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Swine flu vaccination in pregnant women did not increase risk of autism in offspring

Large study refutes any association of flu vaccination with autism-spectrum disorder in the offspring.

Two recent studies were unable to rule out that H1N1 ("swine flu") vaccination ("Pandemrix") and seasonal influenza vaccination given to pregnant women might be associated with autism-spectrum disorder in the offspring. Now, a large study by researchers at Karolinska Institutet in Sweden, published in the journal *Annals of Internal Medicine*, refutes any such association.

Autism spectrum disorder is a severe neurodevelopmental childhood disorder characterized by impaired communication, lack of social skills and repetitive behavior. The disease has its onset in childhood.

While some studies indicate that influenza vaccination during pregnancy protects against morbidity in both the woman and her offspring, the long-term risks of H1N1 vaccination during fetal life have not been examined in detail. However two recent studies were unable to rule out that offspring to women undergoing influenza or H1N1 influenza vaccination during pregnancy, and especially during the first trimester, were at increased risk of autism-spectrum disorder.

Researchers from Karolinska Institutet, linked vaccination data in pregnant women from seven Swedish healthcare regions in 2009-2010 to the Swedish Medical Birth Register and the Swedish National Patient Register to identify autism-spectrum disorder in the offspring.

The importance of vaccination research

Of the 39,726 vaccine-exposed children, 394 (cumulative incidence, 1.0%) had a diagnosis of autism-spectrum disorder during the six-year follow-up compared with 330 (1.1%) among 29,293 unexposed children. Adjusting for potential confounders, H1N1 vaccine exposure during fetal life was not associated with a later childhood diagnosis of autism-spectrum disorder (adjusted hazard ratio=0.95; 95%CI=0.81-1.12). Results were similar for vaccinations in the first pregnancy trimester.

"Our null findings are important since some people have suspected that vaccinations could cause autism, and the anti-vaccine movement seems to be growing in the Western world," says lead author, Professor Jonas F Ludvigsson, pediatrician at Örebro University Hospital and professor at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet. "H1N1 vaccination has previously been linked to an increased risk of narcolepsy in young people, but vaccinating pregnant women does not seem to influence the risk of autism-spectrum disorder in the offspring,"

He continues: "Vaccination research has never been more important. Anticipating a vaccine against COVID-19, millions of pregnant women are likely to be offered such a vaccination. While our research group did not study COVID-19 vaccine effects, our research on H1N1 vaccination adds to the current knowledge about vaccines, pregnancy and offspring disease in general."

Adjusted for other factors

The researchers adjusted their analyses for such confounders as maternal smoking, height-weight, maternal age and comorbidity in order to minimize the influence of other factors that might explain any association between vaccination and autism.

"Without taking such factors into consideration, so-called confounding may create spurious associations that do not reflect a true association," adds co-author, Ass. Prof. Bjorn Pasternak, Department of Medicine, Karolinska Institutet (Solna).

This project was supported by grants from the Swedish Research Council, and the Swedish Council for Working Life and Social Research. Dr Pasternak was supported by the

Strategic Research Area Epidemiology program at Karolinska Institutet and the Swedish Research Council.
Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from the Janssen corporation.
Publication: "Maternal influenza A(H1N1) immunization during pregnancy and risk of offspring autism spectrum disorder: A cohort study" Jonas F. Ludvigsson, Henric Winell, Sven Sandin, Sven Cnattingius, Olof Stephansson, and Bjorn Pasternak. Annals Internal Medicine. Online August 31, 2020, doi: 10.7326/M20-0167

https://bit.ly/3bnYHoQ

Dodder uses the flowering signal of its host plant to flower

The plant parasite eavesdrops on its host and uses the host's mobile floral stimulus for timing its own flowering

The plant genus Cuscuta consists of more than 200 species that can be found almost all over the world. The parasites, known as dodder, but also called wizard's net, devil's hair or strangleweed, feed on other plants by attaching themselves to their hosts via a special organ, the haustorium, and withdrawing nutrients from them.

Dodder Cuscuta australis on a soybean host plant: The parasite is flowering and has already produced seed capsules. It uses its host's flowering signal for flower formation. **Jingxiong Zhang, Kunming Institute of Botany, Chinese Academy of Sciences, China**

They have neither roots nor leaves. Without leaves, they are hardly able to photosynthesize. Without roots they cannot absorb nutrients and water from the soil. On the other hand, they are integrated into the internal communication network of their host plants and can even pass on warning signals from plant to plant (see our press release Dodder: a parasite involved in the plant alarm system, July 24, 2017).

A team of scientists led by Jianqiang Wu, who has been the leader of a Max Planck Partner Group at the Kunming Institute of Botany, Chinese Academy of Sciences, now asked how the parasites manage to synchronize flowering with their hosts. They had observed that plants of the Australian dodder (Cuscuta australis) adjusted the time of their flowering to that of their respective host plant species.

Flower promoting signal FT from the host also determines the flowering time of the parasite

"The flowering time is controlled by leaves, as leaves can sense environmental cues and synthesize the flowering signal, a protein named FLOWERING LOCUS T (FT), which travels through the plant vascular system. We therefore wondered how a leafless parasite such as Cuscuta australis controls the timing of its flowering," says lead investigator Jianqiang Wu. In 2018, his team had sequenced the genome of C. australis and found that many genes important for regulation of flowering time were lost in C. australis genome. Therefore, C. australis seems to be unable to activate its own flowering mechanism.

Based on the fact that FT proteins are mobile signals, the researchers hypothesized that dodder eavesdrops on the flowering signals produced by the leaves of its host and uses them for producing its own flowers. To prove this eavesdropping scenario, they used genetically modified host plants in which the expression of FT genes had been altered, and this indeed affected the flowering time of the parasite. They also coupled the FT protein to a green fluorescent protein (GFP) as a tag and detected the host plant's flower promoting signal in the parasite: The tagged FT protein had migrated from host to parasite.

For dodder, it is the best strategy to synchronize flowering with that of its host. If it flowers much later than its host does, it may not be able to produce seeds at all, as the nutrients in the host are rapidly drained by the host's reproductive tissues. The host may even rapidly die before the parasite can even starts to produce seeds.

However, if dodder flowers too early, its growth is likely prematurely ended and it may not be able to produce as many seeds as the dodder plants whose flowering time is synchronized with that of their hosts.

Regressive Evolution: Gene loss as an advantage

In the course of evolution, plant parasites have lost certain traits and "outsourced" physiological processes. As a result, various genes in their genomes may be lost. "This work establishes that for a plant parasite, losing control over flowering processes can be advantageous, as it allows the parasite to hijack its host's mobile flowering signals for its own use. It can thereby readily synchronize its physiology with that of its host", says co-author Ian Baldwin, director of the Department Molecular Ecology at the Max Planck Institute for Chemical Ecology. Because of the gene loss, dodder may be able to better adapt to the parasitic lifestyle and ultimately increase its fitness.

Original Publication:

Shen, G., Liu, N., Zhang, J., Xu, Y., Baldwin, I. T., Wu, J. (2020). Cuscuta australis (dodder) parasite eavesdrops on the host plants' FT signals to flower. Proceedings of the National Academy of Sciences of the United States of America, DOI: 10.1073/pnas.2009445117 https://doi.org/10.1073/pnas.2009445117

https://bit.ly/3gWvani

Fungi in gut linked to higher Alzheimer's risk can be reduced through ketogenic diet

Specific fungi in the gut associated with Alzheimer's and in people with mild cognitive impairment (MCI) can be beneficially altered by eating a modified Mediterranean diet

Winston-Salem, N. C. - Specific fungi in the gut associated with a higher risk of Alzheimer's disease and found in people with mild cognitive impairment (MCI) can be altered in a beneficial manner by eating a modified Mediterranean diet, researchers at Wake Forest School of Medicine have found.

The small study is published in the current online edition of the journal *EBioMedicine*.

"Our study reveals that unique fungi co-living with bacteria in the gut of patients with MCI can be modulated through a Mediterranean ketogenic diet," said principal investigator Hariom Yadav, assistant professor of molecular medicine at Wake Forest School of Medicine, part of Wake Forest Baptist Health.

In the single-center, randomized, double-blind crossover pilot study, Yadav's team identified the organisms in the gut microbiome by sequencing the fungal rRNA ITS1 gene in 17 older adults (11 with diagnosed MCI and six with normal cognition) before and after a six-week intervention of a modified Mediterranean ketogenic diet or the American Heart Association Diet to determine its correlation with Alzheimer's markers in cerebrospinal fluid and gut bacteria.

"Although we do not fully understand how these fungi contribute to Alzheimer's disease, this is the first study of its kind to reveal their role in our mental health, which we hope will ignite thinking in the scientific community to develop better understanding of them in relation to Alzheimer's disease," Yadav said. "It also indicates that dietary habits such as eating a ketogenic diet can reduce harmful fungi in the gut which might help in reducing Alzheimer's disease processes in the brain."

The work was supported by the National Institutes of Health, P30AG049638, R01AG055122, and R01AG018915; the Pepper Older Americans for Independence Center, P30AG21332; and the Department of Defense, W81XWH-19-1-0236.

https://bit.ly/31Z0VrX

Why Blood Clots Are a Major Problem in Severe Covid-19

Out-of-control clotting can endanger some patients even after the virus has gone. Researchers are trying to understand the problem and how to treat it.

By Amber Dance Knowable magazine

In the early days of the New York Covid-19 outbreak, as March turned to April, hematologist Jeffrey Laurence was called to consult on the case of a 32-year-old bodybuilder. Nurses had noticed an odd rash on his buttocks, "as if you had kind of peeled away the skin layer and were seeing what blood vessels look like on his bottom," recalls Laurence, who works at Weill Cornell Medicine in New York City. The vessels were outlined so clearly because the blood inside was coagulating, almost jelly-like.

Within a couple of weeks, Laurence observed several similar, striking cases — making some of the earliest observations that the blood-clotting process could go horribly awry in severe instances of Covid-19. Researchers and clinicians are working to understand why, and trying medications to tamp down the clotting or the intense immune responses that seem to underlie it. Ongoing clinical trials may help to provide clearer guidelines in the future, but with so much about this virus still unknown, for now they must guess at best treatments and doses.

Clotting is normally a good thing. When a blood vessel is injured, cell fragments called platelets rush to plug the leak. Proteins in the blood called clotting factors switch from dormant to active states in a chain reaction, and build a fibrous mesh. "It's sort of a domino effect," says Hanny Al-Samkari, a hematologist at Massachusetts General Hospital in Boston.

Clotting in uninjured blood vessels is a common occurrence in hospital patients, especially those in the intensive care unit. Being bedridden encourages clotting, especially in the legs and pelvis, and the clots may migrate to the lungs where they impede the organs' ability to load the blood with oxygen. Depending on their location, clots can lead to problems such as breathing difficulties, heart attack, stroke and death.

Inflammation due to infection can also tip those clotting-factor dominoes. But as Covid-19 patients filled hospital wards, it became apparent that their clotting was more frequent, more widespread and more severe than in other infections. The clots filled needles used to draw blood, or the tubing connecting patients to medication drips and machines. "Everything was clotting," Al-Samkari says.

The consequences can be devastating. In a July report in the journal *Blood*, Al-Samkari and colleagues found that nearly 10 percent of 400 people hospitalized for Covid-19 developed clots. In a February report by researchers in China, about 70 percent of people who died of Covid-19 had widespread clotting, while few survivors did. And in a July article in the *New England Journal of Medicine*, autopsies revealed that the lungs of people who died of Covid-19 were nine times as likely to be speckled with tiny clots as those of people who died of influenza. Major risk factors for severe Covid-19 — such as diabetes, obesity and advanced age — are linked to worn-out blood vessels that make clotting more likely, says John Atkinson, an immunologist and rheumatologist at Washington University School of Medicine in St. Louis.

What Laurence finds downright "spooky" is that all this clotting happens in spite of the common US practice of prescribing blood thinners, such as heparin, to hospital patients to ward off clotting.

Bad blood

Why does clotting go overboard in some people with Covid-19? Theories abound. One possibility, Al-Samkari speculates, is that the virus activates one of the clotting factors and jump-starts the domino effect — but there's no specific evidence that this is happening.

