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COVID Brings Evolutionary Virologists Out of the Shadows, Into the Fight

It has been a strange, exhausting year for many evolutionary virologists.

Jillian Mock

"Scientists are not used to having attention and are not used to being in the press and are not used to being attacked on Twitter," Martha Nelson, PhD, staff scientist who studies viral evolution at the National Institutes of Health (NIH), told *Medscape Medical News*. Over the past year and a half, the theory of evolution has been thrust into the spotlight — more now than ever, perhaps, as the world is stalked by the Delta variant and fears arise of a mutation that's even worse.

We've also debated the origins of SARS-CoV-2 and the rise of the Delta variant, and have speculated about vaccine efficacy and the possible need for booster shots. In all these instances, consciously or not, we're engaging with the field of evolutionary virology.

It has been central to deepening our understanding of the ongoing pandemic, even as SARS-CoV-2 has exposed gaps in what we understand about how viruses behave and evolve.

Evolutionary virology experts believe that after the pandemic, their expertise and tools could be applied to and integrated with clinical medicine to improve outcomes and our understanding of disease.

"From our perspective, evolutionary biology has been a side dish and something that hasn't been integrated into the core practice of medicine," said Nelson. "I'm really curious to see how that changes over time."

Pandemic Evolution

Novel pathogens, antibiotic-resistant bacteria, and cancer cells are all products of ongoing evolution. "Just like cellular organisms, viruses have genomes, and all genomes evolve," Eugene Koonin, PhD, evolutionary genomics group leader at the NIH, told *Medscape Medical News*.

Compared to cellular organisms, viruses evolve quite fast, he said.

A study recently published in the *Proceedings of the National Academy of Sciences (PNAS)* exemplifies evolutionary virology in action. In the study, Koonin and fellow researchers analyzed more than 300,000 genome sequences of SARS-CoV-2 variants that were publicly available as of January 2021 and mapped all the mutations in each sequence. The researchers identified a small subset of mutations that arose independently more than once and that likely aided viral adaptation, said Nash Rochman, PhD, a research fellow at the NIH and co-author of the *PNAS* study.

Many of these mutations were concentrated in two areas of the genome — the receptor binding domain of the spike protein, and a region of the nucleocapsid protein — and were often grouped together, possibly creating greater advantages for the virus than would have occurred individually, he said.

The researchers also found that from the beginning of the pandemic, the SARS-CoV-2 genome has been evolving and diversifying in different regions around the world, allowing for the rise of new lineages and, possibly, even new species, Koonin said.

During the pandemic, researchers have used evolutionary virology tools to tackle many other questions. For example, Nelson tracked the spread of SARS-CoV-2 across Europe and North America. In a study by Rochman and Koonin that is currently undergoing peer review, the investigators found recently vaccinated individuals, who are only partially immune, are at the highest risk for incubating antibody-resistant variants.

C. Brandon Ogbunu, PhD, an evolutionary geneticist at Yale University whose work is focused on disease evolution, studied whether SARS-CoV-2 would evolve to become more transmissible, and if so, would it also become more or less virulent. His lab also

investigated the transmission and spread of the virus.

"I think the last year, on one end, has been this opportunity to apply concepts and perspectives that we've been developing for the last several decades," Ogbunu told *Medscape Medical News*. "At the same time, this pandemic has also been this wake-up call for many of us with regards to revealing the things we do not understand about the ways viruses infect, spread, and how evolution works within viruses."

He emphasizes the need for evolutionary biology to partner with other fields — including information theory and biophysics — to help unlock viral mysteries: "We need to think very, very carefully about the way those fields intersect."

Nelson also points to the need for better, more centralized data gathering in the United States. The sheer volume of information scientists have collected about SARS-CoV-2 will aid in the study of virus evolution for years to come, said Koonin.

Evolution in Medicine

Evolutionary virology and related research can be applied to medicine outside of the context of a global pandemic. "The principles and technical portions of evolutionary virology are very applicable to other diseases, including cancer," Koonin said.

Viruses, bacteria, and cancer cells are all evolving systems. Viruses and bacteria are constantly evolving to thwart drugs and vaccines. How physicians and healthcare professionals practice medicine shapes the selection pressures driving how these pathogens evolve, Nelson said.

The rise of antibiotic-resistant bacteria is a particularly relevant example of how evolution affects the way physicians treat patients. Having an evolutionary perspective can help inform how to treat patients most effectively, both for individual patients as well as for broader public health, she said.

"For a long time, there's been a lot of interest in pathogen evolution that hasn't translated so much into clinical practice," said Nelson. "There's been kind of a gulf between the research side of evolutionary virology and pathogen emergence and actual practice of medicine."

As genomic sequencing has become faster and cheaper, that gulf has started to narrow, she said. As this technology continues to prove itself by, for example, tracking the evolution of one virus in real time, Nelson hopes there will be a positive snowball effect, leading to more attention, investment, and improvements in genomic data and that its use in epidemiology and medicine will expand going forward.

Bringing viral evolution studies more into medicine will require a mindset shift, Ogbunu said. Clinical practice is, by design, very focused on the individual patient. Evolutionary biology, on the other hand, deals with populations and probabilities. Being able to engage with evolutionary biology would help physicians better understand disease and explain it to their patients, he said.

To start, Nelson recommends requiring at least one course in evolutionary biology or evolutionary medicine in medical school and crafting continuing education in this area for physicians (presentations at conferences could be one way to do this, she notes).

Nelson also recommends deeper engagement and collaboration between physicians who collect samples from patients and evolutionary biologists who analyze genetic data. This would improve the quality of the data, the analysis, and the eventual findings that could be relevant to patients and clinical practice.

Still, "my first and inevitable reaction is I would so much rather prefer to exist in relative obscurity," said Koonin, noting that the tragedy of the pandemic outweighs the advancements in the field.

Although there's no going back to prepandemic times, there is an enormous opportunity in the aftermath of COVID to increase

dialogue between physicians and evolutionary virologists to improve medical practice as well as public health.

Nelson summed it up: "Everything we uncover about these pathogens may help us prevent something like this again."

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Controversy flares over informing research subjects about 'incidental' genetic findings

Should people who volunteer for genomic studies be told about unrelated disease mutations that turn up in their sequence data?

By Meredith Wadman

The decadeslong debate about such "incidental findings," which can include genes that boost risk for cancer or heart disease, flared up again last week after bioethicists at the National Institutes of Health (NIH) published a study showing many participants who at first refuse those findings can change their minds. Controversially, it went on to suggest all research participants should routinely be told about their genetic risks for conditions that can be prevented or treated—a change from current practice.

The controversy pits researchers, many of them physicians, who see incidental findings as an opportunity to boost the health of the millions who have had their genomes analyzed, against others, mainly bioethicists, who stress the need to respect study participants' hesitation about receiving information that might expose them to genetic discrimination or simply be unwelcome. Deepening the divide, the study showed Black participants were more likely to refuse incidental results. "That strengthens the argument for saying we've really got to get true consent, opt-in consent from everyone," says Susan Wolf, a lawyer who teaches health law and bioethics at the University of Minnesota Law School.

In the study, researchers re-contacted research participants in a large NIH study 1 to 3 years after they enrolled. Initially, 1.9% of participants had declined to receive incidental findings. The team reports in *Genetics in Medicine* that of the 83 initial refusers, 41 changed their minds and accepted after being presented with new information, including an assurance that researchers would only return results on genes that raised the risk for serious conditions that were preventable or treatable, such as cancer and heart disease. (Six participants who initially accepted the findings changed their minds and refused after being reapproached.)

"I had a hypothesis that we would have a surprising number of people who would be willing to change their mind, but I had no idea how strong that would be," says senior author Ben Berkman, a lawyer who heads the section on the ethics of genetics and emerging technologies at NIH's Department of Bioethics. Notably, he adds, 46% of those who changed their minds misremembered, and thought they had consented at the get-go.

In current research studies that offer to return incidental findings, participants need to opt-in, affirming their desire to receive such results. Many bioethicists say the ability to actively choose whether to receive such results protects patients' rights to decide what information is generated about them and guard their privacy.

Berkman and his co-authors conclude instead that, given the number of minds that were changed during their study, an opt-out system would be better: Researchers should notify participants during the initial informed consent process that they will receive incidental results, and withhold the findings only if they actively refuse, the authors recommend. NIH itself appears open to that approach; the press release for the study announced, "New study brings into question current policies on receiving secondary genomic findings."

For Berkman, the issue is clear: The results could be lifesaving, spurring people to get medical care or early, preventive screenings against diseases like colon cancer. "There has been this hyperfocus

on this small number of people who don't want this information," says Berkman, who is also the deputy director of the bioethics core at the NIH's National Human Genome Research Institute (NHGRI). "Should we really be making policy on the basis of the interests of this tiny group?"

In the study, however, Black participants were significantly more likely than others to refuse incidental findings, sometimes expressing distrust of NIH. They initially rejected receipt of secondary findings at twice the rate of white participants and were less likely to change their minds after being reapproached. That finding has intensified other bioethicists' qualms about automatically sending incidental results.

"This research makes a recommendation without any regard to the Black participants' answers," says Keisha Ray, a bioethicist at the McGovern Center for Humanities & Ethics at the University of Texas Health Science Center, Houston. "Why isn't this their recommendation: `Based on the answers and hesitation expressed by the Black participants and their fear that their genetic information will be misused by the NIH, we recommend that secondary genetic information should not be given to participants unless they directly consent to knowing?'"

Berkman responds that the small number of Black participants—57--makes him "wary of making a concrete policy suggestion" without more data.

To bioethicist Faith Fletcher of the Baylor College of Medicine, the new study points to the urgent need for more research. She calls for "work to find out why participants refused and how we use information from the study to figure out ethically informed ways to handle secondary findings."

Leslie Biesecker, a clinical and molecular geneticist at NHGRI who was not involved with the study, says "This study specifically highlights the disadvantages of the check-box approach." Asking participants to simply check a box to opt in or out is "a lousy substitute for working together with participants in a thoughtful and flexible way." He also bemoans that the most common reason given for declining, offered by more than half of initial refusers, was that the information would make them "worried or sad." "I am aware of no other specialty in medicine that withholds potentially lifesaving information from patients because of a concern about the patient being worried or sad," he says.

To Robert Green, a physician-scientist and medical geneticist at Harvard University who was not involved with the new study, it is "stunning" that only a small number of research studies return incidental results in the first place. "There have been tens of millions of people around the world who have either been genotyped or sequenced for research. And only a tiny, tiny fraction of those have ever been offered the opportunity to have any of those results returned to them for their potential medical benefit." But he thinks the "zeitgeist" is changing. For instance, NIH's huge All of Us Study is returning incidental findings to those who opt in.

Green, Biesecker, and others stirred controversy in 2013 when they published, for the American College of Medical Genetics and Genomics, a list of more than 50 genes that ACMG recommended should be tested in any patient undergoing genetic screening in a clinical setting, with the information automatically returned to patients. After a storm of pushback, ACMG backed off, saying patients should be allowed to opt out of receiving such findings.

One of the co-authors of the original ACMG list now calls the automatic return of incidental findings from research projects "a bridge too far." "Even though the number of people who did not want the results back is very small," says Robert Nussbaum, chief medical officer at Invitae, a medical diagnostics company, "do we want to `ride roughshod' over [them]? The answer to that is probably no."

https://bit.ly/3rTVHZR

Do you handle stress well? Thank your dad

Research finds that mice display the same stress responses as their fathers

Dana Smith Neuroscience University of Pittsburgh

We all encounter stress in our daily lives, but new research is revealing that the way you respond to stress and adverse experiences may be inherited from your parents. Paternal exposure to stressors creates long-lasting changes in germ cells (sperm and eggs) that may be inherited by future generations and determine how they react to stress.

In a recent study published in the *Journal of Neuroscience*, researchers exposed male mice to chronic stress, then measured how it affected the stress responses of their male and female offspring, produced both through natural mating and artificial insemination. They discovered that offspring displayed the same stress phenotype as their fathers. For example, a father deemed susceptible to stress had offspring that showed more anxiety- and depression-like behaviors when they were exposed to stressors in adulthood, whereas resilient fathers had resilient offspring.

Interestingly, the transmission of stress phenotype occurred in both the offspring resulting from natural mating and those from artificial insemination. This finding indicates that the stress-induced alterations in sperm directly contribute to stress phenotype transmission. The researchers also discovered that exposure to stress drastically affected sperm RNA sequences.

This study provides new insight into how stress responses can be inherited across generations and the role sperm RNA plays in transmitting stress susceptibility or resilience. So, the next time you respond well to a stressful life challenge, you may just want to thank your dad!

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Neuroeconomists find people behave selfishly toward a large group, remain generous to individuals

Financial scandals or just normal human behavior?

Neuroeconomists at the University of Zurich have shown in an experimental setting that most people are willing to steal half of the earnings of a large group if their personal gain exceeds 100 euro, even though the very same people are generous toward individuals.

In recent years, the general public has steadily lost confidence in financial institutions, economic authorities, and in particular, in corporate managers. People hold a view that key economic actors will do anything for profits, including harming large groups of fellow human beings.

And yet, modern behavioral economics and psychology tell a completely different story: Laboratory data has shown that people willingly share monetary gains with others, dislike inequality, and are very often generous. Recent evidence shows that dishonesty levels as measured in certain laboratory tasks are surprisingly low. The message is that people are prosocial and, if given opportunity, cheat just a little.

Opportunity to rob half of the gains from others

How can both observations be simultaneously true? Are high-level economic actors simply different? To find out, Carlos Alós-Ferrer, NOMIS Professor for Decision and Neuroeconomic Theory at the University of Zurich and his team designed the Big Robber Game, an experimental setting with 640 participants in a standard student sample. Students were placed in groups of 32, where all subjects were engaged in some remunerated activity and earned the same amount of money. Half of the participants, the robbers, were given the opportunity to anonymously steal half the earnings of the other 16 members of their group (and one of the 16 robber's decisions was actually implemented), which corresponded to more or less 100

Euros. But they could also steal less, say one-third, or one-tenth or nothing at all. So, what did they do?

Overwhelmingly ruthless in anonymous groups

More than half of all robbers went to the extreme and took the maximum possible, which was half of the earnings of all others. Over 80 percent took one-third or more, and almost nobody declined to rob. The students revealed an overwhelming willingness to inflict significant monetary harm to a large group of others. Furthermore, the decision to take the maximum was made on average more quickly than the decision to refrain from it, revealing a weaker moral struggle in the former case.

However, the very same study, participants displayed predominantly prosocial behavior in standard bilateral games. When asked how they wanted to split 10 Euros with just one other participant, they voluntarily transferred some money, even when the other person was powerless to retaliate if no money came. In general, their actions revealed that they disliked inequality. "Thus, the very same people displayed selfishness in the large high-impact decisions affecting a large group and generosity in the small bilateral, low-stakes interactions," Alós-Ferrer says. "This behavior arose spontaneously within our student population, with no significant differences due to gender or field of studies. Therefore, there is no need for arguments about high-level economic actors being different. The roots of corporate scandals seem to be in all of us."

