang, an immunologist at Stanford University.

“It does suggest the possibility that different groups of patients might have different susceptibility to SARS-CoV-2 infection,” she said.

Experts were also struck by the relatively flat prevalence of coronavirus antibodies in blood samples from the first few weeks.

“I would expect during this time period, where people are not modifying their behavior, you’d get much closer to exponential growth,” Dr. Bedford said.

Other cities, like San Francisco, have similarly shown periods when the virus seemed to percolate until something — perhaps a superspreader event — triggered an exponential rise in infections.

“We’ve seen this elsewhere repeatedly, and it’s still strange to me,” Dr. Bedford said.

Dr. Krammer is continuing to track antibodies in blood samples and plans to do so for at least a year. But he said he would not expect the prevalence to rise much above 20 percent in May or June, because infections in New York City had tapered off by then.

https://bit.ly/3dVVYmc

We May Finally Know The Extreme Route Fish Take Through Air to Colonise New Lakes

It has long been a mystery how some fish can colonise isolated lakes and ponds surrounded by inhospitably dry land.

Tessa Koumoundouros

It's not like fish can get out of the water, shake themselves off, and walk between far-flung pools to spread their spawn.

Yet, from remote crater lakes to desert ponds, these fish are somehow there. Did birds shuttle them in, perhaps? The softness of fish eggs has had biologists thinking the spawn are too squishy to survive an epic adventure through a bird's digestive system. But all may not be what it seems.

A new study has shown that most fish eggs really don't make it out the other side of a duck's digestive tract - but a teeny tiny 0.2 percent were pooped out and still viable. So, while busy doing all their important developmental things, these few egg-encased fish embryos endured being squeezed through body tubes, pummelled in a gizzard, assailed by digestive enzymes, and squashed through a bird's bottom.

This type of journey, called endozoochory (dispersal via the gut of an animal), is a common transport tactic for plant seeds; it's also known in some insects. But the first evidence that fish also have this ability was only found last year, when eggs of killifish survived to hatch after being eaten by a swan.

However, killifish eggs are unusually tough - able to survive dry soil for months in a kind of hibernation, until rains return to their ephemeral desert pools.

It has been widely assumed fish eggs travelled to such secluded locations by catching a sticky lift on bird legs, beaks and feathers, but there was no actual evidence for this. Until now, we didn't know if such eggs could make it through bird bodies alive.

To test the idea, biologist Ádám Lovas-Kiss from the Danube Research Institute in Hungary and colleagues fed captive mallard ducks (*Anas platyrhynchos*) eggs from two types of carp - common carp (*Cyprinus carpio*) and Prussian carp (*Carassius gibelio*).

Each of the eight birds was fed around 500 eggs. Of all these, 18 eggs were recovered from the ducks' poop. Twelve were still viable, but only 3 successfully hatched.

While the odds might seem terrible, when you consider all the available fish eggs and all the waterbirds known to enjoy feasting on nutritious roe, it all adds up. A single common carp can lay up to 1.5 million eggs in one spawning event, and during certain parts of the year fish eggs can make up 100 percent of the stomach content of some waterbirds. A staggering 63,501 fish eggs were once found in a glaucous gull's (*Larus hyperboreus*) stomach.

"Such survival was not a freak event," the team explained in their paper. It "occurred in 75 percent of the experimental ducks and in both fish species studied."

Most of the fish embryos that made it all the way through the birds but then failed to hatch, succumbed to a fungal infection that also decimated the control eggs which didn't have to travel through a duck.

This fungal presence was likely due to experimental set-up, as it is a known problem in artificial fish breeding, so the researchers suspect more eggs would survive through to hatching in the wild.

It took most of the carp eggs only an hour to make their way from one end of the duck out to the other. The team calculated this means a dispersal range of around 60 kilometres (37 miles) for eggs taking their journey via duck. One of the eggs, however, hatched after 4-6 hours, increasing that range to a maximum of 360 kilometres (220 miles).

This explains a lot. Carp are notoriously invasive species. Common carp have come to dominate many Australian waterways, composing over 80 percent of fish biomass in some areas. They cause damage to fragile ecosystems by modifying waterways through their mud-sucking feeding habits, they take valuable food away from native species, and contribute to algal blooms.

Carps' ability to disperse via endozoochory, along with their adaptability across many environment types, helps to explain their incredible success in invading new lands and is a key piece of information for people trying to manage their invasions.

"Given the abundance, diet, and movements of ducks in nature, our results have major implications for biodiversity conservation and invasion dynamics in freshwater ecosystems," Lovas-Kiss and colleagues concluded.

This research was published in *PNAS*.

https://bit.ly/2VKnYTB

Space Weather Lessons from a 1928 Dirigible Debacle

Analysis of a disrupted SOS signal during an early polar expedition showcases the importance of taking space weather into account when exploring new frontiers.

By Rachel Fritts

On 15 April 1928, the dirigible *Italia* lifted off from Milan, Italy, hoping to be the second airship ever to reach the North Pole. Over a month later, on 24 May, expedition leader Umberto Nobile sent a triumphant radio message to a ship anchored at the airship's base camp near Ny-Ålesund, in the Norwegian archipelago of Svalbard: The mission was a success. It would be the last message the base camp would ever receive from the *Italia*.

Ten days later, a young Russian with a homemade radio picked up a desperate SOS signal originating 1,900 kilometers (1,180 miles) away. The *Italia* had crashed on sea ice north of Svalbard on its return journey, leaving nine surviving crew members who had been attempting desperately to contact the base ship to send help. The shipwrecked crew could pick up a news station from Rome, 4,000

kilometers (2,485 miles) away, but no matter what frequency they tried, their cries for help could not reach their camp on the other side of the Svalbard Islands. The stranded crew were eventually rescued after weeks on the ice.

"This was completely mysterious to them, I'm sure," said Delores Knipp, former editor in chief of *Space Weather* and a research professor at the University of Colorado Boulder. "They could not understand how they could receive a signal from Rome—very distant—but not be able to contact what appeared to be a very close-by potential rescue ship."

The wreck of the Italia, associated with unusual space weather phenomena, resulted in 17 fatalities. **Credit: German Federal Archive, CC BY-SA 3.0 DE**

Unbeknownst to the *Italia*'s crew, their plight was caused by an unlucky confluence of space weather disturbances, according to a new retrospective analysis by a team of Italian researchers published this month in *Space Weather*. The crew had crash-landed in what is known as a radio skip zone, where radio signals can't be received, during a period of turbulent solar and geomagnetic activity that prevented the signal from getting through.

"This is a history lesson that could replay during other explorations such as lunar or interplanetary travels, so possible communication issues due to disturbed space weather conditions must be taken in due consideration even more nowadays," said Ljiljana Cander, a visiting scientist at the Rutherford Appleton Laboratory in the United Kingdom and a coauthor of the study.

A Different Kind of Storm

High-frequency radio communication takes advantage of a layer of the atmosphere ionized by solar radiation, which extends from 50 to 1,000 kilometers above Earth's surface. Space weather is the term for the phenomena—often solar and electromagnetic disturbances—that affect this layer.

Explorers knew that the poles were capable of brutal terrestrial weather events with howling winds and icy conditions. But they had no real concept of space weather.In 1928, radio was still a nascent technology and one that had been used largely at midlatitudes. Few had attempted to reach the North Pole, and fewer still had succeeded. Explorers knew that the poles were capable of brutal terrestrial weather events with howling winds and icy conditions. But they had no real concept of space weather or any idea that it behaved dramatically differently at northern latitudes as well.

"Our midlatitude regions are pretty well behaved. We have to have really severe space weather storms to disrupt high-frequency radio communication," Knipp said. But at the transition from midlatitude to polar regions, the ionosphere gets "turbulent." It fluctuates more day to day and is more heavily affected by geomagnetic activity. This causes both longer-term radio disruptions and shorter-term blackouts.

Skip zones, or silent zones, are areas where the radio signal cannot reach the ground, meaning that a radio transmission can't be received within the skip area. These silent zones occur near all radio transmitters, but their size is influenced by the electron density of the ionosphere, which fluctuates more at the poles. Polar latitudes also have unique ionosphere disturbances like polar cap absorption resulting from solar eruptions and auroral radio absorption caused by fluxes in energetic electron activity from the magnetosphere.