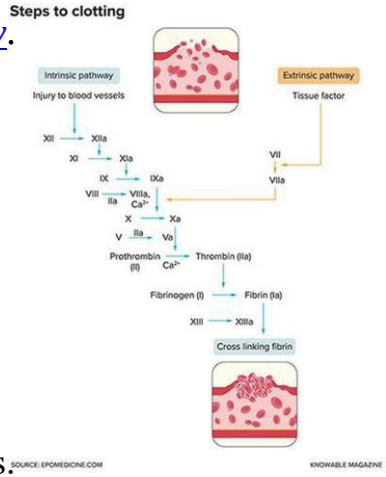
Another idea is that because SARS-CoV-2 infects and damages the cells lining blood vessels, it could expose the tissue underneath. That tissue makes proteins that promote clotting and normally perform a vital function, Al-Samkari says: If blood vessels are injured, the proteins get into the blood and induce clotting to plug any leak.

A third possibility is that clotting results from inflammation. And here, many experts are eyeing a set of proteins called the complement system. These proteins, known collectively as complement, attack invaders and call in other parts of the immune system to assist. They also can activate platelets and promote clotting.

Like the clotting cascade, the proteins of the complement system are activated in sequence, and scientists now know that SARS-CoV-2 can directly activate one of them, Laurence says. So can damaged body tissues, which build up during the virus's attack.

Clinicians have observed that the complement cascade appears to get out of hand in many people with severe Covid-19, says immunologist and complement expert Claudia Kemper of the National Heart, Lung, and Blood Institute, who coauthored an article about complement and immune cells in the *Annual Review of Immunology*.

She and her colleagues found signs of complement activity in the lungs and livers of people who died from Covid-19, for example, and Laurence found several active complement proteins in the skin and blood vessels of his early Covid-19 clotting cases. "There is currently not super-super-hard evidence, but many complementologists think that this is a massive part of the disease," Kemper says.



***A series of proteins activate each other in stepwise fashion to create a blood clot. External trauma to the blood vessel activates clotting by the faster extrinsic pathway, while the slower intrinsic pathway happens when there are problems within the vascular system.* (Source: epomedicine.com, Knowable Magazine)**

In another study of 11,000 people who had Covid-19, which has been posted online prior to review by other scientists, a New York team found that patients were more likely to become very ill and die if they had a history of clotting or bleeding, or if they had macular degeneration, which can indicate complement problems. The team also found that genes involved in complement and clotting responses were more active when the virus was present in patients' nasal swabs.

Not only that, but the researchers also reported that people with certain variants of genes involved in the complement and clotting systems had a higher risk of severe Covid-19 disease.

In addition to complement, another immune element may promote clotting in severe Covid-19 cases: an overreaction called a cytokine storm, in which the body releases an excess of inflammation-promoting cytokine molecules. "Your whole system gets revved up," Atkinson says. "When it's revved up, your clotting system gets revved up, because it senses danger."

Triple threat

As they treat their Covid-19 patients, physicians seek to hit the brakes on these clotting, complement and cytokine effects. "What you try to do is calm the trigger," says Atkinson, who cowrote an overview of abnormal complement control in macular degeneration and a childhood disorder for the *Annual Review of Pathology: Mechanisms of Disease*.

Early in the course of infection, that trigger is the virus itself, so doctors reach for antivirals such as remdesivir. But later on, says Laurence, the body's response is the biggest problem. "The virus, you might as well forget about it," he says. "You've got to control the clotting, you've got to control the inflammation, you've got to control the complement pathway — and that's easier said than done."

For clotting, there are blood thinners like heparin. Hematologists are hotly debating how much to use for Covid-19 patients, Al-Samkari says, because doctors must balance the risk of clotting

with the danger of bleeding. Al-Samkari has most often observed bleeds into the digestive system for these patients, but they may also hemorrhage in the lungs, brain or spots where medical devices pierce the skin.

Many hospitals are discharging Covid-19 patients with a prescription for blood thinners in case the risk of clotting remains high at home, though there are currently no solid data to back up this practice, Al-Samkari says. More than a dozen clinical trials aim to identify the right course of action to manage clotting alongside Covid-19. Al-Samkari stresses that there is no evidence that people with less severe Covid-19, who do not require hospitalization, should take blood thinners or aspirin to ward off clots.

For some patients, stifling inflammation may help. Steroids such as dexamethasone calm the immune system, and other medications specifically block cytokines or individual proteins in the clotting and complement cascades. Argatroban, for example, is a Food and Drug Administration-approved anticoagulant that interferes with thrombin, an element of the clotting cascade. And eculizumab, which blocks one of the complement proteins, is approved for certain inflammatory conditions. Again, physicians await better guidance from trials. “Right now,” says Al-Samkari, “we use clinical judgment as best we can, and just do our best.”

https://bit.ly/32S7Ty7

True holographic movie is within grasp

Researchers produce dynamic holographic projection using 'metasurface' material

Holographic movies, like the one R2D2 projected of Princess Leia in the Star Wars: A New Hope, have long been the province of science fiction, but for most of us, the extent of our experience with holograms may be the dime-sized stamps on our passports and credit cards. By using 'metasurface' materials that can manipulate light in ways that natural materials cannot, researchers reckon they have finally seen the light at the end of the tunnel for creating true holographic movies. The findings, by a team at the Tokyo University of Agriculture and Technology (TUAT), are published on August 3rd in *Optics Express*.

Static holograms are all around us these days on our money, credit cards, and passports. These "surface-relief holograms", stamped onto plastic in a similar way to how vinyl records are embossed, can be useful as a security device or to make wrapping paper twinkle, but they are known for their low image quality, still imagery, and limited viewing angle. In the third decade of the 21st Century, we don't yet have true holographic movies, such as R2D2's projection of Princess Leia in Star Wars: A New Hope, despite their ubiquity in popular culture.

Even the 'holograms' of pop stars that are increasingly common spectacles at concerts aren't true holograms, but an updated version of a very old theatrical trick deceiving the eye with mirrors and light--an illusion that is easily revealed as such if the viewer moves just slightly to the side of the set-up.

But researchers at Tokyo University of Agriculture and Technology have demonstrated a genuine holographic movie, whose concept is inspired by the sequential playback of the very first cinematographic projectors of the 19th Century.

The proof of concept depends on what is called a 'metasurface', a thin film material just nanometers thick whose microstructure is artificially crafted in a way to deliver characteristics, such as clever manipulation of light, that are not found in naturally occurring materials. Metasurfaces involve very tiny repeating patterns at scales smaller than the wavelength of light. It is their shape and particular arrangement, rather than, as with conventional materials, their chemical composition, that allows metasurfaces to alter the path of light.

The researchers "printed" an array of 48 rectangular frames of a metasurface made primarily of gold and which diffracts laser light shone at it in such a way as to produce a true holographic three-dimensional image appearing mid-air (just like Princess Leia), viewable from most angles in the room.

Each of the metasurface frames is slightly different--as with a reel of celluloid film--using 48 images of the Earth rotating. The holographic movie was played back by sequentially reconstructing each frame at a rate of 30 frames per second--the frame rate used in most live TV.

"We're using a helium-neon laser as the light source, which produces a reddish holographic image," said Kentaro Iwami, one of the engineers who developed the system, "so the aim is to develop this to produce full colour eventually. And we want it to be viewable from any angle: a 'whole hemisphere' 3D projection."

It also took an electron-beam lithography printer six and a half hours to draw the 48 frames--an extremely short film run on a loop. A six-minute holographic movie would take just over 800 hours to draw, the researchers reckon.

For more information about the Iwami laboratory, please visit
http://nmems.lab.tuat.ac.jp/en/

Original publication:

Ryota Izumi, Satoshi Ikezawa, and Kentaro Iwami, "Metasurface holographic movie: a cinematographic approach," Opt. Express 28, 23761-23770 (2020)
https://doi.org/10.1364/OE.399369

https://bit.ly/3i8Lfbf

Common medicine used to treat gout found to prevent progression of coronary disease

International study published in New England Journal of Medicine by Perth researchers

An Australian-Dutch trial led by Perth GenesisCare cardiologists, Professor Peter Thompson and Dr Mark Nidorf, in collaboration with the Dutch Network for Cardiovascular Research (WCN) in the Netherlands, confirmed that low dose colchicine was safe, well tolerated over the long-term, and significantly reduced the risk of cardiovascular death, heart attack, and ischemic stroke in patients with chronic coronary disease.

The Australian-Dutch trial was the world's largest trial of colchicine. It examined the effect of low dose colchicine (0.5mg daily) in patients with chronic coronary disease who were already taking established treatments.

Professor Thompson, Deputy Director of Perth's Harry Perkins Institute of Medical Research and a GenesisCare Cardiologist, said the trial involving almost 2000 WA patients and 3,500 from the Netherlands, found low dose colchicine reduced the risk of heart attack and the need for stents or bypass surgery due to progressive angina.

"We found the benefits of colchicine therapy were seen soon after starting on the drug and continued to build over time. Over the course of the trial, colchicine was found to reduce the risk of cardiovascular death, heart attack and stroke by almost one third," Professor Thompson said.

Dr Nidorf from GenesisCare was the first to demonstrate, seven years ago in a small trial of 500 patients, that low dose colchicine might be beneficial in patients with coronary disease. The 2013 pilot trial generated several other trials around the world for conditions including heart attack and stroke. Trials in Sydney and Canada occurred for high-risk patients with coronary disease.

"It's now understood that when cholesterol gets into the arterial wall it can spontaneously form into crystals, which like gout crystals, can incite a low-grade inflammatory response that causes chronic scarring of the artery.

"When this inflammatory process is more acute it can lead to the breakdown of plaques which can lead to heart attack and stroke.

"What we've been unable to do until now is reduce the inflammatory process that goes on inside the arterial wall.

"This is a ground-breaking, practice changing result, because colchicine is inexpensive and widely available.

"We found it to be a profoundly powerful drug at low-dose, with no danger signals associated with long-term use and excellent long-term tolerance.

"This medication does not come with the added cost of bleeding or lowering blood pressure so it is a nice fit with current treatments and will likely form a cornerstone treatment in patients with coronary disease, alongside aspirin and statins," Dr Nidorf said.

Former Fremantle Football Club CEO and Hockey Australia President Mr David Hatt AM enrolled in the two-year trial, hoping to avoid family history repeating.

"I was a patient of Dr Nidorf's and very happy to be involved. I have heart disease which is controlled by tablets to reduce blood pressure and the build-up of plaque. "I was motivated to be a part of the program because at a similar age my father had a serious heart attack and I was anxious to avoid that and I wanted to be involved in something that could help so many others," Mr Hatt said.

"GenesisCare is delighted to partner with Perth's Harry Perkins Institute of Medical Research and the Dutch Network for Cardiovascular Research to deliver the results of this international clinical trial, which will offer new hope to patients with coronary artery disease all over the world," Dr Nidorf said.

https://bit.ly/3qWwlTY

Strokes in babies are surprisingly common; here's how the body rushes to the rescue

Shedding light on how the brain's immune defenses respond to strokes that strike one in 4,000 babies in the first month of life.

New research from the University of Virginia School of Medicine is shedding light on the development of the brain's immune defenses - and how those defenses respond to strokes that strike one in 4,000 babies in the first month of life.

The brain's frontline defenders are immune cells known as microglia. These cells make up 10%-15% of all cells found in the brain. But their origins have been hotly debated. UVA's Chia-Yi "Alex" Kuan, MD, PhD, has discovered that many were previously white blood cells known as monocytes. During brain development - and in response to infant strokes - the monocytes undergo an amazing conversion into troops to defend the brain.

"Most people believe that blood monocytes only come into the brain after injury to provoke damage, and then they either die or leave the brain. Some even say monocytes and microglia live in parallel universes," said Kuan, of UVA's Department of Neuroscience and its Center for Brain Immunology and Glia (BIG). "But our results showed that many microglial cells actually come from the blood monocytes, both in normal development and after newborn brain injury."

The Brain's Immune Defenders

The finding is the latest from UVA's Department of Neuroscience and BIG center, which have in recent years revolutionized our understanding of the brain's relationship with the immune system. To explore the origins of the brain's immune defenses, Kuan and his colleagues developed an innovative new lab model that should greatly benefit future research. That model allowed his team to trace the origins of microglia in the brains of lab mice.

The researchers found that many monocytes transform into microglia over the course of brain development. This was a surprise - prior to UVA's discovery, scientists widely believed that microglia do not come from the blood monocytes. But Kuan's team used a process called "fate mapping" to reveal the microglia's secret origins.