Tradeoff between personal gain and other-regarding concerns

The finding that people behave selfishly toward a large group while being generous toward individuals suggests that harming many individuals might be easier than harming just one, in line with existing evidence that people are more willing to help one individual rather than many. According to the authors, the study also reflects the tradeoff between personal gain and other-regarding concerns: When facing an individual in a bilateral game, appropriating a given monetary amount can result in a large interpersonal difference. When appropriating income from a large group of people, the same personal gain involves a smaller percentual difference, and hence it is more likely to offset the inequality aversion. Alós-Ferrer says, "In economically relevant situations, many human decision makers might be willing to inflict significant harm on a relatively large number of people for personal gain, as long as that gain is of sufficient magnitude. Even more strikingly, in Western societies, 100 Euros might already be enough."

More information: *Carlos Alós-Ferrer et al, Generous with individuals and selfish to the masses, Nature Human Behaviour (2021). DOI: 10.1038/s41562-021-01170-0*

https://bit.ly/3iqjo8J

'Totally new' idea suggests longer days on early Earth set stage for complex life

A novel link between how fast our planet spun on its axis, which defines the length of a day, and the ancient production of additional oxygen

By Elizabeth Pennisi

Today, oxygen fuels much of life on Earth, but it wasn't always that way. Three billion years ago, this gas was scarce in the atmosphere and oceans. Knowing why oxygen became plentiful could illuminate the evolution of our planet's flora and fauna, but scientists have struggled to find an explanation satisfying to all. Now a research team has proposed a novel link between how fast our planet spun on its axis, which defines the length of a day, and the ancient production of additional oxygen. Their modeling of Earth's early days, which incorporates evidence from microbial mats coating the bottom of a shallow, sunlit sinkhole in Lake Huron, produced a surprising conclusion: as Earth's spin slowed, the resulting longer days could have triggered more photosynthesis

from similar mats, allowing oxygen to build up in ancient seas and diffuse up into the atmosphere.

That proposal, described today in *Nature Geoscience*, has intrigued some scientists. “The rise of oxygen [on Earth] is easily the most substantial environmental change in the history of our planet,” says Woodward Fischer, a geobiologist at the California Institute of Technology who was not involved with the work. This study offers “a totally new flavor of an idea. It’s making a connection that people haven’t made before.”

Earth was much different when life first took hold about 4 billion years ago, with vast shallow seas whose only living creatures were one-celled. Many of those early microbes were cyanobacteria, which can form mats on sediments and rock surfaces and today sometimes cause algal blooms deadly to fish and other aquatic animals. Microbes that became cyanobacteria evolved the molecular machinery for photosynthesis early on, letting them convert carbon dioxide and water into sugars and oxygen. Researchers have long thought these microbes provided Earth’s initial supply of oxygen, over the eons creating an environment that favored the evolution of aerobic life in all its forms. But they always puzzled over why about a billion years passed between the first photosynthetic microbes, which fossils indicate arose about 3.5 billion years ago, and the first good geological evidence for a buildup of oxygen.

Researchers already knew, from modeling the Moon’s distance from Earth and the resulting atmospheric and oceanic tides, that the infant Earth turned much faster on its axis than it does today. Many agree that 4.5 billion years ago, a day was only about 6 hours long. By about 2.4 billion years ago, the models predict, the pull of the Moon had slowed that spin to about a 21-hour day. Earth’s rotational speed then stayed constant for about a billion years, as its gravitational pull countered the Moon’s drag. Those forces fell out of balance about 700 million years ago, because the resonance cycle between Earth and the Moon is not completely stable, and the planet’s spin slowed to its current speed, creating a 24-hour day, according to the models

In 2016, after a chance suggestion, Judith Klatt, a biogeochemist now at the Max Planck Institute for Marine Microbiology, realized those slowdowns in Earth’s rate of spin mirrored big leaps in atmospheric oxygen. For example, oxygen first jumped during what’s called the Great Oxygenation Event, some 2.4 billion years ago, and then again during the Neoproterozoic era, more than a billion years later. During the Paleozoic, about 400 million years ago, there was a final major increase in atmospheric oxygen.

As a postdoc at the University of Michigan, Ann Arbor, Klatt had studied microbial mats growing on sediments in the Middle Island Sinkhole in Lake Huron. There, the water is shallow enough for the cyanobacteria to get enough sunlight for photosynthesis. Oxygen-depleted water and sulfur gas bubble up from the lake floor, creating anoxic conditions that roughly approximate conditions of early Earth.

Scuba divers collected samples of the microbial mats and in the lab, Klatt tracked the amount of oxygen they released under various day lengths simulated with halogen lamps. The longer the exposure to light, the more of the gas the mats released.

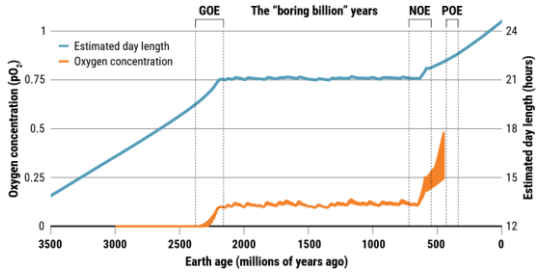
Excited, Klatt and Arjun Chennu, a modeler from the Leibniz Center for Tropical Marine Research, set up a numerical model to calculate how much oxygen ancient cyanobacteria could have produced on a global scale. When the microbial mat results and other data were plugged into this computer program, it revealed a key interaction between light exposure and the microbial mats.

Typically, microbial mats “breathe” in almost as much oxygen at night as they produce during the day. But as Earth’s spin slowed, the additional continuous hours of daylight allowed the simulated

mats to build up a surplus, releasing oxygen into the water. As a result, atmospheric oxygen tracked estimated day length over the eons: Both rose in a stepped fashion with a long plateau.

Did longer days fuel oxygen rise?

Models suggest the amount of oxygen on Earth increased in a stepwise fashion, starting with the Great Oxygenation Event (GOE) about 2.4 billion years ago, followed by a plateau for a "boring billion" years. Oxygen rose again in the Neoproterozoic Oxygenation Event (NOE) and Palaeozoic Oxidation Event (POE). Day length rose in the same stepped pattern, suggesting that the added light boosted photosynthetic microbes, fueling increases in oxygen.



K. Franklin/*Science*

This “elegant” idea helps explain why oxygen didn’t build up in the atmosphere as soon as cyanobacteria appeared on the scene 3.5 billion years ago, says Timothy Lyons, a biogeochemist at the University of California, Riverside. Because day length was still so short back then, oxygen in the mats never had a chance to build up enough to diffuse out. “Long daytimes simply allow more oxygen to escape to the overlying waters and eventually the atmosphere,” Lyons says.

Still, Lyons and others say, many factors likely contributed to the rise in oxygen. For example, Fischer suspects free-floating cyanobacteria, not just those in rock-affixed mats, were big players. Benjamin Mills, an Earth system modeler at the University of Leeds, thinks the release of oxygen-binding minerals by ancient volcanoes likely countered the early buildup of the gas at times and should be factored into oxygen calculations.

Nonetheless, changing day length “is something that should be considered in more detail,” he says. “I'll try to add it to our Earth system models.”

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Physicians Wearing White Coats Rated More Experienced

Female physicians were more likely to be judged as appearing less professional

Diedtra Henderson

Physicians wearing white coats were rated as significantly more experienced and professional than peers wearing casual attire. Regardless of their attire, however, female physicians were more likely to be judged as appearing less professional and were more likely to be misidentified as medical technicians, physician assistants, or nurses, found research published in *JAMA Network Open*.

"A white coat with scrubs attire was most preferred for surgeons (mean preference index, 1.3), whereas a white coat with business attire was preferred for family physicians and dermatologists (mean preference indexes, 1.6 and 1.2, respectively; $P < .001$)," Helen Xun, MD, Johns Hopkins University, Baltimore, and colleagues wrote. "A male model wearing business inner wear with a white coat, fleece jacket, or softshell jacket was perceived as significantly more professional than a female model wearing the same attire (mean professionalism score: male, 65.8; female, 56.2; mean difference in professionalism score: white coat, 12.06; fleece, 7.89; softshell, 8.82; $P < .001$).... A male model wearing hospital scrubs or fashion scrubs alone was also perceived as more professional than a female model in the same attire."

While casual attire, such as fleece or softshell jackets emblazoned with the names of the institution and wearer, has become more popular attire for physicians in recent years, the researchers noted

theirs is the first published research to identify associations between gender, attire, and how people distinguish between various healthcare roles. The study authors launched their web-based survey from May to June 2020 and asked people aged 18 years and older to rate a series of photographs of deidentified models wearing healthcare attire.

Inner wear choices were business attire versus scrubs with and without outer wear options of a long white coat, gray fleece jacket, or black softshell jackets. Survey respondents ranked the images on a 6-point Likert scale with 1 being the least experienced, professional, and friendly and 6 being the most experienced, professional, and friendly. Survey respondents also viewed individual images of male or female models and were asked to rate their professionalism on a scale of 0-100 — with 100 as the "most professional" as well as to identify their profession as either physician, surgeon, nurse, medical technician, or physician assistant.

The study team included 487 (93.3%) of 522 completed surveys in their analyses. Respondents' mean age was 36.2 years; 260 (53.4%) were female; 372 (76.4%) were white; 33 (6.8%) were Black or African American. Younger respondents and those living in the Western United States who had more exposure to physician casual attire appeared more accepting of it, the authors wrote.

"I remember attending my white-coat ceremony as a medical student, and the symbolism of it all representing me entering the profession. It felt very emotional and heavy and I felt very proud to be there. I also remember taking a 'selfie' in my long white coat as a doctor for the first time before my first shift as a resident. But, I've also been wearing that same white coat, and a large badge with a 'DOCTOR' label on it, and been mistaken by a patient or parent for something other than the physician," Alexandra M. Sims, a pediatrician and health equity researcher in Cincinnati, said in an interview.

"So, I'd really hope that the take-home here is not simply that we must wear our white coats to be considered more professional. I think we have to unpack and dismantle how we've even built this notion of 'professionalism' in the first place. Women, people of color, and other marginalized groups were certainly not a part of the defining, but we must be a part of the reimagining of an equitable healthcare profession in this new era."

As sartorial trends usher in more casual attire, clinicians should redouble efforts to build rapport and enhance communication with patients, such as clarifying team members' roles when introducing themselves. Xun and coauthors noted that addressing gender bias is important for all clinicians — not just women — and point to the need for institutional and organizational support for disciplines where gender bias is "especially prevalent," like surgery.

"This responsibility should not be undertaken only by the individuals that experience the biases, which may result in additional cumulative career disadvantages. The promotion of equality and diversity begins with recognition, characterization, and evidence-supported interventions and is a community operation," Xun and colleagues concluded.

"I do not equate attire to professionalism or experience, nor is it connected to my satisfaction with the physician. For myself and my daughter, it is the experience of care that ultimately influences our perceptions regarding the professionalism of the physician," Hala H. Durrah, MTA, parent to a chronically ill child with special healthcare needs and a Patient and Family Engagement Consultant, said in an interview. "My respect for a physician will ultimately be determined by how my daughter and I were treated, not just from a clinical perspective, but how we felt during those interactions."

The authors have disclosed no relevant financial relationships.

JAMA Netw Open. 2021;4:e2117779. Full text

https://bit.ly/2VqrCoE

Prehistoric Cave Art: Neanderthals Indeed Painted Andalusia's Cueva De Ardales

The origin and date of appearance of prehistoric cave art are the subjects of ongoing debate. Spain's Cueva de Ardales is one point of discussion.

There a flowstone formation is stained red in places. This coloring is apparently almost 65,000 years old but until now, a part of the scientific community attributed it to a natural coating of iron oxide deposited by flowing water. However, that hypothesis has just been rejected by the findings of an international team of scientists including a CNRS researcher.

Flowstone formation in the Sala de las Estrellas at Cueva de Ardales (Malaga, Andalusia), with the traces of red pigment analyzed and discussed in the article. **Credit: © João Zilhão, ICREA**

The team members analyzed samples of red residues collected from the flowstone surface and compared them with iron oxide–rich deposits in the cave. They concluded that the ochre-based pigment was intentionally applied, i.e. painted—by Neanderthals, as modern humans had yet to make their appearance on the European continent—and that, importantly, it had probably been brought to the cave from an external source.

Furthermore, variations in pigment composition between samples were detected, corresponding to different dates of application, sometimes many thousands of years apart. Thus, it seems that many generations of Neanderthals visited this cave and colored the draperies of the great flowstone formation with red ochre. This behavior indicates a motivation to return to the cave and symbolically mark the site, and it bears witness to the transmission of a tradition down through the generations. The scientists' findings have been published in *PNAS* today (August 2, 2021).

Reference: "The symbolic role of the underground world among Middle Palaeolithic Neanderthals" 2 August 2021, Proceedings of the National Academy of Sciences.
DOI: 10.1073/pnas.2021495118

https://wb.md/3fCtqSn

Doctors' Offices May Be a Hot Spot for Transmitting Infections

People who are seen after a patient with an influenzalike illness are 31.8% more likely to return to their doctor's office within 2 weeks with similar symptoms, new research shows.

Jaleesa Baulkman

Prior research has examined the issue of hospital-acquired infections. A 2014 study published in the New England Journal of Medicine, for example, found that 4% of hospitalized patients acquired a health care–associated infection during their stay. Furthermore, the Centers for Disease Control and Prevention estimates that, on any given day, one in 31 hospital patients has at least one health care–associated infection. However, researchers for the new study, published in Health Affairs, said evidence about the risk of acquiring respiratory viral infections in medical office settings is limited.

"Hospital-acquired infections has been a problem for a while," study author Hannah Neprash, PhD, of the department of health policy and management at the University of Minnesota School of Public Health, Minneapolis, said in an interview. "However, there's never been a similar study of whether a similar phenomenon happens in physician offices. This is especially relevant now when we're dealing with respiratory infections."

Methods and Results

For the new study, Neprash and her colleagues analyzed deidentified billing and scheduling data from 2016-2017 for

105,462,600 outpatient visits that occurred at 6,709 office-based primary care practices. They used the World Health Organization case definition for influenzalike illness "to capture cases in which the physician may suspect this illness even if a specific diagnosis code was not present." Their control conditions included exposure to urinary tract infections and back pain.

Doctor visits were considered unexposed if they were scheduled to start at least 90 minutes before the first influenzalike illness visit of the day. They were considered exposed if they were scheduled to start at the same time or after the first influenzalike illness visit of the day at that practice. Researchers quantified whether exposed patients were more likely to return with a similar illness in the next 2 weeks, compared with nonexposed patients seen earlier in the day. They found that 2.7 patients per 1,000 returned within 2 weeks with an influenzalike illness. Patients were more likely to return with influenzalike illness if their visit occurred after an influenzalike illness visit versus before, the researchers said.

The authors of the paper said their new research highlights the importance of infection control in health care settings, including outpatient offices.

Where Did the Exposure Occur?

Diego Hijano, MD, MSc, pediatric infectious disease specialist at St. Jude's Children's Research Hospital, Memphis, Tenn., said he was not surprised by the findings, but noted that it's hard to say if the exposure to influenzalike illnesses happened in the office or in the community. "If you start to see individuals with influenza in your office it's because [there's influenza] in the community," Hijano explained. "So that means that you will have more patients coming in with influenza."