An Expedition on Thin Ice

As some of the first polar explorers, the crew of *Italia* became unwitting participants in the earliest-known demonstration of what happens when several of these absorption events conspire to disrupt

a signal at the same time. When the airship crashed on the ice, the nine survivors immediately attempted to contact the base ship using a portable high-frequency radio. Signals fluctuated between the 9.1- and 9.4-megahertz frequencies, to no avail.

The dirigible had crash-landed in a silent zone for those particular frequencies, which extended across most of the Svalbard islands and made it impossible for the crew to contact their base. A geomagnetic storm flared up for several days after the crash, potentially further restricting the range of radio frequencies that could get through.

"The combination of the two—a lowering of usable frequencies and an increase of the absorption—might have caused either a narrowing of the usable frequency spectrum or even a blackout that lasted for a few days, preventing the survivors from being heard," said Michael Pezzopane, a researcher at the Istituto Nazionale di Geofisica e Vulcanologia and a coauthor of the study.

To the North Pole and Beyond

The plight of the *Italia* crew is still relevant today. Space weather as a discipline has been officially recognized only since the 1990s, and our understanding of space weather still lags behind our understanding of traditional weather patterns. Analyzing key space weather events from the past using modern technology and understanding can help us avoid similar pitfalls in the future.

"I do think these historical reconstructions are useful, especially from the point of view of generating awareness for space weather and how it can either adversely or positively affect what we do here on Earth," said Nathaniel Frissell, an assistant professor in the Physics and Engineering Department at the University of Scranton in Pennsylvania who was not involved in the study.

"The people who were involved in this event were very much explorers and frontiers people," Knipp said. "We can draw a parallel with that now for humanity as we try to go back and establish some kind of base on the Moon and as we reach out to cross to a new planet—Mars."

—Rachel Fritts (@rachel_fritts), Science Writer

Citation: *Fritts, R. (2020), Space weather lessons from a 1928 dirigible debacle, Eos, 101, https://doi.org/10.1029/2020EO146304. Published on 01 July 2020.*

https://bit.ly/3f0l8Se

First exposed planetary core discovered allows glimpse inside other worlds

The surviving core of a gas giant has been discovered orbiting a distant star by University of Warwick astronomers, offering an unprecedented glimpse into the interior of a planet.

The surviving core of a gas giant has been discovered orbiting a distant star by University of Warwick astronomers, offering an unprecedented glimpse into the interior of a planet.

The core, which is the same size as Neptune in our own solar system, is believed to be a gas giant that was either stripped of its gaseous atmosphere or that failed to form one in its early life.

The team from the University of Warwick's Department of Physics reports the discovery today (1 July) in the journal *Nature*, and is thought to be the first time the exposed core of a planet has been observed. It offers the unique opportunity to peer inside the interior of a planet and learn about its composition.

Located around a star much like our own approximately 730 light years away, the core, named TOI 849 b orbits so close to its host star that a year is a mere 18 hours and its surface temperature is around 1800K.

TOI 849 b was found in a survey of stars by NASA's Transiting Exoplanet Survey Satellite (TESS), using the transit method: observing stars for the tell-tale dip in brightness that indicates that a planet has passed in front of them. It was located in the 'Neptunian desert' - a term used by astronomers for a region close to stars where we rarely see planets of Neptune's mass or larger.

The object was then analysed using the HARPS instrument, on a program led by the University of Warwick, at the European Southern Observatory's La Silla Observatory in Chile. This utilises the Doppler effect to measure the mass of exoplanets by measuring their 'wobble' - small movements towards and away from us that register as tiny shifts in the star's spectrum of light.

The team determined that the object's mass is 2-3 times higher than Neptune but it is also incredibly dense, with all the material that makes up that mass squashed into an object the same size.

Lead author Dr David Armstrong from the University of Warwick Department of Physics said: "While this is an unusually massive planet, it's a long way from the most massive we know. But it is the most massive we know for its size, and extremely dense for something the size of Neptune, which tells us this planet has a very unusual history. The fact that it's in a strange location for its mass also helps - we don't see planets with this mass at these short orbital periods.

"TOI 849 b is the most massive terrestrial planet - that has an earth like density - discovered. We would expect a planet this massive to have accreted large quantities of hydrogen and helium when it formed, growing into something similar to Jupiter. The fact that we don't see those gases lets us know this is an exposed planetary core.

"This is the first time that we've discovered an intact exposed core of a gas giant around a star."

There are two theories as to why we are seeing the planet's core, rather than a typical gas giant. The first is that it was once similar to Jupiter but lost nearly all of its outer gas through a variety of methods. These could include tidal disruption, where the planet is ripped apart from orbiting too close to its star, or even a collision with another planet. Large-scale photoevaporation of the atmosphere could also play a role, but can't account for all the gas that has been lost.

Alternatively, it could be a 'failed' gas giant. The scientists believe that once the core of the gas giant formed then something could have gone wrong and it never formed an atmosphere. This could have occurred if there was a gap in the disc of dust that the planet formed from, or if it formed late and the disc ran out of material.

Dr Armstrong adds: "One way or another, TOI 849 b either used to be a gas giant or is a 'failed' gas giant.

"It's a first, telling us that planets like this exist and can be found. We have the opportunity to look at the core of a planet in a way that we can't do in our own solar system. There are still big open questions about the nature of Jupiter's core, for example, so strange and unusual exoplanets like this give us a window into planet formation that we have no other way to explore.

"Although we don't have any information on its chemical composition yet, we can follow it up with other telescopes. Because TOI 849 b is so close to the star, any remaining atmosphere around the planet has to be constantly replenished from the core. So if we can measure that atmosphere then we can get an insight into the composition of the core itself."

** 'A remnant planetary core in the hot-Neptune desert' will be published in Nature, DOI: 10.1038/s41586-020-2421-7*

** Dr Armstrong's research was supported by the Science and Technology Facilities Council (STFC), part of UK Research and Innovation, through an Ernest Rutherford Fellowship.*

https://bit.ly/3dWs811

Review finds major weaknesses in evidence base for COVID-19 antibody tests

Evidence does not support continued use of existing point-of-care tests for COVID-19, warn researchers

Major weaknesses exist in the evidence base for covid-19 antibody tests, finds a review of the latest research published by *The BMJ* today. The evidence is particularly weak for point-of-care tests

(performed directly with a patient, outside of a laboratory) and does not support their continued use, say the researchers.

Serological tests to detect antibodies against covid-19 could improve diagnosis and be useful tools for monitoring levels of infection in a population. The UK Prime Minister Boris Johnson has described antibody tests as "game-changing" in its response to the pandemic, but it is important to formally evaluate whether there is sufficient evidence that they are accurate.

So an international team of researchers set out to determine the diagnostic accuracy of antibody tests for covid-19.

They searched medical databases and preprint servers from 1 January to 30 April 2020 for studies measuring sensitivity and/or specificity of a covid-19 antibody test compared with a control test.

Sensitivity measures the percentage of people who are correctly identified as having a disease, while specificity measures the percentage of people who are correctly identified as not having a disease.

Of 40 eligible studies, most (70%) were from China and the rest were from the UK, US, Denmark, Spain, Sweden, Japan and Germany. Half of the studies were not peer reviewed and most were found to have a high or unclear risk of bias (problems in study design that can influence results). Only four studies included outpatients and only two evaluated tests at the point of care.

When sensitivity results for each study were pooled together, they ranged from 66% to 97.8% depending on the type of test method used, meaning that between 2.2% and 34% of patients with covid-19 would be missed.

Pooled specificities ranged from 96.6% to 99.7%, depending on the test method used, meaning that between 3.4% and 0.3% of patients would be wrongly identified as having covid-19.

Pooled sensitivities were consistently lower for the lateral flow immunoassay (LFIA) test compared with other test methods. The LFIA test is the potential point-of-care method that is being considered for 'immunity passports.'

Based on these results, the authors explain that, if an LFIA test is applied to a population with a covid-19 prevalence of 10%, for every 1000 people tested, 31 who never had covid-19 will be incorrectly told they are immune, and 34 people who had covid-19 will be incorrectly told that they were never infected.

Pooled sensitivities were also lower with commercial test kits (65%) compared with non-commercial kits (88.2%) and in the first and second week after symptom onset compared with after the second week.

The researchers point to some limitations, such as differences in study populations and the potential for missing studies. However, strengths include thorough search strategies and assessment of bias.

"These observations indicate important weaknesses in the evidence on covid-19 serological tests, particularly those being marketed as point-of-care tests," they write.

"While the scientific community should be lauded for the pace at which novel serological tests have been developed, this review underscores the need for high quality clinical studies to evaluate these tools," they conclude. "With international collaboration, such studies could be rapidly conducted."