In addition, Kuan's team found that monocytes rush to the rescue during neonatal stroke. Neonatal strokes are interruptions of blood flow to the baby's brain in the first 28 days after birth. Such strokes have a wide variety of causes, from blood clots to developmental abnormalities. Common symptoms include seizures and extreme sleepiness, though in some cases there are no symptoms until much later in life, when children can develop speech difficulties and balance problems.

In such strokes, Kuan found, there is an initial rush of monocytes, which then gradually become more like microglia. This lasts at least 62 days after the brain injury. Some of these monocytes are ultimately reprogrammed to join the brain's defense forces, the UVA researchers determined.

"But do monocyte-descended microglia continue to impair brain development in infants that suffered from newborn stroke, leading to neurological deficits? Can we target these disguised monocytes to improve the outcomes of newborn brain injury?" said researcher Hong-Ru Chen, PhD, the first author of the new study. "These are fascinating questions that beg for more research."

Findings Published

The researchers have published their findings in the scientific journal Science Advances. The research team consisted of Chen, Yu-Yo Sun, Ching-Wen Chen, Yi-Min Kuo, Irena S. Kuan, Zheng-Rong Tiger Li, Jonah C. Short-Miller, Marchelle R. Smucker and Kuan.

The research was supported by National Institutes of Health grants NS095064, NS100419, NS108763 and NS106592. Hong-Ru Chen was supported by American Heart Association postdoctoral fellowship 18POST34080334.

https://bit.ly/2DweWnq

Your paper notebook could become your next tablet

New technology can help transform paper sheets from a notebook into a music player interface

WEST LAFAYETTE, Ind. - Innovators from Purdue University hope their new technology can help transform paper sheets from a notebook into a music player interface and make food packaging interactive.

Purdue engineers developed a simple printing process that renders any paper or cardboard packaging into a keyboard, keypad or other easy-to-use human-machine interfaces. This technology is published in the Aug. 23 edition of Nano Energy. Videos showing this technology are available at https://youtu.be/TfA0d8IpjWU, https://youtu.be/J0iCxjicJIQ and https://youtu.be/c9E6vXYtIw0.

"This is the first time a self-powered paper-based electronic device is demonstrated," said Ramses Martinez, an assistant professor in Purdue's School of Industrial Engineering and in the Weldon School of Biomedical Engineering in Purdue's College of Engineering. "We developed a method to render paper repellent to water, oil and dust by coating it with highly fluorinated molecules. This omniphobic coating allows us to print multiple layers of circuits onto paper without getting the ink to smear from one layer to the next one."

Martinez said this innovation facilitates the fabrication of vertical pressure sensors that do not require any external battery, since they harvest the energy from their contact with the user.

This technology is compatible with conventional large-scale printing processes and could easily be implemented to rapidly convert conventional cardboard packaging or paper into smart packaging or a smart human-machine interface.

"I envision this technology to facilitate the user interaction with food packaging, to verify if the food is safe to be consumed, or enabling users to sign the package that arrives at home by dragging their finger over the box to proper identify themselves as the owner of the package," Martinez said. "Additionally, our group demonstrated that simple paper sheets from a notebook can be transformed into music player interfaces for users to choose songs, play them and change their volume."

https://bit.ly/3jM6cJm

New Drug Combo for ALS Slows Decline in Small Clinical Study

After six months, patients with fast-progressing amyotrophic lateral sclerosis who had received the experimental treatment had less loss of function than those who received a placebo.

Jef Akst

A trial of 137 patients with amyotrophic lateral sclerosis showed that a new combination of an existing drug and a supplement lessened declines in a standard measure of function over six months, according to a study published today (September 3) in *The New England Journal of Medicine*.

While the effect was modest and the trial early stage, "I am convinced that we are at the beginning of a new era in ALS treatment discovery," Sabrina Paganoni, a researcher at the Sean Healey & AMG Center for ALS at Massachusetts General Hospital and Harvard Medical School who led the study, tells *NPR*. "[Patients] want to be able to continue to use their hands so they can cut their own food and type emails, or they want to be able to walk and climb stairs, and this is exactly what we measured in the trial."

There are currently two approved drugs to treat ALS: riluzole, which can extend lifespan by an average of a few months and has been on the market for 25 years, and the 2017-approved edaravone, which was shown in clinical trials to help patients function for longer into their disease. Even with these treatment options, ALS is still a death sentence for most patients, typically within three to five years of diagnosis.

The new drug combo, called AMX0035, was conceived by Joshua Cohen and Justin Klee as undergraduates at Brown University several years ago and is now being developed by the company they founded, Cambridge, Massachusetts–based Amylyx. The treatment includes sodium phenylbutrate, which is a medication for urea cycle disorders, and the supplement taurursodiol—a combo that Cohen hypothesized back in 2013 as a biomedical engineer major would maintain functioning of the mitochondria and endoplasmic reticulum to protect against neuronal damage, *The New York Times* reports.

The data from the trial suggested it might be working. In six months, patients who had received AMX0035 saw a smaller decline in the ALS Functional Rating Scale, which assesses a patient's ability to do activities such as swallow and climb stairs, than those in the placebo group—about 2.9 points less, on average. Most also saw improvement in certain fine motor skills. "Even a small change in a couple of points can mean a large change in what daily life looks like," Paganoni tells *STAT*.

"This is very encouraging," Neil Shneider, the director of the Eleanor and Lou Gehrig A.L.S. Center at Columbia University who did not participate in the study, tells the *Times*. "The question is, is the effect on function sustained beyond the six-month trial period and does it have an effect on survival?" Matthew Kiernan, chair of neurology at the University of Sydney who was also not involved in the research, points out to *STAT* that the trial found no evidence that the treatment improved patients' ability to breathe, but says he awaits future results from Amylyx.

Most of the patients in the trial were already taking an approved drug, and they continued their normal regimen throughout the trial of AMX0035. Merit Cudkowicz, director of the Healey Center and senior author of the study, tells the *Times* that, if approved, the new treatment would likely be used in combination with existing medications.

The trial was the first supported with funds from the ALS Association that were generated by the Ice Bucket Challenge, the *Times* reports, and if the drug is approved, Amylyx will repay 150

percent of the ALS Association's funding to support additional research.

"What makes this time so exciting is there are over 50 different clinical trials that are enrolling and recruiting ALS patients right now," Kuldip Dave, the ALS Association's vice president of research, tells *NPR*. "And they're all going after different targets."

https://bit.ly/3qZLMe7

Venom from honeybees found to kill aggressive breast cancer cells

Honeybee venom rapidly destroyed triple-negative breast cancer and HER2-enriched breast cancer cells

Australian research published in Nature Precision Oncology

Using the venom from 312 honeybees and bumblebees in Perth Western Australia, Ireland and England, Dr Ciara Duffy from the Harry Perkins Institute of Medical Research and The University of Western Australia, tested the effect of the venom on the clinical subtypes of breast cancer, including triple-negative breast cancer, which has limited treatment options.

Results published in the prestigious international journal *npj Precision Oncology* revealed that honeybee venom rapidly destroyed triple-negative breast cancer and HER2-enriched breast cancer cells.

Dr Duffy said the aim of the research was to investigate the anti-cancer properties of honeybee venom, and a component compound, melittin, on different types of breast cancer cells. "No-one had previously compared the effects of honeybee venom or melittin across all of the different subtypes of breast cancer and normal cells.

"We tested honeybee venom on normal breast cells, and cells from the clinical subtypes of breast cancer: hormone receptor positive, HER2-enriched, and triple-negative breast cancer.

"We tested a very small, positively charged peptide in honeybee venom called melittin, which we could reproduce synthetically, and found that the synthetic product mirrored the majority of the anti-cancer effects of honeybee venom," Dr Duffy said.

"We found both honeybee venom and melittin significantly, selectively and rapidly reduced the viability of triple-negative breast cancer and HER2-enriched breast cancer cells.

"The venom was extremely potent," Dr Duffy said.

A specific concentration of honeybee venom can induce 100% cancer cell death, while having minimal effects on normal cells.

"We found that melittin can completely destroy cancer cell membranes within 60 minutes."

Melittin in honeybee venom also had another remarkable effect; within 20 minutes, melittin was able to substantially reduce the chemical messages of cancer cells that are essential to cancer cell growth and cell division.

"We looked at how honeybee venom and melittin affect the cancer signalling pathways, the chemical messages that are fundamental for cancer cell growth and reproduction, and we found that very quickly these signalling pathways were shut down.

"Melittin modulated the signalling in breast cancer cells by suppressing the activation of the receptor that is commonly overexpressed in triple-negative breast cancer, the epidermal growth factor receptor, and it suppressed the activation of HER2 which is over-expressed in HER2-enriched breast cancer," she said.

Western Australia's Chief Scientist Professor Peter Klinken said "This is an incredibly exciting observation that melittin, a major component of honeybee venom, can suppress the growth of deadly breast cancer cells, particularly triple-negative breast cancer.

"Significantly, this study demonstrates how melittin interferes with signalling pathways within breast cancer cells to reduce cell replication. It provides another wonderful example of where compounds in nature can be used to treat human diseases", he said.

Dr Duffy also tested to see if melittin could be used with existing chemotherapy drugs as it forms pores, or holes, in breast cancer cell membranes, potentially enabling the entry of other treatments into the cancer cell to enhance cell death.

"We found that melittin can be used with small molecules or chemotherapies, such as docetaxel, to treat highly-aggressive types of breast cancer. The combination of melittin and docetaxel was extremely efficient in reducing tumour growth in mice."

Dr Duffy's research was conducted as part of her PhD undertaken at Perth's Harry Perkins Institute of Medical Research at the Cancer Epigenetics laboratory overseen by A/Prof. Pilar Blancafort. "I began with collecting Perth honeybee venom. Perth bees are some of the healthiest in the world.

"The bees were put to sleep with carbon dioxide and kept on ice before the venom barb was pulled out from the abdomen of the bee and the venom extracted by careful dissection," she said.

While there are 20,000 species of bees, Dr Duffy wanted to compare the effects of Perth honeybee venom to other honeybee populations in Ireland and England, as well as to the venom of bumblebees.

"I found that the European honeybee in Australia, Ireland and England produced almost identical effects in breast cancer compared to normal cells. However, bumblebee venom was unable to induce cell death even at very high concentrations.

One of the first reports of the effects of bee venom was published in Nature in 1950, where the venom reduced the growth of tumours in plants. However, Dr Duffy said it was only in the past two decades that interest grew substantially into the effects of honeybee venom on different cancers.

In the future, studies will be required to formally assess the optimum method of delivery of melittin, as well as toxicities and maximum tolerated doses.

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Elderly people protected against respiratory infections by BCG vaccine

However, the effect of the vaccine specifically against COVID-19 has not been demonstrated

The BCG vaccine has a broad, stimulating effect on the immune system. This gives it an effective preventive action against various infections - possibly also against COVID-19. New studies are investigating that.

BCG is frequently given to children, but a double-blind randomized clinical study, a collaboration between Radboud university medical center and the National and Kapodistrian University of Athens shows that elderly people also benefit from it. The results are published in *Cell*.

At Radboudumc, Professor of Experimental Internal Medicine Mihai Netea is conducting research into this protective effect against various infections by the BCG vaccine, an effect called "trained immunity".

Prof. Mihai Netea: "Two years ago we started the ACTIVATE study, with the aim of showing whether BCG vaccination could protect against infections in vulnerable elderly people. Patients over 65 years of age who were admitted to hospital were randomized to receive BCG or placebo vaccination at their discharge. We followed them for a year to see if BCG could protect them against a broad range of infections."

Study started before the pandemic

The ACTIVATE study had already started before the corona pandemic. 198 elderly people were given either a placebo or a BCG vaccine upon discharge from the hospital. The last follow-up was scheduled for August 2020, but due to the arrival of COVID-19, the researchers looked at the preliminary results, published today in *Cell*.

Protective effect

There was a noticeable difference: in the placebo group, 42.3% of the elderly developed an infection, while this was the case in only 25% of the BCG group. It also took longer: the BCG-vaccinated participants had their first infection on average 16 weeks after vaccination, compared to 11 weeks for the placebo group. There was no difference in side effects.

Prof. Evangelos J. Giamarellos-Bourboulis, co-coordinator of the study at the 4th Department of Internal Medicine at ATTIKON University Hospital: "In addition to the clear effect of BCG vaccination on infections in general, the most important observation was that BCG could mainly protect against respiratory infections: BCG-vaccinated elderly people had 75% fewer respiratory infections than the elderly who received placebo."