To reduce the transmission of infections, Neprash suggested that doctors' offices follow the CDC guidelines for indoor conduct, which include masking, washing hands, and "taking appropriate infection control measures."

So potentially masking within offices is a way to minimize transmission between whatever people are there to be seen when it's contagious, Neprash said. "Telehealth really took off in 2020 and it's unclear what the state of telehealth will be going forward. [These findings] suggest that there's a patient safety argument for continuing to enable primary care physicians to provide visits either by phone or by video," he added.

Hijano thinks it would be helpful for doctors to separate patients with respiratory illnesses from those without respiratory illnesses.

Driver of Transmissions

Neprash suggested that another driver of these transmissions could be doctors not washing their hands, which is a "notorious issue," and Hijano agreed with that statement.

"We did know that the hands of physicians and nurses and care providers are the main driver of infections in the health care setting," Hijano explained. "I mean, washing your hands properly between encounters is the single best way that any given health care provider can prevent the spread of infections."

"We have a unique opportunity with COVID-19 to change how these clinics are operating now," Hijano said. "Many clinics are actually asking patients to call ahead of time if you have symptoms of a respiratory illness that could be contagious, and those who are not are still mandating the use of mask and physical distance in the waiting areas and limiting the amount of number of patients in any given hour. So I think that those are really big practices that would kind of make an impact in respiratory illness in terms of decreasing transmission in clinics."

The authors, who had no conflicts of interest said their hope is that their study will help inform policy for reopening outpatient care settings. Hijano, who was not involved in the study also had no conflicts.

https://bit.ly/3jwVCYb

Oral Vaccines Sometimes Fail in Resource-Poor Countries – New Research Helps Explain Why

Chronic gut disorder that occurs in regions with poor sanitation disrupts intestinal immune responses

A chronic gut disorder that occurs in regions with poor sanitation disrupts intestinal immune responses and impairs oral vaccine effectiveness in a mouse model of the disease, according to research led by UPMC Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine scientists.

The finding, published today (August 3, 2021) in *Immunity*, is important because oral vaccines delivered by liquid drops to the mouth, such as polio and rotavirus vaccines, are especially useful in low-income countries that may not have health care workers trained in administering vaccines through needles. They may also stimulate better local immunity in the gut, which is key for fending off diseases contracted by contaminated food and water — including some of the very infections that contribute to the gut disorder, called environmental enteric dysfunction, or EED.

"It is tragic that the exact vaccines that might help prevent EED don't work in children who have the disease," said Timothy Hand, Ph.D., senior author of the study and assistant professor of pediatrics and immunology at the R.K. Mellon Institute for Pediatric Research at UPMC Children's and director of Pitt's Gnotobiotic Core.

EED is caused by malnutrition and chronic gastrointestinal infection from contaminated food and water. Infection with viruses, parasites or bacteria combined with poor diet can trigger gut inflammation and damage the finger-like projections called villi that help absorb nutrients from food.

"EED can affect anyone, but it's a major problem in children because they're still developing," said Hand. "The result is that children with EED are stunted. They end up shorter in stature. But perhaps more importantly, it can significantly affect brain development: These children have less cognitive ability. And this is a lifelong problem; you can't restore that development later in life."

To learn more about the mechanisms behind oral vaccine failure, Hand and his team developed a mouse model of the disease. They induced EED-like symptoms by feeding the rodents a diet deficient in fat and protein and inoculating them with a strain of E. coli bacteria that invades gut cells.

Like humans with the disease, EED mice had stunted growth, shifts in the gut microbiome composition, elevated gut inflammation and shortened gut villi compared with control mice that received a normal diet with adequate fat and protein or animals that received a normal diet and bacteria or a poor diet without bacteria.

After giving the mice an oral vaccine, the researchers found that immune responses were severely compromised in those with EED. Vaccine-specific CD4+ T cells in the small intestine were about 18 times lower than in control mice.

Further experiments indicated that oral vaccine failure in EED mice was mediated by their gut microbiome. In response to microbiome-associated inflammation, T regulatory (Treg) cells accumulate in the small intestine of EED mice.

"Treg cells arise because there's too much inflammation and they help tamp down that inflammation," said Hand. "But unfortunately, a side effect is that they prevent local accumulation of vaccine-specific CD4+ T cells."

When the team used antibiotics to eliminate gut bacteria, vaccine effectiveness was restored in EED mice.

According to Hand, these findings support the idea that targeting the microbiome could help treat EED and improve vaccine success in children.

"Judicious use of antibiotics in these children might be able to reset

the small intestinal microbiome, reduce inflammation in the small intestine and reduce those Tregs," he said.

EED is rare in resource-rich countries but common in poorer countries that lack sewage systems and sanitation. About 150 million children worldwide live in conditions that put them at risk of getting the disease.

"If we could get flush toilets and plumbing to the world, we wouldn't have this disease," said Hand. "What's causing these chronic infections is that people are either drinking contaminated water or flies are transporting diseases from sewage to food."

In the future, Hand and his team plan to collaborate with researchers in countries where EED is a problem to better understand vaccine outcomes in children with this disease.

Reference: "Environmental enteric dysfunction induces regulatory T cells that inhibit local CD4+ T cell responses and impair oral vaccine efficacy" by Amrita Bhattacharjee, Ansen H.P. Burr, Abigail E. Overacre-Delgoffe, Justin T. Tometich, Deyi Yang, Brydie R. Huckestein, Jonathan L. Linehan, Sean P. Spencer, Jason A. Hall, Oliver J. Harrison, Denise Morais da Fonseca, Elizabeth B. Norton, Yasmine Belkaid and Timothy W. Hand, 3 August 2021, Immunity. DOI: 10.1016/j.immuni.2021.07.005

Additional authors on the research are Amrita Bhattacharjee, Ph.D., Ansen H.P. Burr, Abigail E. Overacre-Delgoffe, Ph.D., Justin T. Tometich and Brydie R. Huckestein, all of Pitt or UPMC, or both; Deyi Yang, of UPMC and Central South University, China; Jonathan L. Linehan, Ph.D., Sean P. Spencer, M.D., Ph.D., Jason A. Hall, Ph.D., Oliver J. Harrison, Ph.D., Denise Morais da Fonseca, Ph.D., and Yasmine Belkaid, PhD., all of the National Institutes of Health; and Elizabeth B. Norton, Ph.D., of Tulane University.

This research was supported by National Institutes of Health awards R21AI142051, 2015/25364-0 and T32AI089443, the R.K. Mellon Institute for Pediatric Research and UPMC Children's Hospital of Pittsburgh.

https://bit.ly/3ClLTwp

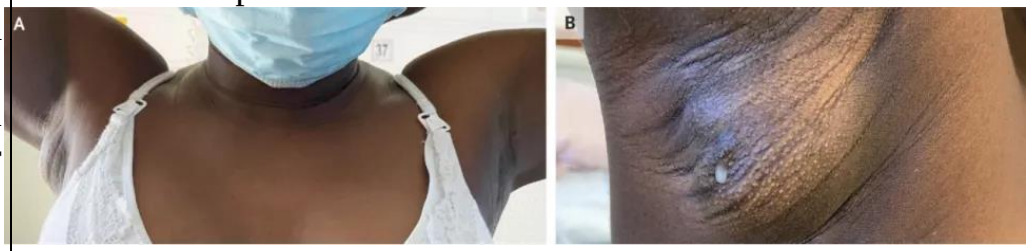
What caused a woman to lactate from her armpit?

The woman developed a painful mass in her right armpit two days after giving birth.

By Rachael Rettner - Senior Writer

Childbirth can trigger a number of odd body changes, but for a woman in Portugal, post-pregnancy symptoms were particularly curious: She started to lactate from her armpit, according to a new report.

The 26-year-old woman told doctors that she developed pain in her right armpit two days after giving birth, according to the report, published July 29 in The New England Journal of Medicine. When doctors examined the area, they found a round mass in her armpit. Surprisingly, the mass "released a white discharge when pressed," the authors, from Hospital de Santa Maria in Lisbon, Portugal, wrote in the report.



A woman in Portugal started to lactate from her armpit after giving birth. Above, images showing the mass in the woman's right armpit (left), and white discharge leaking from the mass (right.) **(Image credit: The New England Journal of Medicine ©2021)**

She was diagnosed with polymastia, or the presence of extra breast tissue in the body. Up to 6% of women are born with such "accessory" breast tissue, according to a 1999 paper published in the journal Mayo Clinic Proceedings. In some cases, this extra breast tissue includes a nipple or areola (the pigmented area surrounding the nipple), but in other cases, the breast tissue alone is present, without nipples or areola, Live Science previously reported.

The condition happens during fetal development, when the precursor cells to the mammary glands form along the "mammary ridge" or "milk line" that runs from the armpit to the groin on either side of the body, according to a 2014 paper in the American Journal of Roentgenology. Usually, these ridges disappear everywhere except for the breast. But when this doesn't happen, the body is left with residual breast tissue. The most common location for

accessory breast tissue is the armpit (also called the "axilla"), according to the 2014 paper.

If the accessory breast tissue does not have a nipple or areola, people might not realize they have extra breast tissue until they become pregnant or start breast-feeding, according to the 1999 paper. At this point, milk "comes in" to the accessory breast tissue just as it does in typical breast tissue, and women may experience swelling or pain in the area.

Some women can even pump breast milk from the accessory breast tissue. In the 1999 paper, the authors describe the case of an 18-year-old woman with accessory breast tissue in the armpit who was able to successfully pump axillary breast tissue for eight weeks to relieve discomfort and continue breast-feeding.

In the Portugal woman's case, she was reassured that the condition is benign. Doctors also told her that when undergoing routine breast cancer screening, the extra breast tissue would need to be examined for cancer just like typical breast tissue. It's unclear if the woman was able to breast-feed or pump milk from the accessory tissue.

https://bit.ly/3lC7NWk

Giant bird-eating centipedes exist — and they're surprisingly important for their ecosystem

Giant bird-eating centipedes may sound like something out of a science-fiction film — but they're not.

Authors Luke Halpin[*] Rohan Clarke[**] Rowan Mott[***]

On tiny Phillip Island, part of the South Pacific's Norfolk Island group, the Phillip Island centipede (*Cormocephalus coynei*) population can kill and eat up to 3,700 seabird chicks each year.

And this is entirely natural. This unique creature endemic to Phillip Island has a diet consisting of an unusually large proportion of vertebrate animals including seabird chicks.

As large marine predators, seabirds usually sit at the top of the food chain. But our new study, published in The American Naturalist, demonstrates this isn't always the case.

We show how large, predatory arthropods can play an important role in the food webs of island ecosystems. And the Phillip Island centipede achieves this through its highly varied diet.

A well-armed predator stirs in the night

Phillip Island centipede and black-winged petrel. **Luke Halpin, Author provided (no reuse)**

This centipede can grow to almost one foot (or 30.5cm) in length. It is armed with a potent venom encased in two pincer-like appendages called "forcipules", which it uses to immobilise its prey. Its body is protected by shield-like armoured plates that line each of the many segments that make up its length.

On warm and humid nights, these strictly nocturnal arthropods hunt through thick leaf litter, navigating a labyrinth of seabird burrows peppered across the forest floor. A centipede on the prowl will use its two ultra-sensitive antennae to navigate as it seeks prey.

The centipede hunts an unexpectedly varied range of quarry, from crickets to seabird chicks, geckos and skinks. It even hunts fish — dropped by seabirds called black noddies (*Anous minuta*) that make their nests in the trees above.

A frightful discovery

Soon after we began our research on the ecology of Phillip Island's burrowing seabirds, we discovered chicks of black-winged petrels (*Pterodroma nigripennis*) were falling prey to the Phillip Island centipede. We knew this needed further investigation, so we set out to unravel the mystery of this large arthropod's dietary habits.

To find out what these centipedes were eating, we studied their feeding activities at night and recorded the prey species they were targeting. We also monitored petrel chicks in their burrow nests

every few days, for months at a time. We eventually began to see consistent injury patterns among chicks that were killed. We even witnessed one centipede attacking and eating a chick.

From the rates of predation we observed, we calculated that the Phillip Island centipede population can kill and eat between 2,109 and 3,724 petrel chicks each year. The black-winged petrels — of which there are up to 19,000 breeding pairs on the island — appear to be resilient to this level of predation.

And the predation of black-winged petrels by Phillip Island centipedes is an entirely natural predator-prey relationship. By preying on vertebrates, the centipedes trap nutrients brought from the ocean by seabirds and distribute them around the island.

In some sense, they've taken the place (or ecological niche) of predatory mammals, which are absent from the island.

Restoration and recovery

Up until just a few decades ago the Phillip Island Centipede was very rare. In fact, it was only formally described as a species in 1984. After an intensive search in 1980, only a few small individuals were found. The species' rarity back then was most likely due to severely degraded habitats caused by pigs, goats and rabbits introduced by humans to the island.

The removal of these invasive pests enabled black-winged petrels to colonise. Their population has since exploded and they're now the most abundant of the 13 seabird species that breed on Phillip Island. They provide a high-quality food source for the Phillip Island centipede and have therefore likely helped centipede population to recover.

Ancient bone deposits in the soil suggest that prior to the black-winged petrel's arrival, Phillip Island was home to large numbers of other small burrow-nesting seabird species. It's likely the Phillip Island centipede preyed on these seabirds too.

Now, thanks to the conservation efforts of Norfolk Island National Park, the island's forest is regenerating alongside endemic species like the centipede, as well as the critically endangered Phillip Island hibiscus (*Hibiscus insularis*).

As a driver of nutrient transfer, the persistence of the Phillip Island centipede (and its healthy appetite) might just be key to the island's ecosystem recovery. But we'll need to do more research to fully understand the intricate links in this bustling food web.

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Disclosure statement
Luke Halpin is a recipient of the Endeavour Postgraduate Leadership Award from the Australian Government. This research was funded by the Holsworth Wildlife Research Endowment – Equity Trustees Charitable Foundation & the Ecological Society of Australia, BirdLife Australia Stuart Leslie Bird Research Award and the Australasian Seabird Group. Support was also provided by the New South Wales Department of Planning, Industry and Environment and Norfolk Island National Park.
Rohan Clarke receives funding from Parks Australia, the Australia and the Pacific Science Foundation. Rohan Clarke is affiliated with Monash University.
Rowan Mott is affiliated with the University of Adelaide.

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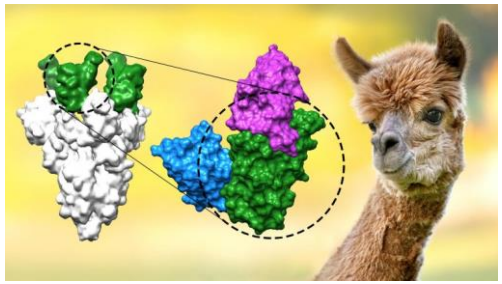
Highly Potent COVID Treatment: New Nanobodies Stop SARS-CoV-2 and Its Dangerous Variants

"Nanobodies" bind and neutralize the virus up to 1000 times better than previously developed mini-antibodies

Göttingen researchers have developed mini-antibodies that efficiently block the coronavirus SARS-CoV-2 and its dangerous new variants. These so-called nanobodies bind and neutralize the virus up to 1000 times better than previously developed mini-antibodies. In addition, the scientists optimized their mini-antibodies for stability and resistance to extreme heat. This unique combination makes them promising agents to treat COVID-19.