Peer reviewed? Yes
Evidence type: Systematic review and meta-analysis
Subjects: Antibody tests for covid-19

https://bit.ly/38rdvl2

Nitrous oxide may bring relief to veterans suffering from PTSD, new study suggests

Early glimpse of how veterans suffering from posttraumatic stress disorder may benefit from one treatment involving nitrous oxide

A new pilot study by the University of Chicago Medicine and the Stanford University School of Medicine team from the VA Palo

Alto Health Care System (principal investigators Carolyn Rodriguez, MD, PhD, and David Clark, MD, PhD) provides an early glimpse of how veterans suffering from posttraumatic stress disorder (PTSD) may benefit from one simple, inexpensive treatment involving nitrous oxide, commonly known as laughing gas.

For military veterans suffering from PTSD, symptoms such as anxiety, anger and depression can have a devastating impact on their health, daily routine, relationships and overall quality of life.

"Effective treatments for PTSD are limited," said anesthesiologist Peter Nagele, MD, chair of the Department of Anesthesia & Critical Care at UChicago Medicine and co-author of the paper. "While small in scale, this study shows the early promise of using nitrous oxide to quickly relieve symptoms of PTSD."

The findings, based on a study of three military veterans suffering from PTSD and published June 30 in the *Journal of Clinical Psychiatry*, could lead to improved treatments for a psychiatric disorder that has affected thousands of current and former members of the U.S. military.

For this new study, three veterans with PTSD were asked to inhale a single one-hour dose of 50% nitrous oxide and 50% oxygen through a face mask. Within hours after breathing nitrous oxide, two of the patients reported a marked improvement in their PTSD symptoms. This improvement lasted one week for one of the patients, while the other patient's symptoms gradually returned over the week. The third patient reported an improvement two hours after his treatment but went back to experiencing symptoms the next day.

"Like many other treatments, nitrous oxide appears to be effective for some patients but not for others," explained Nagele, who is himself a veteran of the Austrian Army and grateful to have identified an opportunity to help other veterans. "Often drugs work only on a subset of patients, while others do not respond. It's our role to determine who may benefit from this treatment, and who won't."

The next step for the team is to determine whether nitrous oxide effects are replicated in a larger sample under randomized, controlled conditions and whether the effects benefit specific PTSD domains (http://ClinicalTrials.gov ID: NCT04378426). If these findings are replicated in independent samples, it may be feasible that nitrous oxide can be implemented to achieve rapid symptom reduction while longer-term PTSD treatments like psychotherapy or pharmacology are allowed to take effect over a longer time course.

Nagele is a pioneer in the field of using nitrous oxide to treat depression. Most commonly known for its use by dentists, nitrous oxide is a low-cost, easy-to-use medication. Although some patients may experience side effects like nausea or vomiting while receiving nitrous oxide, the reactions are temporary.

Exactly how and why nitrous oxide relieves symptoms of depression in some people has yet to be fully understood. Most traditional antidepressants work through a brain chemical called serotonin. Nitrous oxide, like ketamine, an anesthetic that recently received FDA-approval in a nasal spray form to treat major depression, works through a different mechanism, by blocking N-methyl-D-aspartate (NMDA) receptors.

A 2015 landmark study by Nagele found that two-thirds of patients with treatment-resistant depression experienced an improvement in symptoms after receiving nitrous oxide.

For his next study, Nagele is researching the ideal dose of nitrous oxide to treat intractable depression. Study participants with treatment-resistant depression received different doses of nitrous oxide so that Nagele and his team could compare each dose's effectiveness and side effects. The study is being funded by the Brain & Behavior Research Foundation.

"Does nitrous oxide help veterans with post traumatic stress disorder" was funded by the VA Office of Research and Development Clinical Science Research & Development Service.

https://bit.ly/3eZVAoj

A scientific measure of dog years

How old is your tail-wagging bundle of joy in human years?

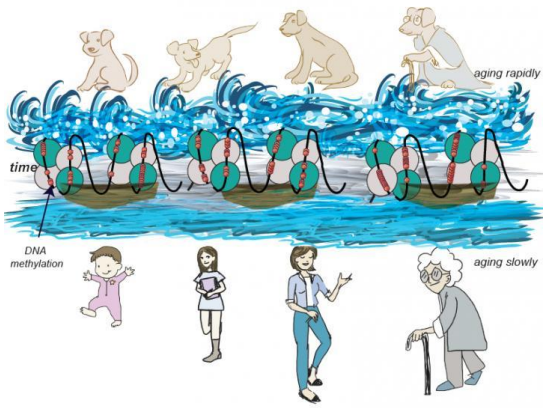
According to the well-known "rule of paw," one dog year is the equivalent of 7 years. Now, in a study published July 2, in the journal *Cell Systems*, scientists say it's wrong. Dogs are much older than we think, and researchers devised a more accurate formula to calculate a dog's age based on the chemical changes in the DNA as organisms grow old.

Dogs share the same environment as their owners and receive almost the same standard of health care as humans, providing a unique opportunity for scientists to understand aging across species. Like humans, dogs follow similar developmental trajectories that lead them to grey and become more susceptible to age-related diseases over time. However, how they age on a molecular level is more complicated--aging rapidly at first and slowing down later in life.

"In terms of how physiologically mature a 1-year-old dog is, a 9-month-old dog can have puppies. Right away, you know that if you do the math, you don't just times seven," says senior author Trey Ideker (@TreyIdeker) of the University of California, San Diego. "What's surprising is exactly how old that one-year-old dog is--it's like a 30-year old human."

Human and dog DNA, which codes who we are, doesn't change much throughout the course of life, but chemical marks on the DNA, called methylation marks, do. Ideker considers these marks like wrinkles in the genome. "I tend to think of it very much like when you look at someone's face and guess their age based on their wrinkles, gray hair, and other features," he says. "These are just similar kinds of features on the molecular level."

The researchers studied 104 Labrador retrievers spanning from few-week-old puppies to 16-year-old dogs with the help of two canine experts, Danika Bannasch of the University of California, Davis, and Elaine Ostrander of the National Institutes of Health. They compared the changes in the methylation pattern to humans.



This graphic depicts the epigenetic translation from dog age to human age.
Ideker Lab, UC San Diego

The comparison revealed a new formula that better matches the canine-human life stages: human age = 16 ln(dog age) + 31. Based on the new function, an 8-week-old dog is approximately the age of a 9-month-old baby, both being in the infant stage where puppies and babies develop teeth. The average 12-year lifespan of Labrador retrievers also corresponds to the worldwide life expectancy of humans, 70 years.

"I like to take my dogs on runs, and so I'm a little bit more sympathetic to the 6-year-old now," says Ideker, who realized that his dog is pushing 60 according to the new calculation.

In both species, they found that the age-driven methylation largely happens in developmental genes that are hotly fired up to create body plans in utero and regulating childhood development. By the time one becomes an adult and stops growing, "you've largely shut off these genes, but they're still smoldering," says Ideker. "If you look at the methylation marks on those developmental genes, they're still changing."

Focusing on the smoldering developmental genes, the team developed a clock that can measure age and physiological states across different species, while other methylation-quantifying age-predicting methods only do well in one species. Ideker also noted that future investigation in different dog breeds with various lifespans could provide more insight into the new clock. The clock may not only serve as a tool to understand cross-species aging but also apply as clinical practice for veterinarians to take proactive steps to treat animals.

This work is supported by the following: the California Institute for Regenerative Medicine, the National Institute for Environmental Health Sciences, the National Institute of General Medical Sciences, the National Institute on Aging, the National Institute of Dental and Craniofacial Research, the Maxine Adler Endowed Chair Funds, and the Intramural Program of the National Human Genome Research Institute.

Cell Systems, Wang et al.: "Quantitative Translation of Dog-to-Human Aging by Conserved Remodeling of the DNA Methylome" https://www.cell.com/cell-systems/fulltext/S2405-4712(20)30203-9

https://bit.ly/2NVlAFh

Surgeons Successfully Reattach Man's Penis Nearly a Day After It Was Cut Off

Surgeons in the United Kingdom have reattached a man's penis nearly a day after it was cut off, the longest documented time the organ has been without a blood supply and still successfully replanted.

Carly Cassella

Six weeks after the operation, the young man's urethra was not only working once again, sensation had also returned to his penis. Thanks to a carefully reattached artery and vein, the patient was even able to achieve a full erection.