It is unclear whether it works against the coronavirus

Although most protection seems to have been against respiratory infections of (probably) viral origin, whether or not BCG also works against COVID-19 has not yet been demonstrated, due to the low prevalence of COVID-19 in this study. The study does show that the BCG vaccination is safe to give to the elderly, and that it can protect them against various infections. Several studies are underway that look specifically at the effects of BCG on COVID-19. Only these follow-up studies can provide clarity as to whether BCG vaccination can also protect against infections with the new coronavirus.

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Handgrip strength shown to identify people at high risk of type 2 diabetes

Findings demonstrate handgrip strength could be a cost-effective early screening tool

A simple test such as the strength of your handgrip could be used as a quick, low-cost screening tool to help healthcare professionals identify patients at risk of type 2 diabetes. In new research, scientists at the universities of Bristol and Eastern Finland measured the muscular handgrip strength of 776 men and women without a history of diabetes over a 20-year period and demonstrated that the risk of type 2 diabetes was reduced by around 50 per cent for every unit increase in handgrip strength value. The findings are published today in *Annals of Medicine*.

Diabetes in all forms is the ninth major cause of death in the world. Around 90 per cent of people with diabetes have type 2 diabetes. In the UK alone, one in ten people over 40 are now living with a diagnosis of type 2 diabetes. It is expected that if nothing changes, more than five million people will have developed diabetes by 2025. Though older age, obesity, family history and lifestyle factors such as physical inactivity, smoking, unhealthy diet and excessive alcohol contribute substantially to the risk of developing type 2 diabetes, these factors alone do not explain all of the risk for type 2 diabetes. It appears other factors may be involved. Reduced muscular strength, which can be measured by handgrip strength, has consistently been linked to early death, cardiovascular disease, and disability.

Until recently, there was inconsistent evidence on the relationship between handgrip strength and type 2 diabetes. In a recent literature review of ten published studies on the topic the same researchers demonstrated that people with higher values of handgrip strength had a 27 per cent reduced risk of developing type 2 diabetes.

However, while findings from this review suggested handgrip strength could potentially be used to predict type 2 diabetes, researchers needed to test this formally using individual patient data. In this latest study, the researchers from Bristol Medical School and Eastern Finland's Institute of Public Health and Clinical Nutrition followed 776 men and women aged 60-72 years without a history of diabetes over a 20-year period and measured the power of their

hand grip strength using a handgrip dynamometer. Patients were asked to squeeze the handles of the dynamometer with their dominant hand with maximum isometric effort and maintain this for five seconds.

An analysis of the results demonstrated that the risk of type 2 diabetes was reduced by about 50 per cent for every unit increase in handgrip strength value. This association persisted even after taking into account several established factors that can affect type 2 diabetes such as age, family history of diabetes, physical activity, smoking, hypertension, waist circumference and fasting plasma glucose. When information on handgrip strength was added to these established factors which are already known to predict type 2 diabetes, the prediction of type 2 diabetes improved further.

According to lead author Dr Setor Kunutsor from Bristol's Musculoskeletal Research Unit: "These findings may have implications for the development of type 2 diabetes prevention strategies. Assessment of handgrip is simple, inexpensive and does not require very skilled expertise and resources and could potentially be used in the early identification of individuals at high risk of future type 2 diabetes."

Importantly, the findings appeared to be marked in women compared to men in sex-specific analyses, suggesting that women are likely to benefit from the use of this potential screening tool.

Principal investigator, Professor Jari Laukkanen from the University of Eastern Finland, added: "These results are based on a Finnish population. Given the low number of events in our analyses, we propose larger studies to replicate these findings in other populations and specifically in men and women." The authors add that further research is needed to establish whether efforts to improve muscle strength such as resistance training are likely to reduce an individual's risk of type 2 diabetes.

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The study was funded by the National Institute for Health Research Bristol Biomedical Research Centre (NIHR Bristol BRC) at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol and the Finnish Foundation for Cardiovascular Research.

Paper

'Handgrip strength improves prediction of type 2 diabetes: A prospective cohort study' by Setor K. Kunutsor, Ari Voutilainen, Jari A. Laukkanen in Annals of Medicine.

'Literature review: Handgrip strength - a risk indicator for type 2 diabetes: systematic review and meta-analysis of observational cohort studies' by Kunutsor SK, Isiozor NM, Khan H, Laukkanen JA, in Diabetes Metabolism Research and Reviews.

https://bit.ly/2Femqvy

Using tattoo ink to find cancer

Researchers have discovered how commonly used coloring agents such as tattoo inks and food dyes could help improve cancer detection

The humble ink in a tattoo artist's needle could be the key to improving the detection of cancer, thanks to new research from the USC Viterbi Department of Biomedical Engineering.

WiSE Gabilan assistant professor in the department with a lab at the USC Michelson Center for Convergent Bioscience, Cristina Zavaleta and her team recently developed new imaging contrast agents using common dyes such as tattoo ink and food dyes. When these dyes are attached to nanoparticles, they can illuminate cancers, allowing medical professionals to better differentiate between cancer cells and normal adjacent cells. The work has been published in *Biomaterials Science*.

Early detection is crucial for patients to have the best possible outcomes from cancer; a disease that will affect over 38% of Americans at some point in their lifetime.

However, detection is challenging without good imaging agents; contrast materials which when injected into patients, allow for imaging such as MRI and CT to function with better sensitivity and

specificity, enabling medical professionals to diagnose with accuracy, and for surgeons to identify the exact margins of tumors.

"For instance, if the problem is colon cancer, this is detected via endoscopy," Zavaleta said. "But an endoscope is literally just a flashlight on the end of a stick, so it will only give information about the structure of the colon - you can see a polyp and know you need to take a biopsy."

"But if we could provide imaging tools to help doctors see whether that particular polyp is cancerous or just benign, maybe they don't even need to take it," she said.

Illuminated nanoparticles move through a blood vessel to find cancer. The coloring dyes were incorporated into nanoparticles to allow for more sensitive imaging contrast when identifying cancerous cells.

To achieve this, the team has discovered a unique source of optical contrasting agents from the household coloring dyes and pigments that we routinely encounter. These "optical inks" can be attached to cancer-targeting nanoparticles to improve cancer detection and localization.

The dyes and pigments were discovered from common coloring agents that already have U.S. Food and Drug Administration (FDA) approval, which the team hopes may enable them to be more easily and safely implemented in imaging practice.

For Zavaleta, inspiration struck in an unusual place -- an animation class with Pixar artists in Emeryville, California, the home of the famed studio. Zavaleta, who enjoys art and animation among her hobbies, said she was intrigued by the inks and paints that the artists brought to class.

"I was thinking about how these really high pigment paints, like gouache watercolors, were bright in a way I hadn't seen before, and I was wondering if they had interesting optical properties," Zavaleta said.

The idea led her to tattoo artist in nearby San Francisco, Adam Sky, another artisan working with bright dyes.

"I remember I brought a 96-well plate and he squirted tattoo ink into each of the wells," Zavaleta said. "Then I took the inks to our Raman scanner (used to sensitively detect our tumor-targeting nanoparticles) and discovered these really amazing spectral fingerprints that we could use to barcode our nanoparticles. It was super cool."

One of the safety challenges of imaging using nanoparticles, is that often these nanoparticles can have a prolonged retention in organs like the liver and the spleen, which are responsible for trying to break down the nanoparticle. Because of these safety concerns, it's crucial to consider biodegradable nanomaterials. Currently, there are a limited amount of optical contrast agents approved for clinical use.

With this in mind, Zavaleta's team considered common food dyes that could be used to decorate the nanoparticles, such as the dyes found in colorful candies like Skittles and M&Ms. These brightly colored food products that humans routinely consume have been deemed by the FDA as safe for human consumption.

"We thought, let's look at some of the FDA-approved drug, cosmetic and food dyes that exist and see what optical properties are amongst those dyes," Zavaleta said. "And so that's where we ended up finding that many of these FDA-approved dyes have interesting optical properties that we could exploit for imaging."

The team has developed a nanoparticle that will carry these highly pigmented imaging agents as a "payload." Zavaleta said the particles are of a specific size that enables them to passively penetrate into tumor areas, but can also be retained due to their size.

Most of the imaging contrast agents used in the clinic today are small molecule dyes.

"With small molecules, you may be able to see them accumulate in tumor areas initially, but you'd have to be quick before they end up leaving the tumor area to be excreted," Zavaleta said. "Our nanoparticles happen to be small enough to seep through, but at the same time big enough to be retained in the tumor, and that's what we call the enhanced permeability and retention effect."

The nanoparticle can also be "decorated" with a larger payload of the dye than previous small molecule imaging agents, which the team has shown under fluorescence imaging leads to brighter signal and significant localization of the nanoparticles in tumors.

"If you encapsulate a bunch of dyes in a nanoparticle, you're going to be able to see it better because it is going to be brighter," Zavaleta said. "It's like using a packet of dyes rather than just one single dye."

The research was co-authored by Helen Salinas, Dominie Miyasato, Olga Eremina, Rodolfo Perez, Karen Gonzalez, Alexander Czaja, Sean Burkitt, Arjun Aron, Augusta Fernando, Lauro Ojeda, Kimberly Larson, Ahmed Mohamed and Jos Campbell from USC Viterbi Department of Biomedical Engineering.

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California Rx: State May Dive Into Generic Drug Market

California is poised to become the first state to develop its own line of generic drugs

Angela Hart and Samantha Young

Sacramento — California is poised to become the first state to develop its own line of generic drugs, targeting soaring drug prices and stepping into a fiercely competitive drug market dominated by deep-pocketed pharmaceutical companies.

The Democratic-controlled legislature overwhelmingly approved a measure Monday that would direct the state's top health agency to partner with one or more drug companies by January to make or distribute a broad range of generic or biosimilar drugs — including the diabetes medicine insulin — that are cheaper than brand-name products.

The bill, SB-852, also opens the door for California to make its own generic drugs in the future.

Gov. Gavin Newsom will have until Sept. 30 to sign or veto the measure.

"People need these drugs, but prices are through the roof, so we're saying there's a role for the state to bring prices down," said the bill's author, state Sen. Richard Pan (D-Sacramento).

He argued the measure is more important than ever because COVID-19 has exposed "glaring gaps" in the ability of public and private entities — from major hospitals to government drug purchasers — to maintain adequate supplies of drugs, medical equipment and devices.

"This also creates a model to address drug shortages and other supply chain issues during COVID and future pandemics," he said.

Newsom, a Democrat, floated his own generic drug proposal in January as part of his broader drug agenda to reduce pharmaceutical costs, but was forced to abandon his plan in May as he and lawmakers sought to address a pandemic-induced $54 billion budget deficit.

Though it could take years to successfully bring a new California generic product to the market, the move would put the nation's most populous state in direct competition with major generic and brand-name drug manufacturers that dominate the market, and potentially allow California to use its massive purchasing power to drive down drug prices.

"Other legislative efforts in Congress and in other states have focused on government negotiating with pharmaceutical companies to lower prices on generic drugs," said Edwin Park, research professor at the Health Policy Institute at Georgetown University.

The Pharmaceutical Research and Manufacturers of America, which represents brand-name drugmakers, has taken a neutral position on the bill and declined to comment.

But Brett Michelin, lead lobbyist for the Washington, D.C.-based trade group that represents generic drugmakers, the Association for Accessible Medicines, said generic companies aren't threatened by the possibility of California entering the market — and even welcome it.

"Generic manufacturers are more than open to doing this kind of partnership," Michelin said. "I think having a fair and open process to sell drugs and compete for customers is what the generic industry is very used to and comfortable with."

Under the measure, state-developed generics would be "widely" available to public and private purchasers within California. Taxpayers would pick up the costs, roughly $1 million to $2 million in startup funding, plus ongoing staff costs estimated in the low hundreds of thousands of dollars annually, according to a state fiscal analysis.

It's unclear which drugs the state would make or procure, though it would target drugs that could produce the biggest cost savings for the state and consumers.

But the bill specifically calls for the production of "at least one form of insulin, provided that a viable pathway for manufacturing a more affordable form of insulin exists at a price that results in savings."

Insulin is a biologic drug, made with living cells. Once a biologic hits the market, rival copycat products that follow are called biosimilars.

Three major drug companies — Eli Lilly and Co., Sanofi and Novo Nordisk — have long controlled the lucrative insulin market in the U.S. The state of California would be the first entity to produce a biosimilar version of one of the newer, fast- and long-acting insulins on a not-for-profit basis, said Jane Horvath, a health policy consultant in Washington, D.C.