Since nanobodies can be produced at low costs in large quantities, they could meet the global demand for COVID-19 therapeutics.

The new nanobodies are currently in preparation for clinical trials. Antibodies help our immune system to fend off pathogens. For example, the molecules attach to viruses and neutralize them so that they can no longer infect cells.



The figure shows how two of the newly developed nanobodies (blue and magenta) bind to the receptor-binding domain (green) of the coronavirus spike protein (grey), thus preventing infection with Sars-CoV-2 and its variants. The nanobodies originate from alpacas and are smaller and simpler than conventional antibodies. **Credit: Max Planck Institute for Biophysical Chemistry**

Antibodies can also be produced industrially and administered to acutely ill patients. They then act like drugs, relieving symptoms and shortening recovery from the disease. This is established practice for treating hepatitis B and rabies. Antibodies are also used for treating COVID-19 patients. However, producing these molecules on an industrial scale is too complex and expensive to meet worldwide demand. Nanobodies could solve this problem.

Scientists at the Max Planck Institute (MPI) for Biophysical Chemistry in Göttingen (Germany) and the University Medical Center Göttingen (UMG) have now developed mini-antibodies (also known as VHH antibodies or nanobodies) that unite all the properties required for a potent drug against COVID-19. “For the first time, they combine extreme stability and outstanding efficacy against the virus and its Alpha, Beta, Gamma, and Delta mutants,” emphasizes Dirk Görlich, director at the MPI for Biophysical Chemistry.

At first glance, the new nanobodies hardly differ from anti-SARS-CoV-2 nanobodies developed by other labs. They are all directed against a crucial part of the coronavirus spikes, the receptor-binding domain that the virus deploys for invading host cells. The nanobodies block this binding domain and thereby prevent the virus from infecting cells.

“Our nanobodies can withstand temperatures of up to 95 °C without losing their function or forming aggregates,” explains Matthias Dobbelstein, professor and director of the UMG’s Institute of Molecular Oncology. “For one thing, this tells us that they might remain active in the body long enough to be effective. For another, heat-resistant nanobodies are easier to produce, process, and store.”

Single, double, and triple nanobodies

The simplest mini-antibodies developed by the Göttingen team already bind up to 1000 times more strongly to the spike protein than previously reported nanobodies. They also bind very well to the mutated receptor-binding domains of the Alpha, Beta, Gamma, and Delta strains. “Our single nanobodies are potentially suitable for inhalation and thus for direct virus neutralization in the respiratory tract,” Dobbelstein says. “In addition, because they are very small, they could readily penetrate tissues and prevent the virus from spreading further at the site of infection.”

A ‘nanobody triad’ further improves binding: The researchers bundled three identical nanobodies according to the symmetry of the spike protein, which is comprised of three identical building blocks with three binding domains. “With the nanobody triad, we literally join forces: In an ideal scenario, each of the three nanobodies attaches to one of the three binding domains,” reports Thomas Güttler, a scientist in Görlich’s team. “This creates a virtually irreversible bond. The triple will not let release the spike protein and neutralizes the virus even up to 30,000-fold better than the single nanobodies.” Another advantage: The larger size of the nanobody triad expectedly delays renal excretion. This keeps them in the body for longer and promises a longer-lasting therapeutic effect.

As a third design, the scientists produced tandems. These combine

two nanobodies that target different parts of the receptor-binding domain and together can bind the spike protein. “Such tandems are extremely resistant to virus mutations and the resulting ‘immune escape’ because they bind the viral spike so strongly”, explains Metin Aksu, a researcher in Görlich’s team.

For all nanobody variants – monomeric, double as well as triple – the researchers found that very small amounts are sufficient to stop the pathogen. If used as a drug, this would allow for a low dosage and thus for fewer side effects and lower production costs.

Alpacas provide blueprints for mini-antibodies

“Our nanobodies originate from alpacas and are smaller and simpler than conventional antibodies,” Görlich says. To generate the nanobodies against SARS-CoV-2, the researchers immunized three alpacas – Britta, Nora, and Xenia from the herd at the MPI for Biophysical Chemistry – with parts of the coronavirus spike protein. The mares then produced antibodies, and the scientists drew a small blood sample from the animals. For the alpacas, the mission was then complete, as all further steps were carried out with the help of enzymes, bacteria, so-called bacteriophages, and yeast. “The overall burden on our animals is very low, comparable to vaccination and blood testing in humans,” Görlich explains.

Görlich’s team extracted around one billion blueprints for nanobodies from the alpacas’ blood. What then followed was a laboratory routine perfected over many years: The biochemists used bacteriophages to select the very best nanobodies from the initially vast pool of candidates. These were then tested for their efficacy against SARS-CoV-2 and further improved in successive rounds of optimization.

Not every antibody is ‘neutralizing’. Researchers of Dobbelstein’s group therefore determined if and how well the nanobodies prevent the viruses from replicating in cultured cells in the lab. “By testing a wide range of nanobody dilutions, we find out which quantity suffices to achieve this effect,” explains Antje Dickmanns from Dobbelstein’s team. Her colleague Kim Stegmann adds: “Some of the nanobodies were really impressive. Less than a millionth of a gram per liter of medium was enough to completely prevent infection. In the case of the nanobody triads, even another twenty-fold dilution was sufficient.“

Also effective against current coronavirus variants

Over the course of the coronavirus pandemic, new virus variants have emerged and rapidly became dominant. These variants are often more infectious than the strain that first appeared in Wuhan (China). Their mutated spike protein can also ‘escape’ neutralization by some originally effective antibodies of infected, recovered, or vaccinated persons. This makes it more difficult even for an already trained immune system to eliminate the virus. This problem also affects previously developed therapeutic antibodies and nanobodies.

This is where the new nanobodies show their full potential, as they are also effective against the major coronavirus variants of concern. The researchers had inoculated their alpacas with part of the spike protein of the first known SARS-CoV-2 virus, but remarkably, the animals’ immune system also produced antibodies that are active against the different virus variants. “Should our nanobodies prove ineffective against a future variant, we can reimmunize the alpacas. Since they have already been vaccinated against the virus, they would very quickly produce antibodies against the new variant,” Güttler asserts confidently.

Therapeutic application in view

The Göttingen team is currently preparing the nanobodies for therapeutic use. Dobbelstein emphasizes: “We want to test the nanobodies as soon as possible for safe use as a drug so that they can be of benefit to those seriously ill with COVID-19 and those who have not been vaccinated or cannot build up an effective

immunity." The team is supported by experts in technology transfer: Dieter Link (Max Planck Innovation), Johannes Bange (Lead Discovery Center, Dortmund, Germany), and Holm Keller (kENUP Foundation).

The receptor-binding domain of SARS-CoV-2 is known to be a good candidate for a protein vaccine but so far difficult to manufacture economically on a large scale and in a form, which activates the immune system against the virus. Bacteria programmed accordingly produce incorrectly folded material. The Göttingen researchers discovered a solution for this problem: They identified special nanobodies that enforce correct folding in bacterial cells, without obstructing the crucial neutralizing part of the receptor-binding domain. This might allow for vaccines that can be produced inexpensively, can be quickly adapted to new virus variants, and can be distributed with simple logistics even in countries with little infrastructure. "The fact that nanobodies can help with protein folding was previously not known and is extremely interesting for research and pharmaceutical applications," Görlich says.

Reference: "Neutralization of SARS-CoV-2 by highly potent, hyperthermostable, and mutation-tolerant nanobodies" by Thomas Güttler, Metin Aksu, Antje Dickmanns, Kim M. Stegmann, Kathrin Gregor, Renate Rees, Waltraud Taxer, Oleh Rymarenko, Jürgen Schünemann, Christian Dienemann, Philip Gunkel, Bianka Mussil, Jens Krull, Ulrike Teichmann, Uwe Groß, Volker C. Cordes, Matthias Dobbelstein and Dirk Görlich, 24 July 2021, The EMBO Journal. DOI: 10.15252/embj.2021107985

https://bit.ly/3s1f17h

I went to a party with 14 other vaccinated people; 11 of us got COVID

It was what I expected. But it wasn't supposed to happen: I've been fully vaccinated for months

By Allan Massie For The Baltimore Sun

I was sitting on an examination table at an urgent care clinic in Timonium, giving my history to a physician's assistant. An hour later, she would call me to confirm that I was positive for COVID-19. Given the way that I felt, it was what I expected. But it wasn't supposed to happen: I've been fully vaccinated for months.

Five days earlier, I had gone to a house party in Montgomery County. There were 15 adults there, all of us fully vaccinated. The next day, our host started to feel sick. The day after that, she tested positive for COVID-19. She let all of us know right away. I wasn't too worried. It was bad luck for my friend, but surely she wasn't that contagious. Surely all of us were immune. I'd been sitting across the room from her. I figured I'd stay home and isolate from my family for a few days, and that would be that. And even that seemed like overkill.

The official Centers for Disease Control and Prevention guideline stated that, since I was fully vaccinated, I didn't need to do anything different unless I started developing symptoms. I'm an epidemiologist at a major medical research university, which has a dedicated COVID exposure hotline for staff. I called it, and workers said I didn't need to do anything.

Then, I started to hear that a few other people who had been at the party were getting sick. Then a few more. At this point, 11 of the 15 have tested positive for COVID.

Fortunately, none of us seems to be seriously ill. When fully vaccinated people experience so-called "breakthrough" infection, they tend not to progress to serious disease requiring hospitalization, and I expect that will be the case for us. But I can tell you that even a "mild" case of COVID-19 is pretty miserable. I've had fever, chills and muscle aches, and I've been weak enough that I can barely get out of bed. I don't wish this on anybody.

Our research group at work has shown that the COVID vaccine isn't always fully effective in transplant recipients. I'm proud of the work we've done. But once I got the vaccine, I figured the COVID battle was over for me. Out of an abundance of caution I took an

antibody test shortly after my second vaccine dose. It was off the charts.

As much as I hate me and my fully-vaccinated friends being sick, I've been thinking about what our little outbreak among means for the rest of us. Here's what I've concluded:

State and local health departments, and the CDC, need to do a better job collecting and reporting data on breakthrough infections. The CDC announced in May that it was only going to collect data on breakthrough infections that led to hospitalization or death, which are fortunately rare. But that means that outbreaks like ours will fly under the radar. Any of us could infect others, apparently including other vaccinated people. It's not clear if our group got sick because of a particularly virulent variant, because the vaccine is wearing off or for some other reason. Without good data, we'll never know.

Fully vaccinated people exposed to COVID need to isolate at home and get tested. I thought I might be overreacting by leaving work in the middle of the day and immediately moving to our basement at home. Now I'm glad I did.

Governments and businesses should consider bringing back masking requirements, even for vaccinated people. We're still at risk of getting sick, and we're still at risk of infecting others. The CDC recently recommended masks for vaccinated people in areas with over 50 new infections per 100,000 people per week. In the seven days before my exposure, Montgomery County had 19.4 new infections per 100,000 people.

Pharmaceutical companies, research institutions and governments should prioritize research into booster vaccines. At one point it seemed like two mRNA doses or a single Janssen dose might be the answer. But apparently, whether because of variants or fading immunity, being "fully vaccinated" doesn't necessarily mean you're immune.

COVID-19 vaccines do an enormous amount of good. I expect a milder course of disease since I'm vaccinated. But COVID-19 isn't over, even for the vaccinated. As the pandemic continues to evolve, we need to evolve with it.

Allan Massie (amassie1@jhmi.edu) is an epidemiologist and biomedical researcher at the Johns Hopkins School of Medicine. The views expressed here are his own.

https://bit.ly/3AeHo4U

Polar bears bash walrus skulls with boulders and ice blocks, study suggests

Arctic explorers' accounts of this tool-using behavior date to the late 18th century.

By Mindy Weisberger - Senior Writer

Picture a polar bear stalking an unsuspecting walrus in the frozen Arctic: The predator slowly inches closer, camouflaged by ice and snow, until it's close enough to pounce. And then it delivers the killing blow — by bopping the walrus on the head with a large rock.

A polar bear's paws are broad and powerful, capable of delivering killing blows (or chucking ice boulders at walruses ... maybe). **(Image credit: Alberto Ghizzi Panizza/Science Photo Library)**

That might sound like something you'd see in a cartoon, rather than in nature. But for centuries, Inuit people in the Arctic have shared such stories with non-Native explorers and naturalists, describing polar bears killing or stunning prey with stones and chunks of ice that the bears grasp in their paws (or throw off cliffs onto animals at the bottom, according to a memorable 19th-century engraving).

A new study looked at Inuit anecdotes describing this behavior — "from a diversity of locations and over a long period of time" — and found they were so widespread and consistent that they suggested that in rare cases, polar bears likely wield such objects as weapons. However, until scientific researchers actually catch the

Arctic bears in the act of bludgeoning walruses, it's hard to say for sure.

"I have always been impressed with the accuracy and reliability of the observations of animals reported by experienced Inuit hunters, so I thought it was likely the accounts might not just be myths but the result of reporting of actual observations, even though the behavior itself is likely quite rare," study lead author Ian Stirling, a member of the Scientific Advisory Council for Polar Bears International and an adjunct professor in the Department of Biological Sciences at the University of Alberta, told Live Science in an email.

Inuit descriptions of polar bears (*Ursus maritimus*) hoisting — and sometimes hurling — hefty blocks of rock or ice date to the late 1700s, according to the study. In a description that naturalist Otto Fabricius wrote in 1780 in the book "Fauna Groenlandica," polar bears grab sizable ice chunks and launch them at walruses' heads.

"The bear makes it [the walrus] lose its balance (or 'stagger' is more literal) and thus kills it easily," the scientists wrote in the June issue of the journal Arctic.

An Inuit account from 1883 described another ice-chucking bear that "seized a mass of ice in his paws, reared himself on his hind legs, and threw the ice with great force on the head of a half-grown walrus." A 1925 record of another Inuit report noted that a polar bear "carefully selected a young walrus and threw the ice block down upon it with such a force that it became immobilized," the study authors wrote.

In one astonishing example, illustrated by the 19th-century Arctic explorer Charles Francis Hall, a polar bear allegedly threw a boulder onto a walrus's head from atop a tall cliff. Hall published an engraving of the scene in 1865, basing it on a description by his Inuk guide from Baffin Island.

"The bear mounts the cliff, and throws down upon the animal's head a large rock, calculating the distance and the curve with astonishing accuracy, and thus crushing the thick bullet-proof skull," Hall wrote in the book "Arctic researches, and life among the Esquimaux" (Harper & Brothers, 1865).

This illustration, published by Arctic explorer Charles Francis Hall in 1865, shows a polar bear that's about to get the drop on an unsuspecting walrus. **(Image credit: Smithsonian Libraries)**

"If the walrus is not instantly killed — simply stunned — the bear rushes down to the walrus, seizes the rock, and hammers away at the head till the skull is broken," Hall concluded, according to the study.

Tools in captivity

The scientists also reviewed more recent reports, by Inuit and non-Inuit witnesses, that suggested the bears used rocks and ice for hunting and for disabling human hunters' traps. But these conclusions were based on the placement of rocks and ice that the bears had left behind and did not reflect observations of the bears actually using the objects as tools, the scientists wrote.