"The success of this case therefore should encourage surgeons to attempt penile replantation, even with prolonged ischaemia [loss of blood supply] time, due to possible success and the potential physical and psychosocial effects of organ loss for the patient," write surgeons from the University Hospitals Birmingham NHS Foundation Trust.

Penile reattachment, or replantation, is rare - only a hundred or so have been recorded in the medical literature. But when amputations occur, it's important to move quickly to give the replanted tissue the best chance of survival.

Successful reattachment is an emergency procedure that requires intricate microsurgery, with specialist input from urological and plastic surgeons, as soon as possible.

Unfortunately, treatment is often delayed, as few doctors are familiar with what to do and the emergency is not well documented in the literature.

A medical case reported more than two decades ago describes a 4-year-old's penis being successfully reattached 18 hours after the initial injury. Generally, after a day of being separated, the success rates of replantation are very low.

Surgeons in Birmingham just barely made it under the 24-hour mark. Their patient was a 34-year-old man with a history of paranoid schizophrenia who had tried to take his own life during a psychotic episode. Discovered 15 hours later, the patient was immediately taken to hospital where he was resuscitated and wheeled to the operation room.

Major blood vessels running along the top of the penis were quickly identified, and found to be in working order; linking the vein back up required grafts from an arm vein. Unfortunately, one of the major severed nerves had retreated too far back to be reconnected, but the reconnected vessels returned blood to the penile tissue in the nick of time.

"Arterial flow was established a further 8 hours after arrival into hospital due to the patient's concomitant injuries, thus making the total ischaemia time 23 hours," the case report reads.

In the past, surgeons confronted with a total penile amputation would re-suture the structures without repairing the vessels or the dorsal nerve. Today, however, we know that this might lead to a failure of sensory recovery and scarring in the urethra.

Microsurgical replantation has improved a lot, to the point where many patients can once again achieve erections, but there's still plenty of issues we can improve on, and not only surgically.

Follow-up care is also hugely important, given that the vast majority of genital self-mutilations are penile amputations. Acute schizophrenic attacks are commonly associated, and there are various accounts of microsurgical replants of the penis among these patients in particular. "These reports have noted the need for prolonged follow-up not only to assess the results of replantation, but also to identify those patients who are prone to re-inflict such injuries again," the authors of a 2013 analysis conclude.

Another long-term case study, published in 2015, argues for an "interdisciplinary approach with the involvement of urology, plastic surgery, endocrinology, and psychiatry."

The authors advise that after resuscitation, amputee patients should be transferred to a treatment centre where such expertise exists. Luckily, the young man in this newest case study arrived at such a hospital straight away.

The study was published in *BMJ Case Reports*.

https://bit.ly/2Ayx4LW

Oropharyngeal secretions may help reduce false negative COVID-19 test results

Testing of oropharyngeal secretions (OS) may reduce the number of false negative results from nasal swab testing

Alexandria, Va., USA -- As the global battle to understand and eliminate the coronavirus continues, a new study published in the *Journal of Dental Research* demonstrates that testing of oropharyngeal secretions (OS) may reduce the number of false negative results from nasal swab testing of patients who have seemingly recovered from the disease.

In the study, led by Jingzhi Ma, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Department of Stomatology, Wuhan, China, a small number of patients that had tested negative through nasopharyngeal swabs were found to be positive through the testing of oropharyngeal secretions.

The first prospective study of its kind included 75 ready-for-discharge COVID-19 patients who tested negative using two consecutive nucleic acid amplification testing (NAAT) of viral samples retrieved with nasopharyngeal swabs (NPS).

Because of detection of potential false-negatives in that cohort, NAAT results of paired OS and NPS samples collected from 50 additional COVID-19 recruits during their recovery stage were used in a second prospective study to compare the diagnostic values of the two viral RNA sampling methods.

Oropharyngeal secretions obtained from 2 of the 75 subjects in the first study yielded positive results for SARS-CoV-2 nucleic acid. In the second study, OS samples were significantly more sensitive for detection of the virus that NPS samples and missed only 14% of positive cases compared with 59% for the NPS samples.

Sampling of OS is a simple procedure that can be performed in any quarantine setting and minimizes contact between healthcare workers and patients, thereby reducing the risk of virus transmission.

"The NPS test has a risk of sending home more patients who still have the infection while the OS test will make such errors in fewer patients. Although OS sampling improves the accuracy of SARS-CoV-2 nucleic acid testing, it must be emphasized that this conclusion is based on a very small sample size," stated Ma.

https://lat.ms/2YYaupd

How secret deals could keep a COVID-19 drug out of reach for millions

Licensing deals with manufacturers would prevent the generic version of the drug from being distributed in dozens of countries

By Vidya Krishnan

The American pharmaceutical giant Gilead Sciences is coming under scrutiny for agreements that activists say will restrict global access to remdesivir, an experimental antiviral drug that has shown promise in treating COVID-19.

The Foster City, Calif.-based company has signed confidential licensing deals with nine pharmaceutical manufacturers — including seven in India — that would prevent the generic version of the drug from being distributed in dozens of countries, including the U.S., that account for nearly half the world's population.

Activists and civil society organizations say the licenses allow Gilead to control the global supply of its patented drug even as the World Health Organization warns the COVID-19 pandemic is entering a "new and dangerous phase."

Although the terms of the licenses have not been publicly disclosed, Gilead has said they allow for a cheaper, generic form of remdesivir to be distributed in 127 countries, including nearly all of the world's poorest nations.

But the agreements exclude countries with some of the worst coronavirus outbreaks — including the U.S., Brazil, Russia, Britain and Peru — leading to allegations that Gilead aims to sell only its much costlier, name-brand version of the drug in middle-income and wealthy nations that are desperate for the treatment.

"These bilateral licenses … are highly restrictive in their application," said Brook Baker, a professor of law at Northeastern University. "Gilead excluded these countries because they have commercial potential and because Gilead wants to reserve the right to prevent competition and charge higher prices."

Gilead did not respond to emailed requests for comment.

The company has faced criticism for pricing remdesivir at $390 a vial for governments — or $2,340 per patient for a standard, five-day course — and $520 for U.S. insurance companies, or $3,120 per patient.

The company says the prices are fair when compared with the cost of a longer hospital stay. But critics contend that because Gilead received about $70 million in federal funds to develop the drug, the prices are unfairly high.

One of the Indian companies that has negotiated a license with Gilead, Hetero Labs, has said it will price its generic version at about $71 per vial — still out of reach for many patients in the developing world. A study conducted by Andrew Hill, a drug pricing specialist at the University of Liverpool, estimated that remdesivir could be made for just a few dollars per treatment course.

Remdesivir, originally designed to treat Ebola, has been the subject of intense interest since the National Institutes of Health reported in April that the drug shortened the average recovery time of a COVID-19 patient by four days in a clinical trial. The Food and Drug Administration has approved the drug for emergency use.

With a COVID-19 vaccine believed to be months away — at best — medical experts have identified remdesivir as one of the few effective treatments for a pandemic that has claimed more than half a million lives. Dr. Anthony Fauci, who heads the National Institute of Allergy and Infectious Diseases, called the results of the clinical trial a "really quite important" milestone.

This week the U.S. government announced it had bought up almost all 500,000 treatment courses that Gilead expects to produce through September. That leaves Gilead's licenses with nine generic

drug makers — including companies in Egypt and Pakistan — the best hope for patients in the rest of the world to access the drug.

India has the world's largest generic-drug industry and manufactures some 80% of the drugs sold in the developing world. The country gained a reputation as "the pharmacy of the poor" by driving down the cost of anti-HIV treatment during the AIDS pandemic, thanks to heavy competition among domestic drug makers.

Experts said that by granting licenses to a limited number of companies that are authorized to sell only in certain markets, Gilead would retain control over the global price and marketing of the drug. The licenses "are an attempt to contain the competition by creating an oligopoly," said K.M. Gopakumar, legal advisor for the Third World Network, a think tank that focuses on the pharmaceutical industry. "Gilead not only retains the profitable markets like developed countries, but also eliminates the potential introduction of low-cost drugs into the American market."

As the pandemic continues to rage in poor countries in Asia and Africa, there is growing concern about ensuring an equitable supply of treatment. In March, 150 civil society organizations, including the medical charity Doctors Without Borders, wrote to Gilead expressing concern over the company's attempts to restrict access to remdesivir.

"If remdesivir is found to be effective and is approved, Gilead should not be allowed to enforce its patents nor claim any other types of exclusivities over remdesivir," the group wrote. "No company should profiteer off this pandemic."