Although it would be costly and could take years, the Utah-based nonprofit drug company Civica Rx, which has consulted with Pan on his bill, is discussing partnering with California to produce generic or biosimilar drugs. It has already hammered out deals with major health systems running short on critical drugs, including the Department of Veterans Affairs, and is producing lower-cost generics for insurers, including Blue Shield of California.

"There's no doubt insulin would be a more complex and expensive drug to develop, but it's certainly possible," said Allan Coukell, the company's senior vice president of public policy. "We are watching how the biosimilar market develops."

Patients who need insulin have faced huge cost spikes. A 2019 report by the Health Care Cost Institute concluded that average prices for insulin doubled from 2012 to 2016. And California health insurance regulators found last year that diabetes medications accounted for nine of the 25 costliest brand-name drugs sold in the state.

"It's a big deal — diabetes affects a lot of people who rely on insulin for their very lives," said Larry Levitt, executive vice president for health policy at the Kaiser Family Foundation. "And insulin has probably been the poster child for unreasonable drug pricing." (Kaiser Health News, which produces California Healthline, is an editorially independent program of the foundation.)

Laura Marston, a Washington, D.C.-based lawyer and diabetic who advocates for lower insulin prices, said she's excited about California's idea.

Marston has been on the same insulin, Humalog, since 1996. At that time, the price was $21 a vial, but has since ballooned to more than $275 a vial, she said.

"If there was a lower-cost option and the price wasn't going to be raised, I would absolutely switch from Humalog," she said. "I feel held totally hostage to these pharmaceutical companies."

Marston said she'd like the federal government to do the same thing, "so it could apply to all patients."

Congressional efforts to tackle rising prices for insulin and other drugs fizzled last year in the face of opposition from the influential pharmaceutical lobby. So states have increasingly sought ways to regulate a for-profit industry in which brand-name manufacturers hold near-monopoly power.

Colorado last year became the first state to cap out-of-pocket insulin costs at $100 for a 30-day supply. It was followed by at least nine other states, from New Mexico to New York, whose cost-sharing caps vary.

California had already capped out-of-pocket drug costs at $250 to $500 for a 30-day supply, but a measure that would have lowered the cap for insulin to $100 a month stalled this year — a casualty of a pandemic-shortened legislative calendar.

Newsom's office declined to comment on the generic drug legislation. But recent changes to the proposal reflect direct negotiations with the administration, Pan's office said.

Newsom spokesperson Jesse Melgar said in a statement that "the governor's goal of a sustainable system of universal coverage has not changed and making prescription drugs affordable is one more step toward that goal."

Should Newsom sign the bill into law, the state Health and Human Services Agency would have 18 months to identify a list of drugs the state could manufacture, with a report due to the legislature by July 2022. By July the following year, the state would be required to assess whether it can manufacture its own generics and biosimilars.

The bill calls for state health officials to prioritize development of generics for chronic and high-cost health conditions, and urges production of those that can be delivered through mail order.

California could emerge as a leader in the national drug debate, Levitt said.

"If California can pull it off, it would be a model for other states and federally," he said. "For it to pull this off means it can be done at scale."

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https://bit.ly/3jRxez6

An unprecedented discovery of cell fusion

Researchers uncover how microbial cells from two different species combine to form hybrid cells

Like humans, bacteria live together in communities, sometimes lending a hand -- or in the case of bacteria, a metabolite or two -- to help their neighbors thrive. Understanding how bacteria interact is critical to solving growing problems such as antibiotic resistance, in which infectious bacteria form defenses to thwart the medicines used to fight them.

Now, researchers at the University of Delaware have discovered that bacteria do more than just work together. Bacterial cells from different species can combine into unique hybrid cells by fusing their cell walls and membranes and sharing cellular contents, including proteins and ribonucleic acid (RNA), the molecules which regulate gene expression and control cell metabolism. In other words, the organisms exchange material and lose part of their own identity in the process.

This unprecedented observation, which was reported on Tuesday, Sept. 1 in *mBio*, a journal of the American Society for Microbiology, has the potential to shed light on unexplained

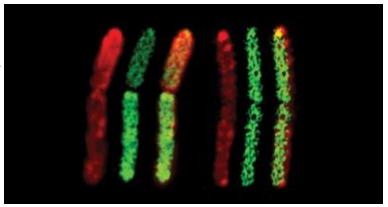
phenomena affecting human health, energy research, biotechnology and more.

The research team, led by Eleftherios (Terry) Papoutsakis, Unidel Eugene Du Pont Chair of Chemical and Biomolecular Engineering, studied interactions between *Clostridium ljungdahlii* and *C. acetobutylicum*. These species of bacteria work together in a syntrophic system, producing metabolites that are mutually beneficial to each other's survival.

The team found that *C. ljungdahlii* invades *C. acetobutylicum*. The two organisms combine cell walls and membranes and exchange proteins and RNA to form hybrid cells, some of which continue to divide and in fact differentiate into the characteristic sporulation program.

"They mix their machinery to survive or do metabolism, and that's kind of extraordinary, because we always assumed that each and every organism has its own independent identity and machinery," said Papoutsakis.

Previously, researchers have observed that bacteria could exchange some material through nanotubes. The combination into hybrid cells was unexpected.



The left side of this image depicts cell fusion between Clostridium ljungdahlii and C. acetobutylicum bacteria as seen through fluorescence microscopy. The right side depicts the formation of hybrid bacterial cells. **Images by Kamil Charubin and Joy Smoker**

"This is the first time we've shown this in this bacteria, and it's also a new mechanism of how material is exchanged," said Kamil Charubin, a doctoral student in chemical and biomolecular Engineering and first author of the paper.

Although this phenomenon of interspecies microbial fusion is now being reported for the first time, it is likely ubiquitous in nature among many bacterial pairs.

So why do bacteria bother to fuse together? The simple answer is likely because this process allows the microbes to share machinery that will increase their odds of survival.

For example, some pathogenic bacteria -- those that can cause disease -- may borrow proteins from other antibiotic-resistant bacteria in order to shore up their own resistance. Some bacteria might borrow machinery from others in order to evade detection by the immune system.

This could also help to explain why some bacteria are difficult to culture, or grow for study or medical diagnostic purposes. These difficult-to-culture bacteria might combine with or work with and depend on other microorganisms for their existence instead of growing and multiplying on their own.

The team's findings may influence understanding of the evolution of biology because once bacterial species share machinery, they can evolve together instead of only evolving on their own, said Papoutsakis.

"These findings will guide new thinking in not just the field of microbial evolution, but also toward biotechnological solutions that can benefit the soldier," said Dr. Robert Kokoska, program manager, Army Research Office (ARO), an element of the U.S. Army Combat Capabilities Development Command's Army Research Laboratory.

"These include studies of how the human microbiome shapes soldier human health and cognition and how microbial communities can be better designed for a broad range of advances including strategies for reliable in-field biological sensing, waste remediation and novel means of biosynthesis."

This work was supported by the Army Research Office (award no. W911NF-17-1-0343, and W911NF-19-1-0274) and the U.S. Department of Energy (DE-SC0019155).

The paper's authors also include Shannon Modla and Jeffrey Caplan of the Delaware Biotechnology Institute and the University of Delaware Bioimaging Center.

https://bit.ly/2ZsXKXR

Has Earth's oxygen rusted the Moon for billions of years?

Hematite has been discovered at high latitudes on the Moon

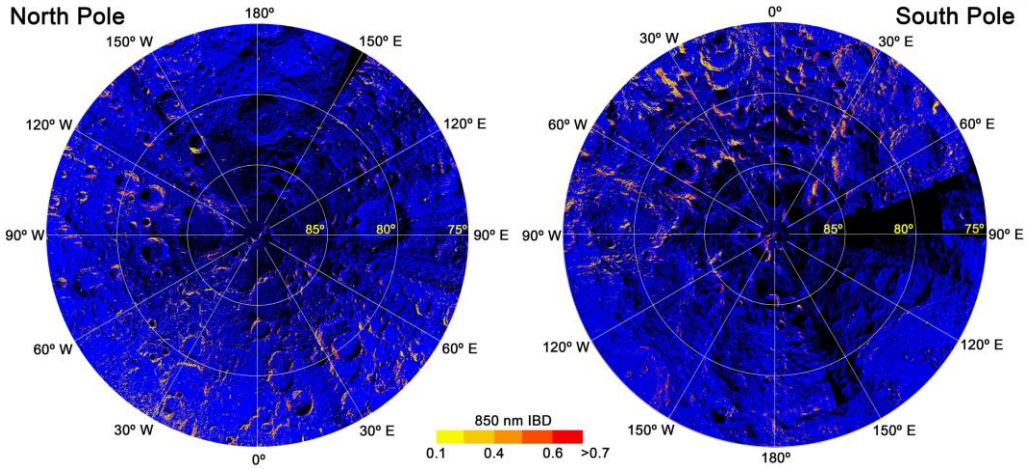
To the surprise of many planetary scientists, the oxidized iron mineral hematite (Fe_2O_3) has been discovered at high latitudes on the Moon, according to a study published today in *Science Advances* led by Shuai Li, assistant researcher at the Hawai'i Institute of Geophysics and Planetology (HIGP) in the UH Mānoa School of Ocean and Earth Science and Technology (SOEST).

Iron is highly reactive with oxygen—forming reddish rust commonly seen on Earth. The lunar surface and interior, however, are virtually devoid of oxygen, so pristine metallic iron is prevalent on the Moon and highly oxidized iron has not been confirmed in samples returned from the Apollo missions. In addition, hydrogen in solar wind blasts the lunar surface, which acts in opposition to oxidation. So, the presence of highly oxidized iron-bearing minerals, such as hematite, on the Moon is an unexpected discovery.

"Our hypothesis is that lunar hematite is formed through oxidation of lunar surface iron by the oxygen from the Earth's upper atmosphere that has been continuously blown to the lunar surface by solar wind when the Moon is in Earth's magnetotail during the past several billion years," said Li.

To make this discovery, Li, HIGP professor Paul Lucey and co-authors from NASA's Jet Propulsion Laboratory (JPL) and elsewhere analyzed the hyperspectral reflectance data acquired by the Moon Mineralogy Mapper (M3) designed by NASA JPL onboard India's Chandrayaan-1 mission.

This new research was inspired by Li's previous discovery of water ice in the Moon's polar regions in 2018. "When I examined the M3 data at the polar regions, I found some spectral features and patterns are different from those we see at the lower latitudes or the Apollo samples," said Li. "I was curious whether it is possible that there are water-rock reactions on the Moon. After months investigation, I figured out I was seeing the signature of hematite."



Map of hematite on the moon--redder color means more hematite. **Shuai Li**

The team found the locations where hematite is present are strongly correlated with water content at high latitude Li and others found previously and are more concentrated on the nearside, which always faces the Earth.

"More hematite on the lunar nearside suggested that it may be related to Earth," said Li. "This reminded me a discovery by the Japanese Kaguya mission that oxygen from the Earth's upper atmosphere can be blown to the lunar surface by solar wind when the Moon is in the Earth's magnetotail. So, Earth's atmospheric oxygen could be the major oxidant to produce hematite. Water and interplanetary dust impact may also have played critical roles"

The blue areas in this composite image from the Moon Mineralogy Mapper (M3) aboard the Indian Space Research Organization's Chandrayaan-1 orbiter show water concentrated at the Moon's poles.

"Interestingly, hematite is not absolutely absent from the far-side of the Moon where Earth's oxygen may have never reached, although much fewer exposures were seen," said Li. "The tiny amount of

water (< ~0.1 wt.%) observed at lunar high latitudes may have been substantially involved in the hematite formation process on the lunar far-side, which has important implications for interpreting the observed hematite on some water poor S-type asteroids."

"This discovery will reshape our knowledge about the Moon's polar regions," said Li. "Earth may have played an important role on the evolution of the Moon's surface."

The research team hopes the NASA's ARTEMIS missions can return hematite samples from the polar regions. The chemical signatures of those samples can confirm their hypothesis whether the lunar hematite is oxidized by Earth's oxygen and may help reveal the evolution of the Earth's atmosphere in the past billions of years.

Shuai Li et al. 2020. "Widespread hematite at high latitudes of the Moon" Science Advances (2020). DOI: 10.1126/sciadv.aba1940

https://bit.ly/2FaGAqB

How to spot patients most likely to die from blood infections

Unprecedented analysis of proteins and metabolites in patient serum provides new biomarkers associated with a patient's risk of dying from Staphylococcus aureus bacteremia

David Gonzalez's "a-ha" moment came when a physician-colleague, George Sakoulas, MD, shared with him one of the biggest problems faced in clinical practice: How long it takes to diagnose a patient.