However, in 2010, photos showed a captive male polar bear named GoGo at the Tennoji Zoological Gardens in Osaka, Japan, using "tools" in his enclosure to reach a piece of food. Caregivers had hung a piece of meat about 10 feet (3 meters) above GoGo's pool — too high for him to grab — "to provide stimulation and distract his attention" by challenging GoGo with solving this puzzle, according to the study.

At first, GoGo tried jumping at the meat. But after a month of failure, he "invented" two tools: a piece of plastic pipe that he chucked at the food, and a branch measuring around 7 feet (2 m) that he used to smack the meat and knock it off its hook. Initially, GoGo took several hours to succeed, but he was soon able to knock

down the meat in just 5 minutes, the researchers reported.

GoGo's example, together with centuries of anecdotes and other recent observations, hints that tool use for hunting among wild polar bears — though likely not a common occurrence — is certainly possible, according to the study.

"An occasional adult polar bear might be capable of mentally conceptualizing a similar use of a piece of ice or a stone as a tool," the study authors reported. However, such extreme measures are probably used only for the biggest prey that polar bears hunt: walruses.

Polar bears prey on walruses and seals, but walruses are much more formidable targets. While an adult ringed seal (*Pusa hispida*) may weigh up to 165 pounds (75 kilograms), a 2-year-old walrus (*Odobenus rosmarus*) can weigh a whopping 750 pounds (340 kg) and full-grown adults may weigh as much as 2,000 pounds (907 kg), according to the Alaska Department of Fish and Game. What's more, walruses have long tusks to defend themselves during melee encounters, and their skulls are denser and harder to crack than seal skulls, Erica Hill, a professor of anthropology at the University of Alaska Southeast, reported in 2017 in the journal Études/Inuit/Studies. (Hill was not involved in the recent study.)

The targets of occasional boulder hurling by adult polar bears are therefore most likely to be walruses, the researchers concluded.

https://bit.ly/3s1TMlN

NASA identifies likely locations of the early molten moon's deep secrets

A pair of NASA studies identified the most likely locations to find pieces of mantle on the surface

by Bill Steigerwald, NASA's Goddard Space Flight Center

Shortly after it formed, the moon was covered in a global ocean of molten rock (magma). As the magma ocean cooled and solidified, dense minerals sank to form the mantle layer, while less-dense minerals floated to form the surface crust. Later intense bombardment by massive asteroids and comets punched through the crust, blasting out pieces of mantle and scattering them across the lunar surface.

Recently, a pair of NASA studies identified the most likely locations to find pieces of mantle on the surface, providing a map for future lunar sample return missions such as those under NASA's Artemis program. If collected and analyzed, these fragments from deep within the moon can provide a better understanding of how the moon, the Earth, and many other solar system worlds evolved.

"This is the most up-to-date evaluation of the evolution of the lunar interior, synthesizing numerous recent developments to paint a new picture of the history of the mantle and how and where it may have been exposed on the lunar surface," said Daniel Moriarty of NASA's Goddard Space Flight Center, Greenbelt, Maryland and the University of Maryland, College Park.

Magma oceans evolve as they cool down and dense materials sink while light materials rise. The formation of magma oceans and their evolution are thought to be common processes among rocky planets and moons throughout our solar system and beyond. Earth's moon is the most accessible and well-preserved body to study these fundamental processes.

"Understanding these processes in more detail will have implications for important follow-up questions: How does this early heating affect the distribution of water and atmospheric gases of a planet? Does water stick around, or is it all boiled away? What are the implications for early habitability and the genesis of life?" adds Moriarty, lead author of the papers, published August 3 in *Nature Communications* and January 2021 in the *Journal of Geophysical Research*.

Large rocky objects such as planets, moons, and large asteroids can form magma oceans with the heat generated as they grow. Our solar

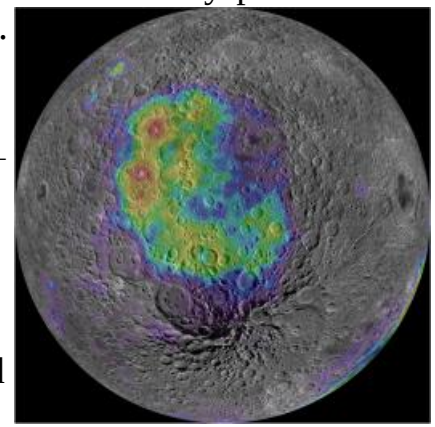
system formed from a cloud of gas and dust that collapsed under its own gravity. As this happened, dust grains smacked into each other and stuck together, and over time this process snowballed into larger and larger conglomerations, eventually forming asteroid and planet-sized bodies. These collisions generated a tremendous amount of heat. Also, the building blocks of our solar system contained a variety of radioactive elements, which released heat as they decayed. In larger objects, both processes can release enough heat to form magma oceans.

However, the details of how magma oceans evolve as they cool and how the various minerals in them crystalize are uncertain, which affects what scientists think mantle rocks may look like and where they could be found on the surface.

"The bottom line is that the evolution of the lunar mantle is more complicated than originally thought," said Moriarty. "Some minerals that crystallize and sink early are less dense than minerals that crystallize and sink later. This leads to an unstable situation with light material near the bottom of the mantle trying to rise while heavier material closer to the top descends. This process, called 'gravitational overturn," does not proceed in a neat and orderly fashion, but becomes messy, with lots of mixing and unexpected stragglers left behind."

The team reviewed the most recent laboratory experiments, lunar sample analysis, and geophysical and geochemical models to develop their new understanding of how the lunar mantle evolved as it cooled and solidified. They used this new understanding as a lens to interpret recent observations of the lunar surface from NASA's Lunar Prospector and Lunar Reconnaissance Orbiter spacecraft, and NASA's moon Mineralogy Mapper instrument on board India's Chandrayaan-I spacecraft. The team generated a map of likely mantle locations using moon Mineralogy Mapper data to assess mineral composition and abundance, integrated with Lunar Prospector observations of elemental abundances, including markers of the last remaining liquid at the end of lunar magma ocean crystallization, and imagery and topography data from Lunar Reconnaissance Orbiter.

At around 1,600 miles (about 2,600 kilometers) across, the South Pole—Aitken basin is the largest confirmed impact structure on the moon, and therefore is associated with the deepest depth of excavation of all lunar basins, so it's the most likely place to find pieces of mantle, according to the team.



For years, scientists have been puzzled by a radioactive anomaly in the northwest quadrant of the South Pole—Aitken Basin on the lunar farside. The team's analysis demonstrates that the composition of this anomaly is consistent with the "sludge" that forms in the uppermost mantle at the very end of magma ocean crystallization.

The thorium concentration across the vast South Pole – Aitken Basin on the lunar farside reveals the distribution of mantle materials violently ejected during the basin-forming impact. Here, thorium abundance is represented by a rainbow color scale, with high-thorium areas shown in red, trending to purple and grey with lower abundances. Two craters in the northwestern region of the basin exhibit especially high thorium abundance (indicated in red on the map), suggesting the presence of abundant mantle materials currently exposed on the surface. **Credit: NASA/LRO/Lunar Prospector/D. Moriarty**

Because this sludge is very dense, scientists have previously assumed that it should completely sink into the lower mantle early in lunar history.

"However, our more nuanced understanding from recent models and experiments indicates that some of this sludge gets trapped in the upper mantle, and later excavated by this vast impact basin,"

said Moriarty. "Therefore, this northwest region of the South Pole—Aitken Basin is the best location to access excavated mantle materials currently on the lunar surface. Interestingly, some of these materials may also be present around the proposed Artemis and VIPER landing sites around the lunar South Pole."

More information: *Daniel P. Moriarty et al, The search for lunar mantle rocks exposed on the surface of the Moon, Nature Communications (2021). DOI: 10.1038/s41467-021-24626-3*

D. P. Moriarty et al, Evidence for a Stratified Upper Mantle Preserved Within the South Pole-Aitken Basin, Journal of Geophysical Research: Planets (2020). DOI: 10.1029/2020JE006589

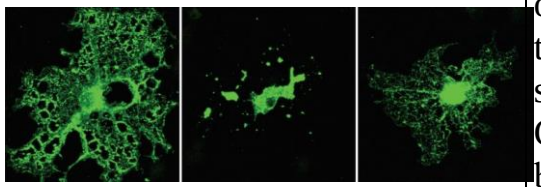
https://bit.ly/3jrn7Cp

Neurodegenerative Disease Protein Linked to Defective Cholesterol Metabolism

Brain cells cannot maintain the cholesterol-rich myelin sheath that protects and insulates neurons in the absence of TDP-43

Researchers in Singapore have discovered that brain cells cannot maintain the cholesterol-rich myelin sheath that protects and insulates neurons in the absence of a protein called TDP-43.

The study, which will be published today (August 4, 2021) in the *Journal of Cell Biology* (*JCB*), suggests that restoring cholesterol levels could be a new therapeutic approach for diseases associated with TDP-43.



Compared with a normal cell (left), an oligodendrocyte lacking TDP-43 (center) produces less myelin (green) because it is unable to synthesize or take up sufficient amounts of cholesterol. Supplementing TDP-43–deficient cells with cholesterol (right) restores myelin production. **Credit: ©2021 Ho et al. Originally published in Journal of Cell Biology. https://doi.org/10.1083/jcb.201910213**

The TDP-43 protein is linked to multiple neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). TDP-43 plays many vital roles within cells, but, under certain circumstances, it can clump together to form toxic aggregates that damage cells and prevent TDP-43 from performing its normal functions. TDP-43 aggregates are found in the brains of most ALS patients and ~45% of FTD patients and are also linked to several other neurodegenerative disorders, including some cases of Alzheimer's disease. The aggregates form not only in neurons, but also in other brain cell types such as oligodendrocytes. These latter cells protect neurons and speed up the transmission of nerve impulses by wrapping neurons in a fatty substance called myelin.

Shuo-Chien Ling and colleagues at the Yong Loo Lin School of Medicine, National University of Singapore, have previously shown that oligodendrocytes need TDP-43 to survive and wrap neurons in myelin. "Specifically, we found that mice with oligodendrocytes lacking TDP-43 develop progressive neurological phenotypes leading to early lethality. These phenotypes were accompanied by the death of oligodendrocytes and progressive loss of myelin," Ling says.

In the new study, Ling and colleagues find that one reason oligodendrocytes are dysfunctional in the absence of TDP-43 is that they are unable to synthesize or take up the cholesterol they need to sustain myelin production.

Cholesterol is such a major component of myelin that 25% of the body's total cholesterol can be found in the central nervous system. Oligodendrocytes are known to synthesize large amounts of cholesterol for themselves, but they can also acquire it from other brain cells called astrocytes. Ling and colleagues determined that, in the absence of TDP-43, oligodendrocytes lack many of the enzymes required to synthesize cholesterol, and also have reduced levels of the low density lipoprotein receptor that can take in cholesterol from outside the cell. Supplementing these TDP-43–deficient cells with cholesterol restored their ability to maintain the

myelin sheath.

Similar defects in cholesterol metabolism may occur in patients, where the formation of aggregates might prevent TDP-43 from performing its normal functions. Ling and colleagues analyzed brain samples from FTD patients and found that their oligodendrocytes produced lower amounts of two key enzymes required for cholesterol synthesis, while the low density lipoprotein receptor was incorporated into TDP-43 aggregates.

“Our results indicate that simultaneous disruption of cholesterol synthesis and uptake is likely one of the causes of the demyelination phenotype observed in mice with TDP-43–deficient oligodendrocytes, and suggest that defects in cholesterol metabolism may contribute to ALS and FTD, as well as other neurodegenerative diseases characterized by TDP-43 aggregates,” Ling says.

Drugs that modulate cholesterol metabolism might therefore be a novel therapeutic strategy to treat these diseases, the researchers suggest.

Reference: 4 August 2021, Journal of Cell Biology.
DOI: 10.1083/jcb.201910213

https://bit.ly/37E53zD

This 3,700-Year-Old Tablet Shows The Oldest Known Example of Applied Geometry

Over 1000 years before Pythagoras

Michelle Starr

An ancient fragment of clay tablet dating back to 3,700 years ago, during the Old Babylonian period, contains what is now the oldest known example of applied geometry, a mathematician has discovered. That's more than a millennium prior to the birth of Pythagoras. And this history-altering artifact, known as Si.427, had just been sitting in a museum in Istanbul for more than 100 years.

"Si.427 dates from the Old Babylonian (OB) period - 1900 to 1600 BCE," said mathematician Daniel Mansfield of the University of New South Wales (UNSW) in Australia. "It's the only known example of a cadastral document from the OB period, which is a plan used by surveyors to define land boundaries. In this case, it tells us legal and geometric details about a field that's split after some of it was sold off."

The clay tablet, Si.427. **(UNSW Sydney)**

That plan uses sets of numbers known as Pythagorean triples to derive accurate right angles, or sets of numbers that fit trigonometric models for calculating the sides of a right-angled triangle. This makes the timing of the artifact particularly interesting, with important implications for the history of mathematics, Mansfield noted.

The discovery is described in a new paper that analyzes the context of this tablet with recent findings about a tablet contemporaneous with Si.427, known as Plimpton 322. In 2017, Mansfield and colleagues revealed that Plimpton 322 was an early trigonometric table, showing a whole list of Pythagorean triples.

At that time, the researchers did not know what the purpose of this list might be. Now, they think it might date to slightly later than Si.427, and contain only Pythagorean triples that would be relevant for making rectangular measurements of the ground. In other words, it's a planning manual.

This is in contrast to the trigonometry laid out by Pythagoras, which was devised by looking at the stars in the sky in the second century BCE. The number of Pythagorean triples that can be used for making land measurements by Babylonian surveyors is very small.

A Pythagorean triple fits the equation $a^2 + b^2 = c^2$, where the sides defining a triangle that are adjacent to the right angle are a and b, and the hypotenuse (the longest side) is c. The simplest example would be $3^2 + 4^2 = 5^2$.

These sets of numbers can be used to draw triangles and rectangles

with perfect right angles. But the sexagesimal, or base 60, Babylonian number system made it difficult to work with prime numbers larger than 5.

"This raises a very particular issue – their unique base 60 number system means that only some Pythagorean shapes can be used," Mansfield said. "It seems that the author of Plimpton 322 went through all these Pythagorean shapes to find these useful ones. This deep and highly numerical understanding of the practical use of rectangles earns the name 'proto-trigonometry' but it is completely different to our modern trigonometry involving sin, cos, and tan."

Now, with Si.427, we finally know what they wanted to use these Pythagorean triples for - laying down land boundaries, according to Mansfield.

"This is from a period where land is starting to become private - people started thinking about land in terms of 'my land and your land', wanting to establish a proper boundary to have positive neighborly relationships," he explained.

"And this is what this tablet immediately says. It's a field being split, and new boundaries are made."

Other tablets from that time period reveal why this was so important. One regards a dispute over date palms on the border between two properties, in which the local administrator had agreed to dispatch a surveyor to settle the matter. It's easy to see why the ability to accurately measure out plots of land might have been important.