Activists also point to another aspect of the licenses: Gilead doesn't receive royalties, but only until another drug or a vaccine is approved to treat or prevent COVID-19. Once that occurs, although the size of the payments hasn't been disclosed, "it is clear that such royalties will add to the price of remdesivir," said Baker, the law professor.

Arguing that private companies have too much control over drug access, a 2016 panel convened by the United Nations secretary-general recommended expanding public funding of research and clinical trials and eliminating monopoly rights over drugs. Health experts say a global treaty is needed, similar to the tobacco control framework adopted at the World Health Organization in 2003 that created universal standards stating the dangers of tobacco and rules governing its production, sale and taxation.

But activists say the U.S., backed by major pharmaceutical companies, has stymied such a treaty for the research and production of drugs and vaccines.

"Though there are many COVID drugs and vaccines under development, there is no guarantee that there would be equitable access," Gopakumar said. "The best way forward to create a legally binding global treaty."

Krishnan is a special correspondent.

https://bit.ly/2C2B1ZE

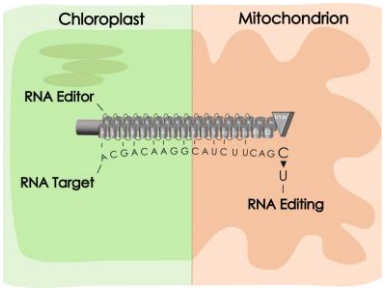
Moss protein corrects genetic defects of other plants

Study by the University of Bonn could contribute to the development of more efficient crops

Almost all land plants employ an army of molecular editors who correct errors in their genetic information. Together with colleagues from Hanover, Ulm and Kyoto (Japan), researchers from the University of Bonn have now transferred one of these proofreaders from the moss Physcomitrium patens (previously known as Physcomitrella patens) into a flowering plant. Surprisingly, it performs its work there as reliably as in the moss itself. The strategy could be suitable for investigating certain functions of the plant energy metabolism in more detail. It may also be valuable for

developing more efficient crops. The study will be published in the journal *The Plant Cell*.

Plants differ from animals in that they are capable of photosynthesis. They do this in specialized "mini-organs" (biologists speak of organelles), the chloroplasts. Chloroplasts produce sugar with the help of sunlight, which in turn is used in other organelles, the mitochondria, to produce energy.



***PPR protein (here called RNA editor) with its target site. RNA editors correct specific errors in the mitochondria and chloroplasts.* © Bastian Oldenkott/Uni Bonn**

Both chloroplasts and mitochondria have their own genetic material. And in both of them this genome contains a lot of errors. "At least that is the case with almost all land plants," explains Dr. Mareike Schallenberg-Rüdinger. The researcher heads a junior research group at the University of Bonn in the Department of Molecular Evolution under Prof. Volker Knoop. "They have to correct these errors so their power supply does not collapse."

In fact, land plants do the same, and in a very complicated way: They do not correct the errors in the genome itself. Instead, they correct the RNA copies that the cell makes of these DNA blueprints, which it then uses to produce certain enzymes, for example. So instead of correcting the original, it only irons out the inaccuracies afterwards in the copies.

Functional despite 400 million years of evolutionary history

Molecular proofreaders, the so-called PPR proteins, are responsible for this. Most of them are specialists for only one particular error in the many gene copies that the cell produces around the clock. These errors occur when, in the course of evolution, a certain chemical building block of DNA (a letter, if you like, in the genetic blueprint) is swapped for another. When the PPR proteins find such a swap, they convert the wrong letter in the RNA copy (the building block cytidine, abbreviated C) into the correct version (uridine, abbreviated U).

"We have now taken a gene for a PPR protein from the moss Physcomitrium patens and transferred it into a flowering plant, the thale cress Arabidopsis thaliana," explains Schallenberg-Rüdinger. "The protein then recognized and corrected the same error there for which it was also responsible in the moss." This is astonishing, since there are more than 400 million years of evolutionary history between Physcomitrium and Arabidopsis. The PPR proteins can therefore also differ significantly in their structure.

For instance, the thale cress contains PPR proteins that can identify errors but still require a separate "white-out" enzyme to correct them. In contrast, the PPR proteins of the moss Physcomitrium perform both tasks simultaneously. "In these cases, the transfer from moss to thale cress works, but the thale cress gene remains inactive in the moss," explains Bastian Oldenkott, doctoral student and lead author of the study. The macadamia nut appeared in evolution a little earlier than Arabidopsis. Its PPR protein being investigated is more similar to that of Physcomitrium. Once introduced into the moss, it therefore performs its service there without any problems.

The study may open up a new way to modify the genetic material of chloroplasts and mitochondria. "Especially for plant mitochondria, this is not yet possible at all," emphasizes Schallenberg-Rüdinger. Using special "designer" PPR genes, for example, one might specifically render certain genome transcripts unusable and test how this affects the plant. In the medium term, this may also result in new findings for breeding particularly high-yielding, high-performance varieties. First, however, the

researchers hope to gain insights into the complex interaction of genes in the functioning of chloroplasts and mitochondria.

The research carried out by co-authors Prof. Hans-Peter Braun and Dr. Jennifer Senkler from the University of Hanover proves that this approach can actually work. They were able to clarify what the PPR protein from the moss is needed for: If it is missing, the plant is no longer able to correctly assemble the machinery for the so-called respiratory chain in the mitochondria, which is used to generate energy. The work in the thale cress was carried out in cooperation with Matthias Burger (University of Ulm) and Prof. Mizuki Takenaka (University of Kyoto), a fine example of successful international cooperation.

Publication: Bastian Oldenkott, Matthias Burger, Anke-Christiane Hein, Anja Jörg, Jennifer Senkler, Hans-Peter Braun, Volker Knoop, Mizuki Takenaka and Mareike Schallenberg-Rüdinger: One C-to-U RNA editing site and two independently evolved editing factors: testing reciprocal complementation with DYW-type PPR proteins from the moss Physcomitrium (Physcomitrella) patens and the flowering plants Macadamia integrifolia and Arabidopsis thaliana; The Plant Cell; DOI: https://doi.org/10.1105/tpc.20.00311

https://bit.ly/2YYmx5V

Study explains potential causes for 'happy hypoxia' condition in COVID-19 patients

Findings could prevent unnecessary intubation

MAYWOOD, IL- A new research study provides possible explanations for COVID-19 patients who present with extremely low, otherwise life-threatening levels of oxygen, but no signs of dyspnea (difficulty breathing). This new understanding of the condition, known as silent hypoxemia or "happy hypoxia," could prevent unnecessary intubation and ventilation in patients during the current and expected second wave of coronavirus.

The condition "is especially bewildering to physicians as it defies basic biology," said Martin J. Tobin, MD, Loyola Medicine and Edward J. Hines Jr. VA Hospital pulmonologist and critical care specialist, and professor, Loyola University Chicago Stritch School of Medicine. Dr. Tobin is lead author of the study, "Why COVID-19 Silent Hypoxemia is Baffling to Physicians," appearing recently in the online *American Journal of Respiratory and Critical Care Medicine*.

"In some instances, the patient is comfortable and using a phone at a point when the physician is about to insert a breathing (endotracheal) tube and connect the patient to a mechanical ventilator," said Dr. Tobin, "which while potentially lifesaving carries its own set of risks."

The study included 16 COVID-19 patients with very low levels of oxygen (as low as 50%; normal blood oxygen saturation is between 95 and 100%), without shortness of breath or dyspnea, and found that "several pathophysiological mechanisms account for most, if not all, cases of silent hypoxemia. This includes the initial assessment of a patient's oxygen level with a pulse oximeter.

"While a pulse oximeter is remarkably accurate when oxygen readings are high, it markedly exaggerates the severity of low levels of oxygen when readings are low," said Dr. Tobin. "Another factor is how the brain responds to low levels of oxygen. As oxygen levels drop in patients with COVID-19, the brain does not respond until oxygen falls to very low levels--at which point a patient typically becomes short of breath," he said.

In addition, more than half of the patients had low levels of carbon dioxide, which may diminish the impact of an extremely low oxygen level.

"It is also possible that the coronavirus is exerting a peculiar action on how the body senses low levels of oxygen," said Dr. Tobin, which could be linked to the lack of smell, experienced by two-thirds of COVID-19 patients.