"The faster we know what's going to happen to our patients, the better we can treat them," said Sakoulas, an infectious disease specialist and associate adjunct professor of pediatrics at University of California San Diego School of Medicine.

Gonzalez is a biochemist who specializes in proteomics. As genomics is the study of all the genes in a cell or organism, proteomics is the study of all of the proteins. He uses leading-edge tools to identify the proteins in a mixed sample based on their molecular weights -- a technique called mass spectrometry.

So Gonzalez thought: What if a proteomic "readout" from a person's blood could help identify who needs the most help early on, so they can be treated quickly and appropriately?

Now, just two years since receiving their first patient blood samples for study, Gonzalez and colleagues have identified a collective signature of proteins and metabolites associated with death due to *Staphylococcus aureus* bacteremia -- a bacterial infection in the blood that kills 20 to 30 percent of patients who contract it. In the lab, scientists say these molecular indicators, or biomarkers, can predict who is at highest risk of dying from the infection with exceptional accuracy.

In the study, published September 3, 2020 in *Cell*, the team describes one of the most comprehensive molecular assessments of blood serum from any human infection response to date. They also validated their findings in mouse models of *S. aureus* bacteremia.

"This finding is a leap forward toward a point-of-care predictive tool for bacteremia risk," said Gonzalez, PhD, senior author and assistant professor at UC San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. "It also opens up lots of new basic biological questions about how our immune systems respond to infections." Gonzalez led the study with first author Jacob Wozniak, PhD, a graduate student in his lab at the time.

Gonzalez and team used mass spectrometry to analyze more than 10,000 proteins and metabolites in more than 200 serum samples collected from the blood of patients with *S. aureus* bacteremia. Serum is notoriously difficult to study, he said, because it is heavily laden with a handful of highly abundant serum proteins.

"So, at first, the depth of our proteomic data was a total let down," Gonzalez said. "We didn't learn as much as we had hoped about the serum proteins."

But that initial hurdle only inspired the team to look deeper, at post-translational modifications -- the chemical additions added to proteins after they are constructed. According to Gonzalez, post-translational modifications are mostly uncharted territory. Many research efforts are geared toward genomics, but the gene that encodes a protein doesn't reveal much about how it might be modified later.

"If I wanted to learn all about you, I'd just talk to you directly, not your second cousin," Gonzalez said. "Same thing here -- we can gain new and important information by directly 'asking' the proteins, rather than their genes, and mass spectrometry is currently the best way to do that in an unbiased manner."

With this approach, the team identified a specific pattern of proteins with and without post-translational modifications that differed in the serum of patients who ultimately died of *S. aureus* bacteremia compared to those who did not. The biomarkers most highly associated with death included lower levels of glycosylated (sugar-coated) fetuin A, unmodified fetuin B and thyroxine, a master regulator of metabolism, as well as higher levels of serum protein carbamylation, another post-translational modification.

Several of these new biomarkers are already known to be associated with disease -- high fetuin levels are associated with obesity and diabetes, carbamylation has been linked with kidney disease -- but few have been previously linked to bacterial infections.

While the analyses revealed serum differences between low- and high-risk patients, it wasn't clear whether these molecules actually contribute to the disease, or are simply bystanders. So Gonzalez and team used a mouse model of *S. aureus* bacteremia to explore cause and effect. They found that mice with higher thyroxine levels had a four-times greater survival rate at 48 hours after infection than control mice. These results indicated that at least one of the identified biomarkers plays a direct role in disease outcome.

In the past, other research groups have developed alternative methods for predicting a patient's risk of death due to bacteremia. At best, Gonzalez says their accuracy was fair to good. With his team's new, proteomics-based prediction method, they could predict who is most likely to die of *S. aureus* bacteremia with excellent predictability. To put it quantitatively, the area under the curve (AUC) was 0.95; 1.0 is perfect and anything above 0.90 is considered excellent in this standard measure of the ability of a test to correctly classify those with and without the disease.

"We tend to treat all bacteremia patients with the same cheap antibiotics, yet we know they only work for 80 percent of these patients," said Sakoulas, a co-author of the study. "We need to know from the beginning who falls into that 20 percent that will require a more complex treatment regimen, so we don't waste time with trial-and-error."

Now the team is working to translate their mass spectrometry observations in the laboratory into a rapid clinical test that uses antibody probes to detect *S. aureus* bacteremia-associated proteins. They are also expanding the approach to look at proteomic and metabolomic markers indicative of high-risk patients with other types of infections, including COVID-19. In addition, researchers are following up on the proteins and modifications that were revealed in the study, exploring their origins, roles in the immune response and potential as therapeutic targets.

Co-authors of the study also include: Robert H. Mills, Joshua Olson, Gregory D. Sepich-Poore, Marvic Carrillo-Terrazas, Chih-Ming Tsai, Fernando Vargas, Rob Knight, Pieter C. Dorrestein, George Y. Liu, Victor Nizet, UC San Diego; JR Caldera, UC San Diego and Cedars-Sinai Medical Center; and Warren Rose, University of Wisconsin-Madison.

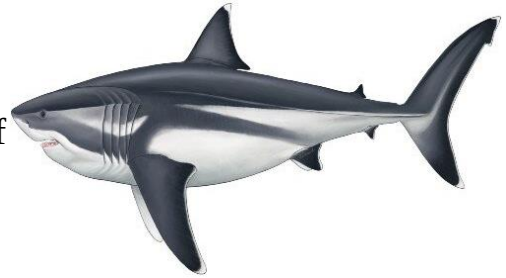
Disclosure: George Sakoulas has received speaking honoraria from Allergan and Melinta Pharmaceuticals and consulting fees from Allergan and Paratek Pharmaceuticals.

https://bit.ly/3bEvyGq

True size of prehistoric mega-shark finally revealed

New study has revealed the size of the rest of its body

To date only the length of the legendary giant shark Megalodon had been estimated but now, a new study led by the University of Bristol and Swansea University has revealed the size of the rest of its body, including fins that are as large as an adult human.



Palaeoartist reconstruction of a 16 m adult Megalodon. **Oliver E. Demuth**

There is a grim fascination in determining the size of the largest sharks, but this can be difficult for fossil forms where teeth are often all that remain.

Today, the most fearsome living shark is the Great White, at over six meters (20 feet) long, which bites with a force of two tons.

Its fossil relative, the big tooth shark Megalodon, star of Hollywood movies, lived from 23 to around three million years ago, was over twice the length of a Great White and had a bite force of more than ten tons. The fossils of the Megalodon are mostly huge triangular cutting teeth bigger than a human hand.

Jack Cooper, who has just completed the MSc in Palaeobiology at the University of Bristol's School of Earth Sciences, and colleagues from Bristol and Swansea used a number of mathematical methods to pin down the size and proportions of this monster, by making close comparisons to a diversity of living relatives with ecological and physiological similarities to Megalodon.

The project was supervised by shark expert Dr. Catalina Pimiento from Swansea University and Professor Mike Benton, a paleontologist at Bristol. Dr. Humberto Ferrón of Bristol also collaborated.

Their findings are published today in the journal *Scientific Reports*.

Jack Cooper said: "I have always been mad about sharks. As an undergraduate, I have worked and dived with Great whites in South Africa—protected by a steel cage of course. It's that sense of danger, but also that sharks are such beautiful and well-adapted animals, that makes them so attractive to study.

Megalodon was actually the very animal that inspired me to pursue paleontology in the first place at just six years old, so I was over the moon to get a chance to study it. This was my dream project. But to study the whole animal is difficult considering that all we really have are lots of isolated teeth."

Comparison of an adult Megalodon's dorsal fin to a 1.6 m diver. **Oliver E. Demuth**

Previously the fossil shark, known formally as Otodus megalodon, was only compared with the Great White. Jack and his colleagues, for the first time, expanded this analysis to include five modern sharks.

Dr. Pimiento said: "Megalodon is not a direct ancestor of the Great White but is equally related to other macropredatory sharks such as the Makos, Salmon shark and Porbeagle shark, as well as the Great white. We pooled detailed measurements of all five to make predictions about Megalodon."

Professor Benton added: "Before we could do anything, we had to test whether these five modern sharks changed proportions as they grew up. If, for example, they had been like humans, where babies have big heads and short legs, we would have had some difficulties in projecting the adult proportions for such a huge extinct shark. But we were surprised, and relieved, to discover that in fact that the

babies of all these modern predatory sharks start out as little adults, and they don't change in proportion as they get larger."

Jack Cooper said: "This means we could simply take the growth curves of the five modern forms and project the overall shape as they get larger and larger—right up to a body length of 16 meters."

The results suggest that a 16-meter-long Otodus megalodon likely had a head round 4.65 meters long, a dorsal fin approximately 1.62 meters tall and a tail around 3.85 meters high. This means an adult human could stand on the back of this shark and would be about the same height as the dorsal fin.

The reconstruction of the size of Megalodon body parts represents a fundamental step towards a better understanding of the physiology of this giant, and the intrinsic factors that may have made it prone to extinction.

More information: Jack A. Cooper et al. Body dimensions of the extinct giant shark Otodus megalodon: a 2D reconstruction, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-71387-y

https://bit.ly/2R1sPwQ

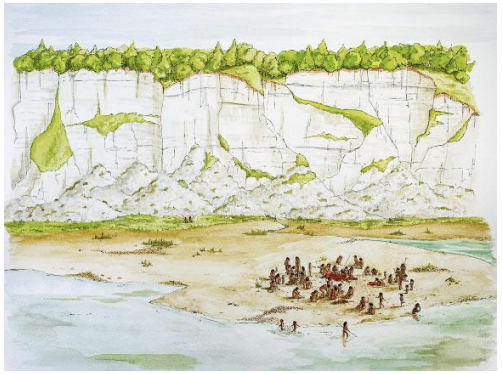
Homo heidelbergensis was Extremely Resourceful, New Research Shows

New research pieces together the activities and movements of a group of Homo heidelbergensis

New research pieces together the activities and movements of a group of *Homo heidelbergensis*, a poorly understood species of archaic humans that lived between 700,000 to 200,000 years ago, as they made tools, including the oldest bone tools documented in Europe, and extensively butchered a large horse at the 480,000-year-old archaeological site near Boxgrove, Sussex, the United Kingdom.

The Horse Butchery Site is one of many excavated in quarries near Boxgrove, an internationally significant area that is home to Britain's oldest human remains.

During the excavations in the 1980-90s, archaeologists recovered more than 2,000 razor sharp flint fragments from eight separate groupings, known as knapping scatters. These are places where individual early humans knelt to make their tools and left behind a dense concentration of material between their knees.



An artistic rendering of the Horse Butchery Site and the Boxgrove people; it shows how the site was situated in front of towering chalk cliffs on the edge of an intertidal lagoon; the cliffs to the north provided all the flint used in tool making at the site and, within a few hours, the tide would have begun to cover the site in fine silt, preserving evidence of the day's activity. **Lauren Gibson / Institute of Archaeology, University College London.**

Embarking on an ambitious jigsaw puzzle to piece together the individual flints, Dr. Matthew Pope from the Institute of Archaeology at University College London and his colleagues discovered that in every case *Homo heidelbergensis* were making large flint knives called bifaces, often described as the perfect butcher's tool.

"This was an exceptionally rare opportunity to examine a site pretty much as it had been left behind by an extinct population, after they had gathered to totally process the carcass of a dead horse on the edge of a coastal marshland," Dr. Pope said.

"Incredibly, we've been able to get as close as we can to witnessing the minute-by-minute movement and behaviors of a single apparently tight-knit group of early humans: a community of people, young and old, working together in a co-operative and highly social way."

"We established early on that there were at least eight individuals at the site making tools, and considered it likely that a small group of

adults, a 'hunting party,' could have been responsible for the butchery," he said.

"However, we were astonished to see traces of other activities and movement across the site, which opened the possibility of a much larger group being present."

The detailed study of the horse bones shows the animal was not just stripped of meat, but each bone was broken down using stone hammers so that the marrow and liquid grease could be sucked out.

The horse appears to have been completely processed, with the fat, marrow, internal organs and even the partially digested stomach contents providing a nutritious meal for the early human group of 30 or 40 individuals envisaged for the site.

However, the horse provided more than just food, and the detailed analysis of the bones found that several bones had been used as tools called retouchers.