Nevertheless, it demonstrates a sophisticated understanding of geometry. It may not have been as advanced as the trigonometry later described by the ancient Greeks, but it does suggest that our understanding of mathematics may have been more incremental than current historical knowledge tells us.

"Nobody expected that the Babylonians were using Pythagorean triples in this way," Mansfield said. "It is more akin to pure mathematics, inspired by the practical problems of the time."

The research has been published in *Foundations of Science*.

https://bit.ly/37r8IAo

Genetic analysis of ancient brown bear skull suggests multiple waves of bears migrated to Honshu

Multiple waves of brown bears migrated Honshu over vast periods of time

by Bob Yirka , Phys.org

An international team of researchers has found evidence of multiple waves of ancient brown bears migrating to the Japanese island of Honshu over vast periods of time. In their paper published in the journal *Royal Society Open Science*, the group describes their genetic analysis of tissue recovered from a brown bear skull found near Tokyo, and what they learned from it.

The only brown bears living in modern Japan reside on the northern island of Hokkaido—but thousands of years ago, some of them lived on Japan's main island, Honshu. Researchers have found approximately 10 incomplete brown bear remains on Honshu, all believed to have been from the Pleistocene. In this new effort, the researchers analyzed a newly found skull. More specifically, they studied material from its petrosals—the thick bony material that surrounds a bear's inner ear. Prior research has shown these bones retain more DNA than other bones.

The researchers found that the bear lived approximately 32,000 years ago, putting it at the end of the Pleistocene—a time when it is believed there was a land bridge between parts of the Japanese islands. The team then compared the DNA of the bear with that of other ancient samples and also with modern brown bears on Hokkaido. They found that the new skull was from a bear belonging to a previously unknown lineage—one that had split off from the bear lineage on Hokkaido approximately 160,000 years ago.

Prior research had found evidence that a bear occupied Honshu approximately 340,000 years ago, suggesting that different lineages of bears made their way across the Tsugaru strait to get to Honshu during a time when the waters were shallow. They also note that all of the bears living on Honshu appear to have died out at the end of the Pleistocene, along with a giant deer species, Naumann's elephants and other large mammals. Notably, humans arrived on Honshu approximately 30,000 years ago, though it is not known if they were responsible for the disappearance of the other creatures on the island.

More information: *Takahiro Segawa et al, Ancient DNA reveals multiple origins and migration waves of extinct Japanese brown bear lineages, Royal Society Open Science (2021). DOI: 10.1098/rsos.210518*

https://bit.ly/2VzdGZw

Muscle protein that makes vertebrates more fit linked to limited lifespan

Gene for CaMKII contributes to improved fitness but also increased susceptibility to age-associated diseases

Researchers from Johns Hopkins Medicine say they have added to evidence that a protein called CaMKII improves strength, endurance, muscle health and fitness in young animals. Their experiments working with mice and fruit flies, however, found that the gene for CaMKII also contributes to an evolutionary tradeoff: increased susceptibility to age-associated diseases, frailty and mortality.

The research, published May 26 in *Nature Communications*, indicates that future therapies targeting CaMKII could stave off diseases of old age, the investigators say.

According to the study leaders, the evolutionary conservation of genes that enable the young to run faster and respond robustly to "fight or flight" responses makes sense: It helps them to catch prey or evade predators, thereby ensuring their reproductive success. However, some of these genes carry a steep price that animals need to pay when they grow older. The new research shows that turning on CaMKII through a chemical reaction caused by adding oxygen, known as oxidation, strengthens these survival responses for young animals. However, oxidative stress increases with aging, which leads to excessive activation of CaMKII. Elevated CaMKII activity has long been linked to tissue damage seen in heart failure, atrial fibrillation, cancer, lung and neurodegenerative diseases, says study co-lead Mark Anderson M.D., Ph.D., professor of medicine and director of the department of medicine at the Johns Hopkins University School of Medicine.

In a bid to further explore oxidative stress and its links to aging and fitness, Anderson and his research team genetically engineered mice so their CaMKII is resistant to oxidation. They then used mouse-sized treadmills to compare the athletic performance of mice with and without CaMKII oxidation.

They found that mice with oxidized CaMKII were able to run, on average, about 150 meters further and about 5 meters per minute faster than the mice with oxidation-resistant CaMKII.

When the researchers biopsied muscle tissue from the mice and searched for other genes previously linked to muscle growth, recovery from exercise, improved blood flow and immune cell activation—factors that increase physical endurance—they found them activated only in mice with oxidizable CaMKII.

Further experiments showed that CaMKII activity in the mouse muscle tissue increased the expression of cellular pathways related to inflammation, diabetes, enlarged heart, seizures and obesity.

These experiments are further evidence that diseases of aging are natural tradeoffs built into our genetic makeup, says Qinchuan Wang, Ph.D., co-lead and assistant professor of medicine at the Johns Hopkins University School of Medicine. "But they give us some hope that it may be possible to target this genetic architecture

to combat age-related illnesses."

The Johns Hopkins Medicine team also performed experiments in genetically modified fruit flies to see whether an oxidizable CaMKII produced similar performance and health effects in invertebrates, which do not naturally have an oxidation-sensitive CaMKII protein. The researchers used a gene-cutting and insertion tool called CRISPR to add the oxidation site to the CaMKII gene in fruit fly DNA.

In one experiment, the flies were placed into glass tubes and allowed to climb to the top of the tube. The researchers found that flies genetically modified to have the oxidizable CaMKII climbed higher and 5mm per second faster than flies with the oxidation-resistant CaMKII. The result suggested that a physiological level of oxidative stress can enhance physical performance by oxidizing and activating CaMKII.

When the researchers fed the flies an antioxidant diet to cancel out the oxidative stress effects on the modified CaMKII, flies with and without the genetic modification performed similarly in the climbing test.

In another experiment, the researchers fed the flies a diet containing the herbicide paraquat, which overloads the flies with an excess of oxidants that activate CaMKII only in the genetically modified, but not the unmodified, flies. They found that the climbing performance of flies with the oxidant-resistant CaMKII gene was not affected by the paraquat diet, which was expected since there is no protein to activate.

In contrast, under such an oxidative stress, the genetically modified flies with the oxidizable CaMKII suffered a significant reduction in climbing performance: They climbed almost 10mm per second slower than their counterparts fed normal diets, suggesting that excessive oxidative stress leads to physical decline through oxidizing and activating CaMKII.

The researchers made similar observations in the fly hearts. They found that the hearts of flies with the oxidizable CaMKII contracted more forcefully and relaxed more quickly than flies with oxidation-resistant CaMKII. However, the performance advantage of the hearts in the genetically modified flies was reversed when the researchers neutralized the oxidants with an antioxidant. The researchers also found that the hearts of the genetically modified flies are more vulnerable to damaging effects of excessive oxidant, as they became dysfunctional or stopped beating altogether when treated by paraquat, the oxidant-generating chemical.

The most striking finding, says Wang, was that despite having better physical performance and cardiac function, the genetically modified flies experienced a more rapid age-related decline and they died at a younger age.

"A main role of evolution is to improve the ability to carry on the species, including producing more offspring and being adept at finding food. Our findings affirm that improvements in the longevity or lifespan of a species is not always necessary for this to happen," explains Gabriel Bever, Ph.D., associate professor of Functional Anatomy and Evolution at the Johns Hopkins University School of Medicine and a collaborator on the study. "In fact, some of the very adaptations that make a species successful also contribute to aging and age-associated diseases."

Overall, the researchers say these findings may provide new targets to address diseases related to an abundance of oxidative damage and may also provide an explanation for why studies of broad spectrum antioxidants, such as Vitamins C and E, have yielded mixed results in the treatment of heart diseases, Parkinson's disease and Huntington's disease.

The scientists say that designing treatments to specifically target gene regulators such as CaMKII may work better.

"For hundreds of millions of years, these diseases have been

programmed into animal genomes to plague us at the end of our lives," says Bever. "It's evident we need a more complete understanding of their evolutionary roots if we ever hope to find cures."

The researchers found additional evidence that CaMKII activates genes associated with early immune responses, an adaptation of early vertebrates that confers fitness by helping to ward off infectious diseases. Scientists have found that when people get older, abnormal activation of the immune system contributes to systemic and chronic inflammation and increases the risk for all major age-related diseases. "CaMKII's ability to activate immune response in the face of oxidative stress may hold the clue for its involvement in aging and disease," says Wang.

More information: *Qinchuan Wang et al, CaMKII oxidation is a critical performance/disease trade-off acquired at the dawn of vertebrate evolution, Nature Communications (2021). DOI: 10.1038/s41467-021-23549-3*

https://bit.ly/3s61ews

Vaccines cut chance of being infected with delta variant by half, UK study finds

The study examined nearly 100,000 people who took COVID-19 swab tests at home between June 24 and July 12.

By Yasemin Saplakoglu - Staff Writer

People who are fully vaccinated with a two-dose coronavirus vaccine have a 50% to 60% reduced risk of being infected with the delta variant, even asymptomatically, compared with unvaccinated people, according to a new study conducted in England.

The study examined nearly 100,000 people who took COVID-19 swab tests at home between June 24 and July 12. In that sample group, 527 people tested positive for the coronavirus and 254 of the samples were genetically analyzed; all of the sequenced samples turned out to be the highly transmissible delta variant.

Once the researchers adjusted for factors such as age, they found that people who received two vaccine doses were 49% as likely to test positive for the coronavirus, even without symptoms, compared with people who were unvaccinated and that vaccinated people were 59% less likely to test positive with symptoms.

The findings, which were posted as a preprint and haven't been peer-reviewed yet, are the newest results from Imperial College London's "Real-time Assessment of Community Transmission," or REACT-1, an ongoing coronavirus monitoring study.

"These findings confirm our previous data showing that both doses of a vaccine offer good protection against getting infected," Paul Elliott, director of the REACT program from Imperial's School of Public Health, said in a statement. The researchers didn't untangle the effectiveness of specific vaccines.

Their findings conflict with previous studies. For example, a study conducted by Public Health England found that the Pfizer-BioNTech vaccine was 88% effective against symptomatic disease caused by the delta variant (people vaccinated were 88% less likely to develop symptomatic infection compared to people who were unvaccinated), compared with about 93% effective against the alpha variant, the previous dominant variant. That study found that the two-dose AstraZeneca vaccine was 60% effective against the delta variant, compared with 66% against the alpha variant, Live Science previously reported.

Meanwhile, early data from Israel suggested that the Pfizer-BioNTech vaccine was 64% effective against symptomatic disease caused by the delta variant, and data from Canada found it was 87% effective against symptomatic disease, according to an internal presentation from the Centers for Disease Control and Prevention. But newer data from Israel found that the efficacy of the Pfizer-BioNTech vaccine against Delta slipped to 39% (but is still 88% effective against hospitalization and 91% protective against severe illness), according to CNBC.

The new study also found that vaccinated people had a smaller viral load on average, meaning they likely shed less virus and are less contagious than unvaccinated people. That result differs from other data that suggested the delta variant caused similar viral loads in the unvaccinated and in vaccinated people who test positive (so-called breakthrough cases), Live Science previously reported.

"The delta variant is known to be highly infectious, and as a result, we can see from our data and others' that breakthrough infections are happening in fully vaccinated people," Steven Riley, a professor of infectious disease dynamics at Imperial College London, said in the statement. "We need to better understand how infectious fully vaccinated people who become infected are, as this will help to better predict the situation in the coming months, and our findings are contributing to a more comprehensive picture of this."

The researchers also found that the trends between infections and hospitalizations, which had weakened in the spring, were converging again, according to the statement. That could be due to the dominant variant switching from alpha to delta and more younger people, who may be less likely to be vaccinated, becoming hospitalized than before.

Young people ages 13 to 24 had the highest infection rate, and people 75 and older had the lowest infection rate. Roughly 50% of the infections occurred in people ages 5 to 24, even though they make up only a quarter of the population, Riley told Reuters.

"Today's report shows the importance of taking personal responsibility by self-isolating if you are contact traced, getting tested if you have symptoms and wearing face coverings where appropriate," U.K. Health and Social Care Secretary Sajid Javid said in the statement. "I urge anyone who has yet to receive a vaccine to get jabbed and take up both doses — the vaccines are safe, and they are working."

https://bit.ly/3ios8w9

We may need to vaccinate children as young as 5 to reach herd immunity with Delta, our modelling shows

Vaccinating children as young as 5 years old is vital if we are to reach herd immunity

Emma McBryde*

Recently released modelling from the Doherty Institute, which the federal government used to back its roadmap out of the pandemic, misses one critical point — the importance of vaccinating children.

The Doherty modelling instead focuses on vaccinating 70-80% of the adult population as thresholds for easing various restrictions, such as lockdowns. It says vaccinating younger adults, in particular, is important to reach these thresholds.

However, our modelling shows vaccinating children is vital if we are to reach herd immunity, which would allow us to ease restrictions and safely open up. This would mean potentially vaccinating children as young as 5 years old.

However, we are still waiting to see if this is safe and effective, with trials under way in the United States. So we need a plan that assumes we may never achieve herd immunity.

Here's what our modelling shows and how it differs from the modelling used to advise the federal government.

Here's what we did

Our modelling, which we've uploaded as a pre-print and has yet to be peer-reviewed, considers different vaccine strategies for Australia to achieve herd immunity. That's when we can expect no sustained transmission of the virus in the community.

We take into account the Delta variant, which is twice as infectious as the original Wuhan strain of the virus, and has a reproduction number estimated between 5 and 10. In other words, this is when one person infected with Delta is estimated to infect 5-10 others.

We also consider different contact patterns across various age

groups. This is because some age groups are more mobile and have many contacts. If infected, these people are more likely to infect many others, particularly of similar age, which can lead to reservoirs of transmission.

We combine this information with possible vaccine effects. These include the possibility of having the vaccine then becoming infected, having symptoms, and if infected, how serious the illness is and how infectious people are.

This allows us to model what's likely, given we're focused on the Delta variant for now, and allows us to assess the impact of strategies across different age groups, types of vaccines and percentage vaccinated. Our interactive tool also allows rapid response to changing information, such as new variants, or new evidence about vaccine impact.

Delta is more infectious

The Wuhan strain had a basic reproduction number of 2.5. This means, at the start of the pandemic, one person infected with it was expected to infect 2.5 others. If the Delta variant is twice as infectious, this means its basic reproduction number may be over 5 (at the lower range of international estimates). So this changes the number (and type) of people we need to vaccinate to reach herd immunity considerably.

The simplest form of the herd immunity equation would suggest we needed to fully immunise 60% of the population to achieve herd immunity for the Wuhan strain but as much as 80% for the Delta variant. If we take into account how different age groups mingle or are in contact with others, the situation is worse.

For the Wuhan strain, children were not as infectious or susceptible to infection and we predict that if we vaccinate 65% of the adults, transmission would not continue among children.

However, with the Delta variant, we predict children will continue to infect other children, even when most adults are vaccinated.

We also know both the AstraZeneca and Pfizer vaccines are less able to protect against the Delta variant, with a reduced efficacy after one dose and slightly reduced efficacy after two doses.

All this makes achieving herd immunity a great challenge.

We estimate if the reproduction number is 5, then vaccinating 85% of the population, including children down to age 5, will be necessary to achieve herd immunity.