While acknowledging that further research is needed, the study concludes that "features about COVID-19 that physicians find

baffling become less strange when viewed in the light of long-established principles of respiratory physiology."

"This new information may help to avoid unnecessary endotracheal intubation and mechanical ventilation, which presents risks, when the ongoing and much anticipated second wave of COVID-19 emerges," said Dr. Tobin.

https://bit.ly/3e2b3CX

Dominant Coronavirus Strain Appears to Be a Mutated, More Virulent Version, Study Finds

Novel coronavirus that dominates the world today infects human cells more readily than the original that emerged in China

Ivan Couronne, AFP

The genetic variation of the novel coronavirus that dominates the world today infects human cells more readily than the original that emerged in China, according to a new study published in the journal *Cell* on Thursday.

The lab-based research suggests this current mutation is more transmissible between people in the real world compared to the previous iteration, but this hasn't yet been proven.

"I think the data is showing that there is a single mutation that actually makes the virus be able to replicate better, and maybe have high viral loads," Anthony Fauci, the United States's top infectious disease specialist, who wasn't involved in the research, commented to *Journal of the American Medical Association*.

"We don't have a connection to whether an individual does worse with this or not. It just seems that the virus replicates better and may be more transmissible, but this is still at the stage of trying to confirm that," he added.

Researchers from the Los Alamos National Laboratory in New Mexico and Duke University in North Carolina partnered with the University of Sheffield's COVID-19 Genomics UK research group to analyze genome samples published on GISAID, an international resource for sharing genome sequences.

They found that the current variant, called "D614G", makes a small but potent change in the "spike" protein that protrudes from the surface of the virus, which it uses to invade and infect human cells.

The scientists first posted their paper to the medical preprint site bioRxiv in April, where it received 200,000 hits, a record.

But it was initially criticized because the scientists had not proved that the mutation itself was responsible for its domination; it could have benefitted from other factors or from chance.

The team therefore carried out additional experiments, many at the behest of the editors of *Cell*.

They analyzed the data of 999 British patients hospitalized with COVID-19 and observed that those with the variant had more viral particles in them, but without this changing the severity of their disease.

Laboratory experiments meanwhile showed that the variant is three to six times more capable of infecting human cells. "It seems likely that it's a fitter virus," said Erica Ollmann Saphire, who carried out one of the experiments at La Jolla Institute for Immunology.

'This variant is the pandemic'

But everything at this stage can only be said to be "probable": in vitro experiments often do not replicate the dynamics of a pandemic.

As far as we know, although the variant circulating right now is more "infectious," it may or may not be more "transmissible" between people.

At any rate, said Nathan Grubaugh, a virologist at the Yale School of Public Health who was not part of the research: The expansion of the variant "whether through natural selection or chance, means that this variant now is the pandemic".

Writing in a commentary piece, Grubaugh added that, for the general public, these results don't change much.

"While there are still important studies needed to determine if this will influence drug or vaccine development in any meaningful way, we don't expect that D614G will alter our control measures or make individual infections worse," he said.

"It's more of a live look into science unfolding: an interesting discovery was made that potentially touches millions of people, but we don't yet know the full scope or impact."

https://bit.ly/2YYozD5

Protective antibodies identified for rare, polio-like disease in children

Researchers have isolated human monoclonal antibodies that potentially can prevent acute flaccid myelitis (AFM)

WEST LAFAYETTE, Ind. -- Researchers at Vanderbilt University Medical Center, Purdue University and the University of Wisconsin-Madison have isolated human monoclonal antibodies that potentially can prevent a rare but devastating polio-like illness in children linked to a respiratory viral infection.

The illness, called acute flaccid myelitis (AFM), causes sudden weakness in the arms and legs following a fever or respiratory illness. More than 600 cases have been identified since the U.S. Centers for Disease Control and Prevention began tracking the disease in 2014.

There is no specific treatment for AFM, which tends to strike in the late summer or early fall and which has been associated with some deaths. However, the disease has recently been linked to a group of respiratory viruses called enterovirus D68 (EV-D68).

Researchers at the Vanderbilt Vaccine Center isolated antibody-producing blood cells from the blood of children who had previously been infected by EV-D68. By fusing the blood cells to fast-growing myeloma cells, the researchers were able to generate a panel of monoclonal antibodies that potently neutralized the virus in laboratory studies.

Colleagues at Purdue determined the structure of the antibodies, which shed light on how they specifically recognize and bind to EV-D68. One of the antibodies protected mice from respiratory and neurologic disease when given either before or after infection by the enterovirus.

Comments from researchers

"We were excited to isolate potent human antibodies that inhibit this devastating polio-like virus, and these studies will form the basis for taking them forward to clinical trials," Dr. James Crowe, director, Vanderbilt Vaccine Center; Ann Scott Carell Chair and professor of Pediatrics and Pathology, Microbiology and Immunology in the Vanderbilt University School of Medicine.

"Studying infectious disease from a very basic level and applying the results in an animal model of disease is very powerful; hopefully, our studies will translate to a future therapeutic for this disease in children," Richard Kuhn, Purdue's Trent and Judith Anderson Distinguished Professor in Science; Krenicki Family Director, Purdue Institute of Inflammation, Immunology and Infectious Disease

The study was supported by National Institutes of Health grants HL069765, AI117905, HL070831, AI104317 and AI011219, and the Center for Structural Genomics of Infectious Diseases.

ABSTRACT

Human antibodies neutralize enterovirus D68 and protect against infection and paralytic disease

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Enterovirus D68 (EV-D68) causes outbreaks of respiratory illness, and there is increasing evidence that it causes outbreaks of acute flaccid myelitis (AFM). There are no licensed therapies to prevent or treat EV-D68 infection or AFM disease. We isolated a panel of EV-D68-reactive human monoclonal antibodies that recognize diverse antigenic variants from participants with prior infection. One potently neutralizing cross-reactive antibody, EV68-228, protected mice from respiratory and neurologic disease when given either before or after infection. Cryo-electron microscopy studies revealed that EV68-228 and another potently neutralizing antibody (EV68-159) bound around the fivefold or threefold axes of symmetry on virion particles, respectively. The structures suggest diverse mechanisms of action by these antibodies. The high potency and effectiveness observed in vivo suggest that antibodies are a mechanistic correlate of protection against AFM disease and are candidates for clinical use in humans with EV-D68 infection.

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The sixth sense of animals: An early warning system for earthquakes?

Investigating whether cows, sheep, and dogs can actually detect early signs of earthquakes

by University of Konstanz

Even today, nobody can reliably predict when and where an earthquake will occur. However, eyewitnesses have repeatedly reported that animals behave unusually before an earthquake. In an international cooperation project, researchers from the Max Planck Institute of *Animal Behavior* in Konstanz/Radolfzell and the Cluster of Excellence Center for the Advanced Study of Collective Behavior at the University of Konstanz, have investigated whether cows, sheep, and dogs can actually detect early signs of earthquakes. To do so, they attached sensors to the animals in an earthquake-prone area in Northern Italy and recorded their movements over several months. The movement data show that the animals were unusually restless in the hours before the earthquakes. The closer the animals were to the epicenter of the impending quake, the earlier they started behaving unusually. The movement profiles of different animal species in different regions could therefore provide clues with respect to the place and time of an impending earthquake. Experts disagree about whether earthquakes can be exactly predicted. Nevertheless, animals seem to sense the impending danger hours in advance. For example, there are reports that wild animals leave their sleeping and nesting places immediately before strong quakes and that pets become restless. However, these anecdotal accounts often do not stand up to scientific scrutiny because the definition of unusual behavior is often too unclear and the observation period too short. Other factors could also explain the behavior of the animals.

In order to be able to use animal activity patterns as a kind of early warning system for earthquakes, the animals would have to show measurable behavioral changes. Moreover, if they do indeed react to weak physical changes immediately before an earthquake, they should react more strongly the closer they are to the epicenter of the quake.

18,000 earthquakes and 13 sensitive animals

In an international cooperation project, researchers from the Max Planck Institute of Animal Behavior in Konstanz/Radolfzell and the Center for the Advanced Study of Collective Behavior, a Cluster of Excellence at the University of Konstanz, have investigated whether animals really do this. On an Italian farm in an earthquake-prone area, they attached accelerometers to the collars of six cows, five sheep, and two dogs that had already displayed unusual behavior before earthquakes. The researchers then recorded their movements continuously over several months. During this period, official authorities reported about 18,000 earthquakes in the region. In addition to many small and hardly noticeable quakes, there were also 12 earthquakes with a strength of 4 or higher on the Richter scale.