A small knapping scatter relating to the reshaping of a biface, preserving the imprint of an early human knee in the shards of waste flint, under excavation in 1989 at the Horse Butchery Site near Boxgrove, Sussex, the United Kingdom. **Institute of Archaeology, University College London.**

"These are some of the earliest non-stone tools found in the archaeological record of human evolution," said Simon Parfitt, also from the Institute of Archaeology at University College London.

"They would have been essential for manufacturing the finely made flint knives found in the wider Boxgrove landscape."

"The finding provides evidence that early human cultures understood the properties of different organic materials and how tools could be made to improve the manufacture of other tools," said Dr. Silvia Bello, a researcher at the Natural History Museum, London.

"Along with the careful butchery of the horse and the complex social interaction hinted at by the stone refitting patterns, it provides further evidence that early human population at Boxgrove were cognitively, social and culturally sophisticated."

Cooperative activity amongst larger numbers of people suggests these temporary sites could have been highly social spaces for interaction, learning and the sharing of tools and ideas.

The Horse Butchery Site shows this behavior more vividly than any other site so far discovered in the archaeological record.

"This research is a timely reminder of the power of archaeology to illuminate details of remarkably intimate events across a vast gulf of time and at the same time to improve our understanding of how human beings evolved," said Dr. Barney Sloane, National Specialist Services Director at Historic England.

"The discovery, in a quarry site, demonstrates clearly the value of ensuring that our planning policies take account of archaeology's potential for scientific advancement."

The findings are detailed in the book '*The Horse Butchery Site: A high resolution record of Lower Palaeolithic hominin behaviour at Boxgrove, UK*' published by Spoilheap Publications.

Matt Pope *et al. The Horse Butchery Site: A high resolution record of Lower Palaeolithic hominin behaviour at Boxgrove, UK*. SpoilHeap Publications, 2020

https://bit.ly/3h5JSIW

Evidence slowly building for long-term heart problems post-COVID-19

While there are anecdotes aplenty, there's also some solid science behind the worries.

John Timmer

Coronaviruses spread primarily through material released when we breathe, and they cause respiratory symptoms. And SARS-CoV-2,

with part of its name coming from "severe acute respiratory syndrome," didn't appear to be an exception. But as time went on, additional symptoms became clear—loss of smell, digestive-tract issues—and these weren't likely to be due to infection of the respiratory tract. And over time, what also became apparent is that the symptoms didn't necessarily fade when the virus was cleared.

As we've studied the virus more, we've learned that the protein it uses to latch on to cells is present in a lot of different tissues in the body, suggesting that a wide variety of different effects could be the direct product of infections of the cells there. This week, the effect that seems to be grabbing attention is heart problems, spurred by a Scientific American article that (among other things) considers the stories of professional and college athletes who have been infected. That was followed by a report that roughly 30 percent of college athletes who've contracted the virus end up with inflammation of the heart muscle, called myocarditis—a number that ESPN is now saying is an accidental exaggeration.

Both reports are heavy on anecdote, but this is not a new thing; ESPN had reported on myocarditis in college athletes back in early August. And, more significantly, the scientific community has been looking into the issue for months. So far, its conclusion is that there are likely to be heart complications, even in patients who had mild COVID-19 symptoms. But the long-term implications of these problems aren't yet clear.

Problems for the heart

One of the first indications of a potential problem came all the way back in March, courtesy of researchers in Wuhan who had tracked some of the first COVID-19 patients. In their study, roughly 20 percent of a group of 416 hospitalized patients had some indications of cardiac problems. The researchers used a variety of blood tests to look for proteins that normally reside inside cardiac muscle cells but can be released into the blood when those cells get damaged. (For an example of one of the assays the Wuhan researchers used, see this description of the troponin test that's commonly used to check for heart problems.)

The researchers only managed to hook 14 of the individuals up to an ECG to check the heart's electrical activity during the period when these assays were suggesting there could be problems. All 14 of them, however, showed abnormal heart rhythms.

Although suggestive, that was largely where things stood for a number of months. That changed in July, when a German group reported MRI imaging of a cohort of 100 patients who had been diagnosed as having a SARS-CoV-2 infection. The median age of these patients was just 49 years, meaning they were far younger than the group that's considered to be high risk for COVID-19 complications. And the group had already recovered from the virus (two-thirds without requiring hospitalization), suggesting anything that turned up was due to a lingering problem rather than a direct impact of an ongoing infection.

Yet there were still problems. Seventy-one percent of the patients showed signs of heart problems using the protein test linked above. And MRIs frequently showed problems with the heart tissue itself in 78 percent of them, with inflammation being the most common symptom. None of the problems correlated with time since diagnosis, suggesting that these issues might persist for a while after infections were cleared.

What's at fault?

While evidence was building of some cardiac involvement, the reasons for the problem were far less clear. Breathing difficulties could cause the heart to work harder, which could exacerbate any underlying conditions. And COVID-19 appears to involve an inflammatory response, which could involve the heart even without the organ being directly infected. But the fact that younger people with mild symptoms also seemed to be having problems makes

these explanations less likely. And a study from late July used heart tissue from autopsies of COVID-19 patients to confirm that the virus was detectable in the heart itself.

But, on its own, this finding is not particularly informative. The heart is a complex organ that relies on a combination of muscle cells, blood vessels to keep them supplied with nutrients and oxygen, and specialized conductive cells that help coordinate the electrical impulses that drive its beating. Problems with any of those could conceivably produce some of the issues seen here.

While details of what the virus might be doing hasn't yet hit the peer-reviewed literature, there is a draft paper that seems to fill in many of the details. To figure out what cells the virus might infect, the researchers directed stem cells to produce cardiac muscle cells, then exposed those to the virus. These could be infected by the virus, although it's relatively easy to infect cells in culture dishes.

Still, the researchers identified key signs of the viral infection in these culture cells: alterations in the activity of specific genes, and disruption of some of the muscle structures. They then turned to samples of heart tissue from donors who had died of COVID-19 and used these to show that similar changes had occurred in this heart tissue. Combined, these results indicate that at least some of the issues seen in COVID-19 patients are likely to be the result of the infection of heart muscles by the virus.

Too many unknowns

So, there's definitely support for the possibility that some of the athletes mentioned in the recent news reports are seeing a direct impact of COVID-19 on heart function. But without the sort of data seen in these studies, establishing a direct connection is impossible at this point. The studies have identified what to look for using blood tests and MRIs; whether these tests have been done isn't clear based on public statements.

A lot of follow-up work is needed to understand what's going on in the heart of COVID-19 patients. We still don't know when the cardiac symptoms arise, how long they persist, or what factors might make their occurrence more likely. The fact that they exist at all, however, should inform our management of the pandemic. Some suggested approaches involve allowing otherwise healthy, younger people to be put at elevated risk of infection. If cardiac complications occur at the rates seen in some of these studies, that approach could involve unacceptable risks.

Updated with new information from ESPN.

https://bit.ly/3bwPzya

The evidence is in. WHO says corticosteroids really do save lives of people critically ill with COVID-19

Readily available drugs, which dampen the runaway inflammatory response in patients severely ill with COVID-19, save lives, according to evidence released this week.

Andrew McLachlan*

An analysis by the World Health Organisation (WHO), which drew together results from several studies, confirms the benefit of this group of anti-inflammatory steroid drugs, known as corticosteroids.

While earlier studies showed the apparent benefit of one of these drugs, dexamethasone, this latest evidence goes further.

It shows other cheap and readily available corticosteroid drugs, including hydrocortisone, could benefit patients at the life-threatening stages of coronavirus infection.

Remind me again, what are corticosteroids?

Corticosteroids have been used for decades to treat a variety of inflammatory conditions. These include severe forms of lung inflammation, such as pneumonia, shock due to infection, and severe respiratory syndromes. They are also used to treat more common conditions, including asthma and eczema.

These medicines are on the WHO list of essential medicines, meaning they are widely available (usually at low cost).

What do we already know about corticosteroids for COVID-19?

In June, early release of results from the RECOVERY trial showed dexamethasone reduced the risk of death by up to a third in people hospitalised with COVID-19 who needed a ventilator to help them breathe. Results of the dexamethasone trial were released early. Despite the early release of the trial results, and limited details at the time, the findings were compelling and clinical practice changed. Several other trials were stopped. All patients switched to receive active treatment with a corticosteroid. The results of the RECOVERY trial have since been formally peer reviewed and published.

What does the latest evidence say?

The WHO drew together results from seven randomised clinical trials, including data from 1,703 critically ill patients with COVID-19. This is a powerful and compelling way to combine information and truly address the question of whether these medicines benefit people in hospital critically unwell with COVID-19.

The study, which included patients from Australia and New Zealand, found almost 33% of people treated with corticosteroids died within 28 days of treatment. This was compared with 41% of patients who received supportive care (or placebo). Corticosteroid treatment helped patients whether or not they needed ventilation or oxygen. Importantly, the analysis also concluded the benefits were not specific to one corticosteroid drug but were the same for dexamethasone and hydrocortisone.

Corticosteroids can also have an impact on the immune system. So the researchers looked at the risk of infection from other causes, for example bacterial pneumonia, and found it was not a major concern.

What does this mean for patients?

The weight of evidence has led WHO guidelines this week to strongly recommend using corticosteroids to treat people with severe or critical COVID-19.

This aligns with current Australian guidelines for treating hospitalised patients with COVID-19 needing oxygen support.

Corticosteroids are not for everyone and are not a cure

It is important to remember these findings only apply to using corticosteroids in critically ill people hospitalised with COVID-19. There is currently limited information to suggest these medicines are appropriate for people with mild COVID-19.

While corticosteroids help treat the body's response to the coronavirus infection, they are not antiviral drugs. They do not inhibit the virus itself, so they are not a cure.

A new way of doing research

Usually, several clinical trials on a common theme are published over a series of years. Then a meta-analysis draws together their results, publishing these combined results much later.

But the amazing thing about this latest evidence is the meta-analysis included data from clinical trials published *at the same time*. This shows a degree of co-operation and collaboration between researchers to share data to urgently address important research questions that guide clinical care.

Evidence to guide the best treatments and management for people with COVID-19 continues to emerge. You can follow the evidence and how it's applied in Australia here.

Andrew McLachlan is a Friend of The Conversation.

** Head of School and Dean of Pharmacy, University of Sydney*

Disclosure statement

Andrew McLachlan receives research funding from the NHMRC and the Sydney Pharmacy School receives research scholarship funding from GSK for a PhD student under his supervision. Andrew has served as a paid consultant on Australian government committees related to medicines regulation and anti-doping. Andrew does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article.

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https://bit.ly/3bAPQjC

Common cold combats influenza

As the flu season approaches, a strained public health system may have a surprising ally -- the common cold virus.

Rhinovirus, the most frequent cause of common colds, can prevent the flu virus from infecting airways by jumpstarting the body's antiviral defenses, Yale researchers report Sept. 4 in the journal *The Lancet Microbe*.

The findings help answer a mystery surrounding the 2009 H1N1 swine flu pandemic: An expected surge in swine flu cases never materialized in Europe during the fall, a period when the common cold becomes widespread.

A Yale team led by Dr. Ellen Foxman studied three years of clinical data from more than 13,000 patients seen at Yale New Haven Hospital with symptoms of respiratory infection. The researchers found that even during months when both viruses were active, if the common cold virus was present, the flu virus was not.

"When we looked at the data, it became clear that very few people had both viruses at the same time," said Foxman, assistant professor of laboratory medicine and immunobiology and senior author of the study.

Foxman stressed that scientists do not know whether the annual seasonal spread of the common cold virus will have a similar impact on infection rates of those exposed to the coronavirus that causes COVID-19.

"It is impossible to predict how two viruses will interact without doing the research," she said.

To test how the rhinovirus and the influenza virus interact, Foxman's lab created human airway tissue from stem cells that give rise to epithelial cells, which line the airways of the lung and are a chief target of respiratory viruses. They found that after the tissue had been exposed to rhinovirus, the influenza virus was unable to infect the tissue. "The antiviral defenses were already turned on before the flu virus arrived," she said.

The presence of rhinovirus triggered production of the antiviral agent interferon, which is part of the early immune system response to invasion of pathogens, Foxman said. "The effect lasted for at least five days," she said. Foxman said her lab has begun to study whether introduction of the cold virus before infection by the COVID-19 virus offers a similar type of protection.