If the reproduction number is as low as 3, then vaccinating children will not be necessary to achieve herd immunity and we will only need to vaccinate 60% of the population.

The Doherty modelling uses an effective reproduction number of 3.6. This explains why its modelling does not see vaccinating children as critical to reaching herd immunity. This is the major difference between our model and theirs.

What happens next?

Of course, new variants may arise pushing Delta aside, and the world post-COVID is unpredictable. The lesson from Delta is if we don't vaccinate children, we may need to continue some form of public health action to prevent large-scale circulation of the virus.

This would not require stringent lockdown, but may require ongoing mask use and physical distancing, including in children. The alternative is to reduce the focus on case numbers, expect transmission and focus on protecting the most vulnerable.

Do we need to reach herd immunity?

Herd immunity is not the only possible target. Even if we don't reach full herd immunity, we may achieve "herd protection". This provides some reduced risk to people who can't or won't be vaccinated, and it will make outbreaks smaller and easier to control. And without full herd immunity, individuals still benefit from vaccination as they are dramatically less likely to die from COVID.

Do we need to change our vaccination strategy?

We predict Australia's strategy of vaccinating the elderly and

vulnerable first is the best strategy for reducing deaths under most circumstances, particularly when there is insufficient vaccine available. But once the most vulnerable groups have been covered, we should turn our attention to the highest transmitters to achieve herd protection. In Australia, this group is the late teens and young adults.

Whether we next focus on vaccinating children is controversial and many people have voiced their concerns about going down this path. This is because COVID is generally a very mild illness for most children — although long COVID and life-threatening complications can arise. So we need to balance the risks with benefits. But included in the benefits should be the potential benefit of herd protection and the freedoms that may bring.

*Professor of Infectious Disease and Epidemiology, James Cook University

Disclosure statement

Emma McBryde receives funding from NHMRC. She is affiliated with the Australian Tuberculosis Forum and the Austrasian Society of Infectious Diseases.

https://bit.ly/3ismZTO

Nearby Planetary System Could Hold a Habitable Super-Earth, Astronomers Say

A star just 35 light-years away has been found to host a number of rocky exoplanets, and one that has a good chance of habitability.

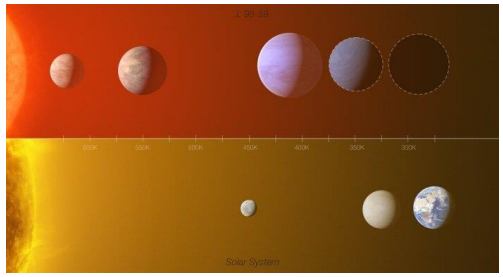
Michelle Starr

Around the red dwarf L 98-59 orbit at least four planets, and the system looks to be fascinating. New observations confirm what prior research had already suggested – the existence of a terrestrial world with half the mass of Venus.

But the new observations also reveal new worlds in the same system, including an ocean planet, and what seems to be a super-Earth bang in the middle of the star's habitable zone.

"The planet in the habitable zone may have an atmosphere that could protect and support life," said astrophysicist María Rosa Zapatero Osorio of the Centre for Astrobiology in Spain.

The discoveries mark a pretty big milestone, not just in our search for potentially habitable worlds, but also our search for rocky exoplanets like Earth, Mars, and Venus, since the small half-Venus represents a technical breakthrough.



Comparison of the temperatures of L 98-59 and the Solar System. **(ESO/L. Calçada/M. Kornmesser)**

It's the least massive exoplanet ever measured by examining its gravitational effect on the position of the star.

Although there are potentially many more exoplanets out there in the Milky Way than there are stars, to date we've only conclusively found and identified a few thousand of them.

That's because they're a lot smaller and dimmer and harder to see. Our most prolific methods therefore work best on more massive exoplanets that are relatively close to their stars.

Most exoplanets are discovered using the transit method. This is where a telescope such as Kepler or TESS (or, in the case of L 98-95's initial research, the Carnegie Planet Finder Spectrograph) stares at a patch of sky and looks for repeated, regular dips in starlight as an orbiting exoplanet transits between us and the host star.

The radial velocity method, on the other hand, looks for changes in a star's position. This is because planets exert a very small gravitational pull on their stars, causing them to move around a little in a mutual orbit (the Sun does this too). The more massive the exoplanet, the more pronounced the signal.

The L 98-59 system was discovered in 2019, with three planets orbiting the star, using the exoplanet-hunting space telescope TESS,

which relies on the transit method. This can supply some information about the exoplanets themselves, such as a rough size estimate based on the amount by which the starlight dims.

Radial velocity measurements can add more information. Based on how much the star moves, astronomers can calculate the exoplanet's mass. Once they know the mass and size of a planet, they can calculate its density, which means we can take a good punt at determining its composition: denser exoplanets are likely rocky, while fluffier ones are likely gaseous.

"If we want to know what a planet is made of, the minimum that we need is its mass and its radius," explained astronomer Olivier Demangeon of the University of Porto in Portugal.

A team of astronomers led by Demangeon used the European Southern Observatory's Very Large Telescope to conduct radial velocity measurements of the star L 98-59. They confirmed that the innermost exoplanet, L 98-59 b, was around half the mass of Venus, and likely rocky. The second-innermost exoplanet, at 1.4 times the size of Earth, is also likely rocky.

The third exoplanet is about 1.5 times the size and twice the mass of Earth, with a density profile, the researchers found, that suggests high water content. As much as 30 percent of the exoplanet's mass could be water, which would make it an ocean world.

Surprisingly, the team's radial velocity measurements registered two periodic signals that didn't match any of the known exoplanets. These suggested two more exoplanets in the system that don't orbit in the same plane as the others, so they don't actually transit.

The first has a mass of around three times that of Earth, and an orbital period of about 12.8 days. The second, more tentative detection is really interesting, though.

"We have hints of the presence of a terrestrial planet in the habitable zone of this system," Demangeon said.

The fifth exoplanet, if it can be confirmed, seems to clock in at 2.46 times the mass of Earth, with an orbital period of about 23 days. This may seem too close for comfort, but because red dwarf stars are much cooler than the Sun, this means that the exoplanet would be at a temperate distance from the star – not too hot (nor too cold) to support life as we know it.

Unfortunately, we would need a transit to be able to see if the exoplanet has an atmosphere, which means it's not a great candidate for follow-up study in the search for habitability.

But it does show that planetary systems can hide a lot of tricks up their sleeves – and we could take a closer look at the inner exoplanets to study planetary system diversity.

"This system announces what is to come," Demangeon said.

"We, as a society, have been chasing terrestrial planets since the birth of astronomy and now we are finally getting closer and closer to the detection of a terrestrial planet in the habitable zone of its star, of which we could study the atmosphere."

The research has been published in *Astronomy & Astrophysics*.

https://go.nature.com/3lL1Ne1

'Tortured phrases' give away fabricated research papers

Analysis reveals that strange turns of phrase may indicate foul play in science.

Holly Else

In April 2021, a series of strange phrases in journal articles piqued the interest of a group of computer scientists. The group, led by Guillaume Cabanac at the University of Toulouse in France, could not understand why researchers would use the terms 'counterfeit consciousness', 'profound neural organization' and 'colossal information' in place of the more widely recognized terms 'artificial intelligence', 'deep neural network' and 'big data'.

Further investigation revealed that these strange terms — which they dub "tortured phrases" — are probably the result of automated

translation or software that attempts to disguise plagiarism. And they seem to be rife in computer-science papers.

Research-integrity sleuths say that Cabanac and his colleagues have uncovered a new type of fabricated research paper, and that their work, posted in a preprint on arXiv on 12 July[1], might expose only the tip of the iceberg when it comes to the literature affected.

To get a sense of how many papers are affected, the researchers ran a search for 30 tortured phrases in journal articles indexed in the citation database Dimensions.

They found more than 860 publications that included at least one of the phrases, 500 of which were published in a single journal: *Microprocessors and Microsystems*. "It harms science. You cannot trust these papers, so we need to find them and retract them," says Cabanac.

Tortured phrases found in computer-science papers

Scientific term	Tortured phrase
Big data	*Colossal information*
Artificial intelligence	*Counterfeit consciousness*
Deep neural network	*Profound neural organization*
Remaining energy	*Leftover vitality*
Cloud computing	*Haze figuring*
Signal to noise	*Flag commotion*
Random value	*Irregular esteem*

Suspecting that the tortured phrases are the result of automated translation or software that rewrites existing text, Cabanac and colleagues ran a selection of abstracts from *Microprocessors and Microsystems* and other journals through a tool that can identify whether texts have been generated by the artificial-intelligence tool GPT. Of the *Microprocessors and Microsystems* papers flagged by the tool, manual checks revealed "critical flaws" in some of them, such as nonsensical text, as well as plagiarized text and images.

To dig deeper, the group downloaded all papers published in *Microprocessors and Microsystems* between 2018 and 2021, a time frame they chose because an upgraded version of GPT was released in 2019.

Analysis revealed that papers published after February 2021 had an acceptance time that was five times shorter, on average, than those published before that date. A high proportion of these papers came from authors in China. And a subset of papers had identical submission, revision and acceptance dates, the majority of which appeared in special issues of the journal. This is suspicious, the authors say. Unlike standard issues, overseen by the editor-in-chief, special issues are usually proposed and overseen by a guest editor, and focus on a specific area of research.

Microprocessors and Microsystems was not the only affected title — the researchers also found evidence of tortured phrases in papers published in 35 other journals. "Preliminary probes show that several thousands of papers with tortured phrases are indexed in major databases," they write, adding that "other tortured phrases related to the concepts of other scientific fields are yet to be exposed".

Special-issue investigation

Around the time that Cabanac and his colleagues first noticed the tortured phrases, and unbeknown to them, the editor of *Microprocessors and Microsystems* began having concerns about the integrity and rigour of peer review for papers that had been published in some of the journal's special issues.

The journal's publisher, Elsevier, launched an investigation. This is still under way, but in mid-July the publisher added expressions of concern to more than 400 papers that appeared across six special issues of the journal.

The expressions of concern say that the papers in the affected special issues of *Microprocessors and Microsystems* are being "independently re-assessed" one by one, and the journal will give further updates on their status once the investigations have concluded.

The publisher adds that a "configuration error in the editorial system" at the journal meant that neither the editor-in-chief nor the editor designated to handle the papers received them for approval as they should have. "This configuration error was a temporary issue due to system migration and was corrected as soon as it was discovered," says the notice.

A spokesperson for Elsevier told *Nature* in a statement that the *Microprocessors and Microsystems* investigation has found that the authors probably used reverse-translation software to disguise plagiarism, and that this is the likely source of the tortured phrases.

The investigation has also revealed that 49 papers flagged as suspicious by Cabanac and his colleagues and published in standard issues of the journal were originally submitted to its special issues and were accepted by guest editors, "but were subsequently published in regular issues, at the authors' request", the statement says. These papers are already part of Elsevier's investigation, it adds.

Elisabeth Bik, a research-integrity analyst in California known for her skill in spotting duplicated images in papers, says that the findings of Cabanac's research are "shocking". "This is a very new and disturbing type of fabricated paper," she adds.

Jennifer Byrne, a molecular-oncology researcher at the University of Sydney, Australia, who also works on spotting fabricated papers, says that this is probably the tip of the iceberg because the researchers only looked in depth at one journal from one publisher. "These papers were also found because they were of very poor quality, but there could be more plausible AI-generated papers within the literature that are harder to detect," she adds.

doi: https://doi.org/10.1038/d41586-021-02134-0

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1. Cabanac, G., Labbé, C. & Magazinov, A. Preprint at arXiv https://arxiv.org/abs/2107.06751 (2021).

https://nyti.ms/3s9VIZP

Novavax Says U.S. Will Pause Funding for Production of Its Vaccine

The Maryland company, which has a $1.75 billion federal contract to develop and produce a coronavirus vaccine, said it needed to address the concerns of federal regulators.

By Sharon LaFraniere

Washington — Novavax, the Maryland firm that won a $1.75 billion federal contract to develop and produce a coronavirus vaccine, said on Thursday that the federal government would not fund further production of its vaccine until the company resolves concerns of federal regulators about its work.

The firm's disclosure came in a quarterly filing with the Securities and Exchange Commission. The Trump administration agreed to buy 110 million doses of vaccine from Novavax as part of its crash vaccine development program.

Although the company reported in June that its vaccine had an efficacy of 90 percent against symptomatic Covid-19 cases, and 100 percent against severe disease, Novavax has struggled for months to mass manufacture its product. Its vaccine has not been authorized for distribution in the United States, and federal officials said it is unclear when or if it will be.

Four people familiar with Novavax's operation said the company had been unable so far to demonstrate that its production process met Food and Drug Administration standards. They spoke on the condition of anonymity to discuss sensitive contracting issues.

In its S.E.C. filing on Thursday, Novavax said: "The U.S. government has recently instructed the company to prioritize alignment with the U.S. Food and Drug Administration on the company's analytic methods before conducting additional U.S. manufacturing and further indicated that the U.S. government will not fund additional U.S. manufacturing until such agreement has

been made."

An official for the Department of Health and Human Services, which oversees Novavax's federal contract, said the government wanted the company to strengthen its testing and quality control operation. The official spoke on the condition of anonymity to discuss confidential negotiations with the firm.

Novavax said in a statement that the federal government continued to fund other work it had underway, including clinical trials. "We do not expect any impact on our funding arrangement with the U.S. government to support overall development and production of 110 million doses of our vaccine candidate," the firm said.

The company's manufacturing problems come on top of production failures at a federally funded vaccine-making factory in Baltimore operated by Emergent BioSolutions.

Federal regulators halted production at that plant for more than three months this year until the firm resolved quality control problems, including failure to prevent contamination that ruined tens of millions of doses. The plant had produced Johnson & Johnson's and AstraZeneca's vaccines but now manufactures doses only for Johnson & Johnson.

Chris Hamby contributed reporting.

https://bit.ly/2VErhhR

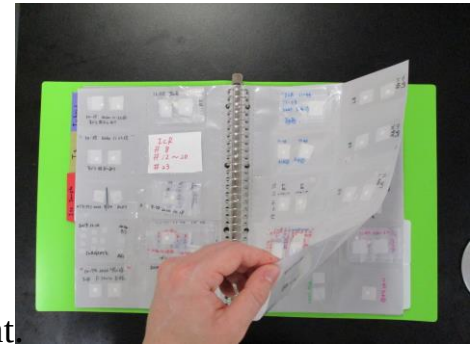
Scientists mail freeze-dried mouse sperm on a postcard

Scientists no longer have to worry about their bottles of mouse sperm breaking in transit.

Researchers in Japan have developed a way to freeze dry sperm on a plastic sheet in weighing paper so that samples can withstand being mailed via postcard. This method allows for mouse sperm to be transported easily, inexpensively, and without the risk of glass cases breaking. The paper appears August 5th in the journal *iScience*.

"When I developed this method for preserving mouse sperm by freeze-drying it on a sheet, I thought that it should be able to be mailed on a postcard, and so when offspring were actually born after being mailed, I was very impressed," says first author Daiyu Ito of the University of Yamanashi in Japan. "The postcard strategy was easier and cheaper compared to any other method. We think the sperm never expected that the day would come when they would be in the mailbox."