The researchers then selected the quakes that triggered statistically relevant earth movements on the farm. These included strong quakes up to 28 km away as well as weaker quakes, the epicenters of which were very close to the farm. However, instead of explicitly looking for abnormal behaviors in the period before these events, the researchers chose a more cautious approach. They first marked all behavioral changes of the animals that were unusual according to objective, statistical criteria. "In this way, we ensure that we not only establish correlations retrospectively but also that we really do have a model that can be used for predictions," says Professor Martin Wikelski, director at the Max Planck Institute of Animal Behavior and Principal Investigator at the Center for the Advanced Study of Collective Behavior.

The data—measured as body acceleration of each farm animal (indicating activity level)—were evaluated using statistical models drawn from financial econometrics. "Because every animal reacts differently in size, speed and according to species, the animal data resemble data on heterogenous financial investors," explains co-author Winfried Pohlmeier, Professor of Econometrics at the University of Konstanz and Principal Investigator at the Center for the Advanced Study of Collective Behavior. The scientists also considered other disturbance factors such as natural changes in animal activity patterns over the day.

Unusual behavioral patterns before an earthquake

In this way, the researchers discovered unusual behavioral patterns up to 20 hours before an earthquake. "The closer the animals were to the epicenter of the impending shock, the earlier they changed their behavior. This is exactly what you would expect when physical changes occur more frequently at the epicenter of the impending earthquake and become weaker with increasing distance," explains Wikelski. However, this effect was clear only when the researchers looked at all animals together. "Collectively, the animals seem to show abilities that are not so easily recognized on an individual level."

It is still unclear how animals can sense impending earthquakes. Animals may sense the ionization of the air caused by the large rock pressures in earthquake zones with their fur. It is also conceivable that animals can smell gasses released from quartz crystals before an earthquake.

Earthquake early warning system

Real-time data measured by the researchers and recorded since December 2019 show what an animal earthquake early warning system could look like: a chip on the collar sends the movement data to a central computer every three minutes. This triggers a warning signal if it registers a significantly increased activity of the animals for at least 45 minutes.

The researchers have once received such a warning. "Three hours later, a small quake shook the region," says Wikelski. "The epicenter was directly below the stables of the animals."

However, before the behavior of animals can be used to predict earthquakes, researchers need to observe a larger number of animals over longer periods of time in different earthquake zones around the world. For this, they want to use the global animal observation system ICARUS on the International Space Station ISS, which will start its scientific operation in a few weeks.

More information: *Martin Wikelski et al. Potential short-term earthquake forecasting by farm animal monitoring, Ethology (2020). DOI: 10.1111/eth.13078*

Journal information: *Animal Behavior*

https://nyti.ms/2BGJPVq

The Pandemic's Big Mystery: How Deadly Is the Coronavirus?

Even with more than 500,000 dead worldwide, scientists are struggling to learn how often the virus kills. Here's why.

By Donald G. McNeil Jr.

More than six months into the pandemic, the coronavirus has infected more than 11 million people worldwide, killing more than 525,000. But despite the increasing toll, scientists still do not have a definitive answer to one of the most fundamental questions about the virus: How deadly is it?

A firm estimate could help governments predict how many deaths would ensue if the virus spread out of control. The figure, usually called the infection fatality rate, could tell health officials what to expect as the pandemic spreads to densely populated nations like Brazil, Nigeria and India.

In even poorer countries, where lethal threats like measles and malaria are constant and where hard budget choices are routine, the number could help officials decide whether to spend more on oxygen concentrators or ventilators, or on measles shots and mosquito nets.

The question became even more complex last month, when the Centers for Disease Control and Prevention released data suggesting that for every documented infection in the United States, there were 10 other cases on average that had gone unrecorded, probably because they were very mild or asymptomatic.

If there are many more asymptomatic infections than once thought, then the virus may be less deadly than it has appeared. But even that calculation is a difficult one.

On Thursday, after the World Health Organization held a two-day online meeting of 1,300 scientists from around the world, the agency's chief scientist, Dr. Soumya Swaminathan, said the consensus for now was that the I.F.R. is about 0.6 percent — which means that the risk of death is less than 1 percent.

Although she did not note this, 0.6 percent of the world's population is 47 million people, and 0.6 percent of the American population is 2 million people. The virus remains a major threat.

At present, countries have very different case fatality rates, or C.F.R.'s, which measure deaths among patients known to have had Covid-19. In most cases, that number is highest in countries that have had the virus the longest.

According to data gathered by The New York Times, China had reported 90,294 cases as of Friday and 4,634 deaths, which is a C.F.R. of 5 percent. The United States was very close to that mark. It has had 2,811,447 cases and 129,403 deaths, about 4.6 percent.

In the chaos that ensues when a new virus hits a city hard, thousands of people may die and be buried without ever being tested, and certainly without them all being autopsied.

It is never entirely clear how many died of the virus and how many died of heart attacks, strokes or other ills. That has happened in both New York City and in Wuhan, China, where the outbreak began.

Normally, once the chaos has subsided, more testing is done and more mild cases are found — and because the denominator of the fraction rises, fatality rates fall. But the results are not always consistent or predictable.

Ten sizable countries, most of them in Western Europe, have tested bigger percentages of their populations than has the United States, according to Worldometer, which gathers statistics. They are Iceland, Denmark, Spain, Portugal, Belgium, Ireland, Italy, Britain, Israel and New Zealand.

But their case fatality rates vary wildly: Iceland's is less than 1 percent, New Zealand's and Israel's are below 2 percent. Belgium, by comparison, is at 16 percent, and Italy and Britain at 14 percent.

Both figures — the infection fatality rate and the case fatality rate — can differ quite a bit by country.

So far, in most countries, about 20 percent of all confirmed Covid-19 patients become ill enough to need supplemental oxygen or even more advanced hospital care, said Dr. Janet Diaz, head of clinical

care for the W.H.O.'s emergencies program. Whether those patients survive depends on a host of factors, including age, underlying illnesses and the level of medical care available.

Death rates are expected to be lower in countries with younger populations and less obesity, which are often the poorest countries. Conversely, the figures should be higher in countries that lack oxygen tanks, ventilators and dialysis machines, and where many people live far from hospitals. Those are also often the poorest countries.

The W.H.O. and various charities are scrambling to purchase oxygen equipment for poor and middle-income nations in which the coronavirus is spreading.

And now, new factors are being introduced into the equation. For example, new evidence that people with Type A blood are more likely to fall deathly ill could change risk calculations. Type A blood is relatively rare in West Africa and South Asia, and very rare among the Indigenous peoples of South America.

Before this week's meeting, the W.H.O. had no official I.F.R. estimate, Oliver Morgan, the agency's director of health emergency information and risk assessment, said in an interview in early June.

Instead, it had relied on a mix of data sent in by member countries and by academic groups, and on a meta-analysis done in May by scientists at the University of Wollongong and James Cook University in Australia.

Those researchers looked at 267 studies in more than a dozen countries, and then chose the 25 they considered the most accurate, weighting them for accuracy and averaged the data. They concluded that the global I.F.R. was 0.64 percent.

The C.D.C. relies on a "symptomatic case fatality ratio" that "is not necessarily equivalent to the number of reported deaths per reported cases." The best estimate for the United States is 0.4 percent, according to a set of planning scenarios released in late May.

The agency did not respond to requests to explain how it arrived at that figure, or why it was so much lower than the W.H.O.'s estimate. By comparison, 0.4 percent of the United States population is 1.3 million people.

The 25 studies that the Australian researchers considered the most accurate relied on very different methodologies. One report, for example, was based on diagnostic PCR tests of all passengers and crew aboard the Diamond Princess, the cruise ship that docked in Japan after it was overcome by the coronavirus. Another study drew data from an antibody survey of 38,000 Spaniards, while another included only 1,104 Swedes.

The current W.H.O. estimate is based on later, larger studies of how many people have antibodies in their blood; future studies may further refine the figure, Dr. Swaminathan said.

But there is "a lot of uncertainty" about how many silent and untested carriers there are, Dr. Morgan of the W.H.O. said.

To arrive at the C.D.C.'s new estimate, researchers tested samples from 11,933 people for antibodies to the coronavirus in six regions in the United States. New York City reported 53,803 cases by April 1, but the actual number of infections was 12 times higher — nearly 642,000, the agency estimated.