Other members of the Yale research team were Anchi Wu, Valia Mihaylova, and Marie Landry. Wu and Mihaylova are co-first authors of the study, which was primarily funded by the National Institutes of Health and the National Institute of General Medical Sciences.

https://bit.ly/2Gwktvb

Scientists develop new compound which kills both types of antibiotic resistant superbugs

Researchers at the University of Sheffield have developed a new compound that is able to kill both gram-positive and gram-negative antibiotic-resistant bacteria.

Gram-positive and gram-negative bacteria have different cell wall structures, but the new antibiotic compound is able to pass through the cell wall of both forms of bacteria and then bind to the DNA.

The findings, published in *Chemical Science*, pave the way for developing new treatments for all kinds of antibiotic resistant bacteria, including the gram-positive MRSA and gram-negative E.Coli.

The team from the University of Sheffield has previously developed new compound leads that specifically target gram-negative bacteria, but this new compound is a broad spectrum antimicrobial which means it is just as effective in both types of bacteria.

Gram-negative bacteria strains are particularly difficult to treat as their cell wall prevents drugs from getting into the microbe, they

can cause infections including pneumonia, urinary tract infections and bloodstream infections.

The team worked with colleagues at the Science and Technology Facilities Council's (STFC) Rutherford Appleton Laboratory (RAL). Professor Jim Thomas, Principal Investigator of the research from the University of Sheffield, said: "Antimicrobial resistance is an increasing problem with many studies predicting a medical global emergency, so broad spectrum antimicrobials which work against resistant pathogens are urgently needed. As the compound is luminescent it glows when exposed to light. This means we were able to follow the uptake and effect on bacteria using advanced microscopy techniques available at STFC's Rutherford Appleton Lab."

Antimicrobial resistance is already responsible for 25,000 deaths in the EU each year, and unless this rapidly emerging threat is addressed, it's estimated by 2050 more than 10 million people could die every year due to antibiotic resistant infections. Doctors have not had a new treatment for gram-negative bacteria in the last 50 years, and no potential drugs have entered clinical trials since 2010.

https://bit.ly/2GCNipZ

Post-COVID syndrome severely damages children's hearts

'Immense inflammation' causing cardiac blood vessel dilation

San Antonio, Texas, USA - Multisystem inflammatory syndrome in children (MIS-C), believed to be linked to COVID-19, damages the heart to such an extent that some children will need lifelong monitoring and interventions, said the senior author of a medical literature review published Sept. 4 in *EClinicalMedicine*, a journal of *The Lancet*.

Case studies also show MIS-C can strike seemingly healthy children without warning three or four weeks after asymptomatic infections, said Alvaro Moreira, MD, MSc, of The University of Texas Health Science Center at San Antonio. Dr. Moreira, a neonatologist, is an assistant professor of pediatrics in the university's Joe R. and Teresa Lozano Long School of Medicine.

"According to the literature, children did not need to exhibit the classic upper respiratory symptoms of COVID-19 to develop MIS-C, which is frightening," Dr. Moreira said. "Children might have no symptoms, no one knew they had the disease, and a few weeks later, they may develop this exaggerated inflammation in the body."

Results

The team reviewed 662 MIS-C cases reported worldwide between Jan. 1 and July 25. Among the findings:

- ***71% of the children were admitted to the intensive care unit (ICU).***
- ***60% presented with shock.***
- ***Average length of stay in the hospital was 7.9 days.***
- ***100% had fever, 73.7% had abdominal pain or diarrhea, and 68.3% suffered vomiting.***
- ***90% had an echocardiogram (EKG) test and 54% of the results were abnormal.***
- ***22.2% of the children required mechanical ventilation.***
- ***4.4% required extracorporeal membrane oxygenation (ECMO).***
- ***11 children died.***

"This is a new childhood disease that is believed to be associated with SARS-CoV-2," Dr. Moreira said. "It can be lethal because it affects multiple organ systems. Whether it be the heart and the lungs, the gastrointestinal system or the neurologic system, it has so many different faces that initially it was challenging for clinicians to understand." The amount of inflammation in MIS-C surpasses two similar pediatric conditions, Kawasaki disease and toxic shock syndrome. "The saving grace is that treating these patients with therapies commonly used for Kawasaki - immunoglobulin and glucocorticosteroids - has been effective," Dr. Moreira said.

Cardiac abnormalities

Most of the 662 children suffered cardiac involvement as indicated by markers such as troponin, which is used with great accuracy in adults to diagnose heart attacks. "Almost 90% of the children (581) underwent an echocardiogram because they had such a significant cardiac manifestation of the disease," Dr. Moreira said.

The damage included:

- ***Dilation of coronary blood vessels, a phenomenon also seen in Kawasaki disease.***
- ***Depressed ejection fraction, indicating a reduced ability for the heart to pump oxygenated blood to the tissues of the body.***
- ***Almost 10% of children had an aneurysm of a coronary vessel. "This is a localized stretching or ballooning of the blood vessel that can be measured on an ultrasound of the heart," Dr. Moreira said.***

Children with an aneurysm are at the most risk of a future event. "These are children who are going to require significant observation and follow-up with multiple ultrasounds to see if this is going to resolve or if this is something they will have for the rest of their lives," Dr. Moreira said.

"And that's catastrophic to a parent who had a previously healthy child and then he/she is in the very small percentage of individuals who developed MIS-C after COVID-19 infection," he said.

Another finding from the case studies: Almost half of patients who had MIS-C had an underlying medical condition, and of those, half of the individuals were obese or overweight.

"Generally, in both adults and children, we are seeing that patients who are obese will have a worse outcome," Dr. Moreira said.

When compared to the initial COVID-19 infection, inflammatory markers in MIS-C were far more abnormal. For instance, troponin, the marker used in adults to diagnose heart attacks, was 50 times its normal level in children with MIS-C.

"Evidence suggests that children with MIS-C have immense inflammation and potential tissue injury to the heart, and we will need to follow these children closely to understand what implications they may have in the long term," Dr. Moreira said.

Researchers at Texas Children's Hospital in Houston, Georgetown University, the National Institutes of Health and the University of Pennsylvania joined Dr. Moreira in conducting this literature review.

Multisystem inflammatory syndrome in children: a systematic review

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Common class of drugs linked to increased risk of Alzheimer's disease

Anticholinergic medications are used for many conditions but might also accelerate cognitive decline, especially in older persons with biological or genetic risk factors

A team of scientists, led by researchers at University of California San Diego School of Medicine, report that a class of drugs used for a broad array of conditions, from allergies and colds to hypertension and urinary incontinence, may be associated with an increased risk of cognitive decline, particularly in older adults at greater risk for Alzheimer's disease (AD). The findings were published in the September 2, 2020 online issue of *Neurology*, the medical journal of the American Academy of Neurology.

Anticholinergic drugs are widely used for dozens of conditions, minor and major. Some of these medications require a prescription, while others can be purchased over the counter. They work by blocking acetylcholine -- a type of neurotransmitter or chemical messenger known to be critical for memory function -- from binding to receptors on certain nerve cells. The effect is to inhibit parasympathetic nerve impulses, which are involved in a variety of involuntary muscle movements, such as those in the gastrointestinal

tract and lungs, and bodily functions like salivation, digestion and urination.

Researchers reported that cognitively normal study participants who were taking at least one anticholinergic drug at baseline were 47 percent more likely to develop mild cognitive impairment (MCI), often a precursor to dementia such as AD, while being tracked over a period of up to a decade compared to participants who did not take such drugs.

"This study, led by Alexandra Weigand, suggests that reducing anticholinergic drug use before cognitive problems appear may be important for preventing future negative effects on memory and thinking skills, especially for people at greater risk for Alzheimer's disease," said senior author Lisa Delano-Wood, PhD, associate professor in the Department of Psychiatry at UC San Diego School of Medicine. Weigand is a graduate student in the San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology.

Six hundred and eighty-eight adults were involved in the study, evenly divided by sex with an average age of 74. None of the participants displayed cognitive or memory problems at the beginning of the study. Each reported whether they were taking anticholinergic drugs. One-third were taking such medications, with an average of 4.7 anticholinergic drugs per person. Participants were given annual comprehensive cognitive tests for up to 10 years.

The scientists also looked at whether participants had biomarkers for AD in their cerebrospinal fluid, such as certain types of proteins, or a well-known genetic risk factor for AD. They found that participants with AD biomarkers who were taking anticholinergic drugs were four times more likely to develop MCI than persons lacking biomarkers and not taking the drugs.

Similarly, persons at genetic risk for AD who took anticholinergic drugs were approximately 2.5 times more likely to develop MCI than those without genetic risk factors and who were not taking the drugs.

"We believe this interaction between anticholinergic drugs and Alzheimer's risk biomarkers acts in a 'double hit' manner," said Weigand, the study's first author. "In the first hit, Alzheimer's biomarkers indicate that pathology has started to accumulate in and degenerate a small region called the basal forebrain that produces the chemical acetylcholine, which promotes thinking and memory. In the second hit, anticholinergic drugs further deplete the brain's store of acetylcholine. This combined effect most significantly impacts a person's thinking and memory."

Study authors noted that, although older persons metabolize anticholinergic drugs differently than younger people, anticholinergic medications were being taken at levels much higher than the lowest effective dose recommended for older adults, with 57 percent taken at twice the recommended dosage and 18 percent at least four times the recommended dosage.

"This points to a potential area for improvement since reducing anticholinergic drug dosages may possibly delay cognitive decline," said Weigand. "It's important for older adults who take anticholinergic medications to regularly consult with their doctors and discuss medication use and dosages."

Delano-Wood noted that more work is needed to examine brain and cognitive effects of anticholinergic medications and whether these medications accelerate age-related cognitive changes or directly lead to neurodegenerative disorders, such as AD. "Clinical 'deprescribing' studies are currently underway at certain research sites across the nation in an effort to investigate whether reducing or stopping use of these drugs does, in fact, lead to reductions in progressive cognitive impairment," Delano-Wood said.

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Sewell, James B. Brewer and Howard H. Feldman, UC San Diego; and Noll L. Campbell, Regenstrief Institute and Indiana University.

https://bit.ly/2QY6tfX

Does the COVID-19 cytokine storm exist?

Research may have an impact on the chances of success of a specific treatment

Inflammatory proteins, also known as cytokines, play a crucial role in the immune response. If this immune response is too strong, a phenomenon known as "cytokine storm", it can cause harm to the patient. It has been thought that a cytokine storm contributes to disease severity in patients with COVID-19. Following the measurement of several important cytokines in patients with COVID-19 and various other severe diseases, researchers at Radboud university medical center now show that COVID-19 is not characterized by a cytokine storm. This may have consequences for the treatment of these patients, the researchers write in *JAMA*.

The cytokine storm in COVID-19 patients is not clearly defined. In many cases, different cytokines are evaluated and no comparison has been made with other diseases. Therefore, uncertainty and doubt exists concerning the cytokine storm in these patients.

Various patient groups

Researchers from the Intensive Care (IC) department at Radboud university medical center have now measured the concentration of three essential cytokines in the blood of patients admitted to the IC with several distinct conditions. They performed these measurements in patients with COVID-19 who met the criteria for a severe acute respiratory infection (ARDS), patients with bacterial septic shock (with and without ARDS), and patients who had been admitted to the IC after a cardiac arrest or severe trauma. The cytokines were measured using the same methods for each of the groups of patients.

Cytokine storm?

In the abovedescribed five patient groups, the concentration of tumor necrosis factor alpha (TNF-?) and interleukins 6 and 8 (IL-6, IL-8) was measured. The results were remarkable. Researcher Matthijs Kox: "The level of cytokines was significantly less elevated in COVID-19 patients than in patients with septic shock and ARDS. Compared to patients with septic shock without ARDS, so without severe pulmonary disease, patients with COVID-19 also displayed markedly lower levels of IL-6 and IL-8. The cytokine concentrations in COVID-19 patients were similar to those in IC patients with trauma or cardiac arrest, conditions that are not noted for a cytokine storm."

Possible consequences

The results from this study show that COVID-19 is not characterized by a cytokine storm. Professor of Intensive Care Medicine Peter Pickkers: "The severe disease observed in critically ill COVID-19 patients is therefore not explained by strongly elevated levels of inflammatory proteins in the blood. This means that critically ill COVID-19 patients likely will not benefit from specific anti-cytokine therapies."

Publication in JAMA: Cytokine levels in critically ill patients with COVID-19 and other conditions - Matthijs Kox, Nicole J.B. Waalders, Emma J. Kooistra, Jelle Gerretsen, Peter Pickkers