New York City's prevalence of 7 percent in the C.D.C. study was well below the 21 percent estimated in a state survey in April. But that number was based on people recruited at supermarkets, and so the results may have been biased toward people out shopping during a pandemic — often the young, who have been less affected.

The global fatality rates could still change. With one or two exceptions, like Iran and Ecuador, the pandemic first struck wealthier countries in Asia, Western Europe and North America where advanced medical care was available. Now it is spreading widely in India, Brazil, Mexico, Nigeria and other countries where millions are crowded into slums, lockdowns have been relatively

brief and hospitals have few resources. But the death rates may also shift in wealthier northern countries as winter approaches. Most of the spread of the virus in Europe and North America has taken place during mild or warm weather in the spring and summer.

Many experts fear that infections and deaths will shoot up in the fall as colder weather forces people indoors, where they are more likely to infect one another. Discipline about wearing masks and avoiding breathing on one another will be even more important then.

In each of the eight influenza pandemics to hit the United States since 1763, a relatively mild first wave — no matter what time of year it arrived — was followed by a larger, much more lethal wave a few months later, noted Michael T. Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota.

More than a third of all the people killed by the Spanish flu, which lasted from March 1918 to late 1920, died in the short stretch between September and December 1918 — about six months after a first, relatively mild version of what may have been the same virus broke out in western Kansas. “We will go much higher in the next 12 to 18 months,” Dr. Osterholm said. Because this is a coronavirus, not influenza, it may not follow the same pattern, but it is “a much more efficient transmitter than influenza.”

https://bit.ly/2NY7zqj

There's Now an Artificial Cartilage Gel Strong Enough to Work in Knees

A material that is a match to the cartilage found in our bodies

David Nield

It's no surprise that scientists have struggled to find an artificial substitute for natural knee cartilage: it's an amazing biological substance that combines the properties of a soft cushion and a tough barrier to keep our busy leg joints from harm.

But it looks like we've arrived at a long-awaited breakthrough - researchers think they may have finally developed a material that is a match to the cartilage found in our bodies, and could be used as a replacement after injuries or in old age.

"We set out to make the first hydrogel that has the mechanical properties of cartilage," says chemist Ben Wiley from Duke University.

A significant number of people could benefit from something like this, as more than 790,000 knee replacements happen in the US every year. Currently those replacements - which involve pretty invasive surgery - may only last for a couple of decades before they need to be replaced again.

Imagine if you could replace just the worn-out or damaged cartilage, instead of having to rip out the entire knee joint.

As with other hydrogels, the main ingredients in this new material are water-absorbing polymers: in this case one polymer made of spaghetti-like strands, intertwined with another polymer that's less flexible and more basket-like. A third polymer, made of cellulose fibres, acts as a mesh holding everything together.

When the material is stretched, it's the third polymer that keeps the gel intact. When it's squeezed, polymers one and two – with negative charges running along their length – repel each other and stick to water, so the original shape can be restored.

The hydrogel passed with top marks in both these crucial categories – stretching and squishing – and showed better performance than other existing hydrogels. In one test of 100,000 repeated pulls, the artificial cartilage held up as well as the porous titanium material used in bone implants.

"Only this combination of all three components is both flexible and stiff and therefore strong," says materials scientist Feichen Yang, also from Duke University.

In tests where the hydrogel was rubbed against natural cartilage – a million times, no less – it was shown to be just as resistant to wear and tear as the real thing, and more durable than the artificial cartilage that's used today in big toe operations (notable because that gel has regulatory approval in the US).

However, getting this new hydrogel approved for use in humans could take up to three years, the researchers say – so there's some way to go yet before patients will be able to take advantage of the innovation.

So far the non-toxicity of the hydrogel has only been tested against lab-grown cells. The next step is to see if it can be safely transplanted into sheep, and only after that can trials on actual people get underway.

Eventually though, the new material shows plenty of promise as an option for those experiencing knee pain: they might one day be able to restore a joint to full working order, without long recovery times or a short lifespan for the replacement cartilage. It should help until we learn how to regrow our own cartilage, at least.

The research has been published in *Advanced Functional Materials*.

https://bit.ly/2C49x5T

Tranquil Planetary System Just 11 Light-Years Away Raises Hopes of Habitability

It could soon become one of the most studied systems in our local neighbourhood

Michelle Starr

Finding a potentially habitable exoplanet isn't as easy as you might think. Orbiting at a temperate distance from the host star is just the first step. Size and composition also play a role - as does the level of flare activity in the star. And all of that doesn't mean much if the system is so far away we can't take detailed observations to find out if it is habitable.

A newly discovered system looks like it could tick a good number of those boxes. And it's incredibly close - just 10.7 light-years away from the Solar System. This means it could soon become one of the most studied systems in our local neighbourhood.

"These planets will provide the best possibilities for more detailed studies, including the search for life outside our Solar System," said astrophysicist Sandra Jeffers of the University of Göttingen in Germany.

The star is called Lacaille 9352, or GJ 887. In its orbit, scientists have found two exoplanets that could be terrestrial - rocky, like Earth and Mars.Tantalisingly, there's also a hint of a third terrestrial exoplanet orbiting at a greater distance - a distance that could make it temperate, neither too hot nor too cold to prohibit liquid water on the surface.

This hint of the third planet is considered inconclusive at this stage, but the discovery of the two close-orbit planets (and the potential for the third planet) are enough to warrant a much closer look at the GJ 887 system.

The star itself, which is about half the mass of the Sun, is a red dwarf - a type of long-lived, relatively cool, small star - which is the most common type of star in the Milky Way.

We've found a lot of exoplanets orbiting red dwarfs; and, because these stars are not as hot as stars like the Sun, the habitable temperate zone for orbiting planets is a lot closer than it is for Earth.

The problem with red dwarfs, however, is that they're often rather rowdy, spitting out intense stellar radiation and flares that would render many of these close planets uninhabitable, by stripping their atmospheres.

This is where GJ 887 stands out. For a red dwarf, it's actually incredibly tranquil - it has very low starspot activity, and its brightness remains more or less uniform. This makes it of great

interest to astronomers with the Red Dots survey - a project to search for terrestrial worlds around nearby red dwarf stars.

As part of this survey, the star was studied for three months using the European Southern Observatory's High Accuracy Radial velocity Planet Searcher instrument at the La Silla 3.6 metre telescope in Chile.

This sensitive instrument stares at stars, looking for the very slight changes in their light as they move just a tiny bit, tugged about by the gravitational influence of planets in orbit around them. In GJ 887, these movements revealed two distinct periodic signals.

The amount the star moves can be used to calculate the mass of the objects doing the tugging. This is how the researchers discovered the two exoplanets, GJ 887b and GJ 887c, confirmed by matching it up with 200 days of archival data obtained from 2002 to 2004.

GJ 887b has a minimum mass of around 4.2 times the mass of Earth, and it orbits the star once every 9.3 days. GJ 887c has a minimum mass of around 7.6 times the mass of Earth, and orbits the star once every 21.8 days.

Those masses put the exoplanets in the 'super-Earth' category, but without further study, it's impossible to tell if they're terrestrial or gaseous. At their respective proximities to the star, the two planets are unlikely to be habitable, but they're very close to the inner edge of the habitable zone.

The third signal, however - if it turns out to represent an exoplanet - would constitute an 8.3 Earth-mass super-Earth right in the middle of the star's habitable zone, with an orbital period of 50.7 days. There's just one problem - the signal was only detected once in the HARPS data.

This suggests that there might not be an exoplanet there at all. "We regard the third signal at ~50 days as dubious and likely related to stellar activity," the researchers wrote in their paper, but the possibility cannot be ruled out with the current data.

That means researchers will be going back for another look, to see if that signal can be picked up again, and planetary scientists will also want to take closer looks at GJ 887b and GJ 887c anyway.

Because of the lack of flare activity from the star, the two exoplanets may have retained their atmospheres, and because the light from the star is so steady, those atmospheres could be detectable as light from the star bounces off them.

Our current instruments aren't yet capable of measuring this, but it's one of the tasks the James Webb Space Telescope, scheduled for launch next year, has been built to perform. It will be sensitive enough to directly image nearby exoplanets, which should revolutionise the field of planetary science.

"These types of observations could tell us about the atmospheric makeup of these planets," astronomer Melvyn Davies of Lund Observatory in Sweden, who was not involved in the research, explains an article accompanying the paper.

"If further observations confirm the presence of the third planet in the habitable zone, then GJ 887 could become one of the most studied planetary systems in the Solar neighbourhood."

The research has been published in *Science*.