Ito is part of Teruhiko Wakayama's lab, which had previously been the first team to succeed in freeze-drying and preserving mammalian sperm, which they sent to the space station to study the effects of space radiation on baby mice. The sperm was originally preserved in a glass ampule, which is a bottle made of glass; although these bottles were small, they were quite bulky and broke easily, rendering the sperm they carried unusable. The team needed large volumes of mouse sperm for their research in space, but because cushions had to be used to prevent breakage during the rocket launch, they could only carry a small amount.



This photo shows how a sperm sheet of hundred or thousand of mouse strains can be preserve only one card-holder or "sperm book". It is very easy to handle. This method also reduces the risk of failure to preserve, preservation costs, and space requirements. **Credit: Daiyu Ito, University of Yamanashi**

Thus, with these setbacks in mind, the lab began its search for a new preservation method—one that didn't break or require much preservation space. Plastic sheets were the best fit because they were compact and wouldn't break. But the sheets were toxic for the sperm, so the team tried and failed as they tested various materials to go inside the plastic sheets. Finally, the researchers discovered that weighing paper was the easiest to handle and had the highest

offspring rate.

With the new method of preservation, thousands of mouse strain's sperm could be stored in a single book, dubbed the "sperm book" by the scientists. The book was stored in a freezer at -30°C until further use for experiments.

Ito, Wakayama, and team wanted to figure out if the sperm would still be potent after being mailed tens of miles and, to their delight, it was. The scientists were able to mail the mouse sperm from the "sperm book" as postcards by attaching the plastic sheet to the postcard with no protection. One scientist even sent another a "Happy New Year" card with mouse sperm attached as a gift.

The scientists believe that the "sperm book" and mailing method, once perfected, will have a strong impact in their field worldwide. Their next goal is to be able to store them for at least one month at room temperature. In the future, they also hope to develop a method that will allow the freeze-dried sperm to come back to life and fertilize on their own when they are rehydrated.

"It is now recognized that genetic resources are an asset to humanity's future. Even though many genetic traits are not needed for survival, depending on the environmental context, it is necessary to preserve them." says senior author Teruhiko Wakayama, also of the University of Yamanashi in Japan. "The plastic sheet preservation method in this study will be the most suitable method for the safe preservation of a large amount of valuable genetic resources because of the resistance to breakage and less space required for storage."

More information: *iScience, Ito et al.: "Mailing viable mouse freeze-dried spermatozoa on postcards" www.cell.com/iscience/fulltext ... 2589-0042(21)00783-5 , DOI: 10.1016/j.isci.2021.102815*

https://bit.ly/3yHLyle

Chronic Pain Has 9 Distinct Types, According to a Large New Body Mapping Study

Computer clustering analysis of patient body pain maps and pain assessments, the researchers discovered that patients fit into nine groups of chronic pain

Tessa Koumoundouros

The relentlessness of chronic pain wears you down. Beyond being a physical distraction in and of itself, it disrupts sleep, interferes with work and relationships, and can even alter the way we process emotions by causing physiological changes in our brains.

But the experience of long-term pain is complicated and varies between individuals, making it difficult to explain and quantify, let alone diagnose and manage.

Now, in a large study of over 21,500 people who visited the University of Pittsburgh's severe pain management clinics, perioperative specialist Benedict Alter and colleagues have developed a new method to try to help work this out. "We found that how a patient reports the bodily distribution of their chronic pain affects nearly all aspects of the pain experience, including what happens three months later," the team wrote in their paper.

Using a computer clustering analysis of patient body pain maps and pain assessments, the researchers discovered that patients fit into nine groups of chronic pain, as defined in the image below.

What's more, these patterns of pain distribution could predict pain intensity, pain quality, pain impact, physical function, mood, sleep and indicate likely patient outcomes.

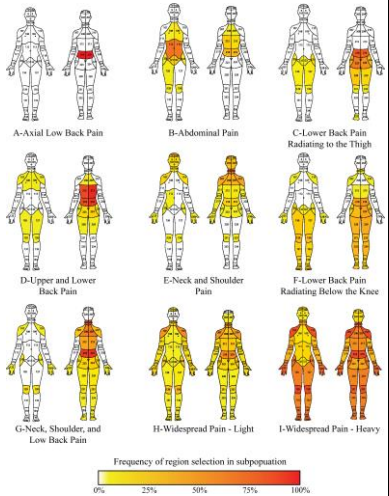
For example, while the group of patients experiencing lower back pain radiating below the knee (group F) had worse physical function difficulties than those experiencing neck and shoulder pain (E) or neck, shoulder and lower back pain (G), these patients reported less anxiety, depression, and sleep disturbance than the

other two groups.

A subset of over 7,000 patients completed a follow-up questionnaire, three months after filling out the initial body pain map and questionnaire. Patients experiencing abdominal pain (group B) showed the most progress, with almost half reporting significant improvement.

Those with neck, shoulder and lower back pain (group G), however, demonstrated the worst outcomes on follow-up, with only 37 percent reporting improvements.

This group shared characteristics with the two widespread pain groups, causing the team to ponder if this subgroup may be an early stage in developing generalized, widespread chronic pain. The researchers recommend a long term study to monitor pain duration and stability over time within this group.



Above: Body pain maps for each of the nine identified chronic pain clusters, with colored heat scale indicating frequency of pain. **(Alter et al., PLOS One, 2021)**

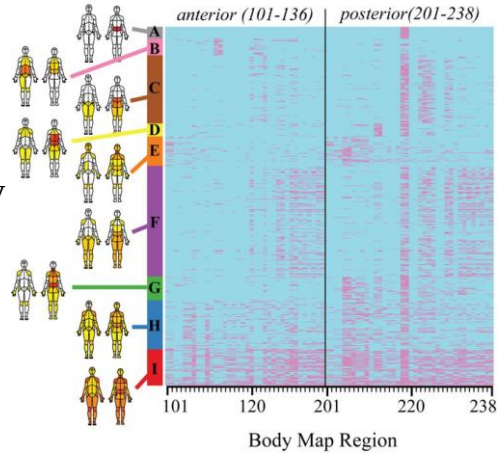
What's more, their findings that the more widespread the pain, the more persistent it is, are consistent with a recent MRI study in fibromyalgia patients that found the more widespread reported pain is on body maps, the more changes observed in brain connectivity around the pain-processing parts of the brain.

"A case can be made that reports of widespread pain collected with digital pain body maps are diagnostic of pathophysiological changes in pain processing," Alter and team suggest.

This ability for body pain maps to indicate likely patient outcomes could help identify patients at risk of poor outcomes even from their first pain clinic visit.

With up to 40 percent of adults in the US currently experiencing chronic pain - which is likely to increase with the potential impacts of long term COVID-19 - diagnostic tools such as this could make a massive difference in many people's lives.

There's still a lot of work to do to untangle all these relationships, and the researchers caution that this is an observational study so they cannot establish causation.



Above: each row on the vertical axis represents an individual patient out of the entire cohort (N = 21,658 unique patients) organized by pain body map cluster membership. **(Alter et al., PLOS One, 2021)**

"Outcome data do not address specific therapies, and therefore, it remains unclear which specific treatment may be helpful for a particular body map cluster," they wrote.

However, Alter and team believe their study supports the idea that chronic pain is a disease process and these aspects of how its physical distribution manifests will be "important for future developments in diagnosis and personalized pain management".

This research was published in *PLOS One*.

https://bit.ly/3yvGH6O

COVID Antibodies Remain Stable – or Even Increase – 7 Months After Infection

The SEROCOV study also provides evidence that pre-existing antibodies to common cold coronaviruses may be protective.

The levels of IgG antibodies against SARS-CoV-2 Spike protein remain stable, or even increase, seven months after infection, according to a follow-up study in a cohort of healthcare workers coordinated by the Barcelona Institute for Global Health (ISGlobal),

an institution supported by "la Caixa" Foundation, in collaboration with the Hospital Clinic of Barcelona. The results, published in *Nature Communications*, also support the idea that pre-existing antibodies against common cold coronaviruses could protect against COVID-19.

In order to predict the pandemic's evolution and develop effective strategies, it is critical to better understand the dynamics and duration of immunity to SARS-CoV-2 as well as the possible role of pre-existing antibodies against the coronaviruses that cause common colds. With this goal in mind, the team led by ISGlobal researcher Carlota Dobaño followed a cohort of healthcare workers at the Hospital Clinic (SEROCOV study) from the beginning of the pandemic, in order to evaluate the levels of antibodies against different SARS-CoV-2 antigens over time. "This is the first study that evaluates antibodies to such a large panel of SARS-CoV-2 antibodies over 7 months," says Dobaño.

The research team analyzed blood samples from 578 participants, taken at four different timepoints between March and October 2020. They used the Luminex technology to measure, in the same sample, the level and type of IgA, IgM or IgG antibodies to 6 different SARS-CoV-2 antigens as well as the presence of antibodies against the four coronaviruses that cause common colds in humans. They also analyzed the neutralizing activity of antibodies in collaboration with researchers at the University of Barcelona. The study had funding from the European innovation network EIT Health.

The results show that the majority of infections among healthcare workers occurred during the first pandemic wave (the percentage of participants with SARS-CoV-2 antibodies increased only slightly between March and October – from 13.5% to 16.4%). With the exception of IgM and IgG antibodies against the nucleocapsid (N), the rest of IgG antibodies (including those with neutralizing activity) remained stable over time, confirming results from other recent studies.

"Rather surprisingly, we even saw an increase of IgG anti-Spike antibodies in 75% of the participants from month five onwards, without any evidence of re-exposure to the virus," says Gemma Moncunill, senior co-author of the study. No reinfections were observed in the cohort.

Regarding antibodies against human cold coronaviruses (HCoV), the results suggest that they could confer cross-protection against COVID-19 infection or disease. People who were infected by SARS-CoV-2 had lower levels of HCoV antibodies. Moreover, asymptomatic individuals had higher levels of anti-HCoV IgG and IgA than those with symptomatic infections. "Although cross-protection by pre-existing immunity to common cold coronaviruses remains to be confirmed, this could help explain the big differences in susceptibility to the disease within the population," says Dobaño.

Reference: "Seven-month kinetics of SARS-CoV-2 antibodies and protective role of pre-existing antibodies to seasonal human coronaviruses on COVID-19" by Ortega N, Ribes M, Vidal M, et al., 6 August 2021, Nature Communications.
DOI: 10.1038/s41467-021-24979-9

https://bit.ly/3rZ4IRa

Arizona man went a month without knowing he had the plague

The delay in diagnosis could have threatened the man's chances of survival.

By Rachael Rettner - Senior Writer

A man in Arizona went nearly a month without knowing he had contracted the plague, which can be deadly if not treated promptly, according to a new report.

The man recovered, but his case underscores the need to identify infections with serious and potentially contagious pathogens, such as *Yersinia pestis* — the bacterium that causes plague — in a timely manner, according to the report, from the Centers for Disease Control and Prevention (CDC).

The 67-year-old man first went to the emergency room on June 18, 2020, with symptoms of dehydration, nausea and weakness, according to the case report, which was published Thursday (Aug. 5) in the CDC journal Morbidity and Mortality Weekly Report. Doctors treated him with IV fluids and released him shortly thereafter. But he came back the next day with three painful red bumps on his leg that he thought were bug bites. This time, doctors suspected he had cellulitis, a skin infection caused by bacteria. He was given prescriptions for two antibiotics and again released from the hospital.

The man came back the next day with more serious symptoms, including fever, dizziness, chills and "swollen glands." He was admitted to the hospital and treated with antibiotics for suspected sepsis, potentially life-threatening body-wide inflammation that can result from an infection.

He tested negative for COVID-19 twice, and a blood sample was sent to a commercial laboratory to help identify the cause of his infection. On June 30, 2020, the lab reported that the man tested positive for *Yersinia pseudotuberculosis*, a bacterium that can spread from animals to people and can cause fever, abdominal pain and, in some cases, a rash and blood infection. It's closely related to *Yersinia pestis*. The man started a two-week course of the antibiotic vancomycin and was allowed to leave the hospital on July 1, 2020.

But the diagnosis of *Y. pseudotuberculosis* would turn out to be wrong. On July 10, 2020, the hospital sent a sample of the man's blood to Arizona State Public Health Laboratory, which identified *Y. pestis* in the sample. Health officials confirmed the diagnosis of plague on July 15, 2020, nearly a month after the man first experienced symptoms.

The man was diagnosed with septicemic plague, a type of plague that causes fever, chills, extreme weakness, abdominal pain and sometimes bleeding into the skin and other organs, according to the CDC. (People with septicemic plague have sepsis caused by *Yersinia pestis*.)

He was then prescribed the appropriate treatment, which in this case was a 10-day course of the antibiotic doxycycline. The delay in diagnosis could have threatened the man's chances of survival. "This patient did not receive high-efficacy antibiotic treatment ... until approximately 30 days after symptom onset," the report said.

The man's eventual recovery may have been due, in part, to his early treatment with antibiotics; although they were not the best antibiotics to treat plague, they do have some effectiveness against plague bacteria, the report said.

Plague is perhaps best known for causing the Black Death in Europe in the 1300s. The infection still occurs today, but it is very rare, with about seven cases of plague occurring in the U.S. each year, on average, according to the CDC. The man's case was the first reported case of plague in Arizona since 2017, the authors said.

Humans can catch the plague through fleabites or contact with the tissue or bodily fluids of an infected animal. The man reported handling a dead pack rat (a rodent belonging to genus *Neotoma*) while wearing gloves before he became ill.

Early and prompt treatment with antibiotics is important to avoid serious complications, including death. Before the advent of antibiotics, the death rate from plague in the U.S. was about 66%, but today the rate is around 11%, according to the CDC.

In Arizona, hospitals and labs that identify any bacterium within the *Yersinia* genus are required to submit the samples to the state public health lab for further testing within one business day, the report said. But in this case, there was a 10-day delay in submitting the sample. The reason for the delay is unclear, but the laboratory staff underwent re-education about this requirement, the report said.

"Rapid reporting might have led to timelier diagnosis of his acute illness and initiation of a more effective antibiotic therapy closer to

disease onset," the report concluded.

https://bit.ly/3jPSV4f

Ancient Herbal Medicine From Asia May Offer Relief to Veterans With Gulf War Illness

Andrographolide is a labdane diterpenoid that has been isolated from the stem and leaves of the Andrographis paniculata plant.

センシンレン(穿心蓮)

Andrographolide, a popular herbal medicine in Southeast Asia, might restore gut microbiomes and viromes that have been altered by chronic multi-symptom illnesses like Gulf War Illness (GWI) according to a study from the University of South Carolina's Environmental Health & Disease Laboratory.

The study found that andrographolide successfully restored bacteriomes and viromes while increasing beneficial bacteria and decreasing harmful bacteria. The treatment also decreased gut inflammation and neuroinflammation.

"Andrographolide, which is widely used in India and China, has been used for ages and has numerous beneficial effects for liver and gastrointestinal disease," says Punnag Saha, a second-year doctoral student in the Department of Environmental Health Sciences and the lead researcher for the study. "Scientists have conducted significant research about its beneficial properties on various disease models including the antiviral properties it possesses; however, andrographolide's efficacy on the various ailments associated with chronic multi-symptom illnesses has never been studied."

Andrographolide's documented benefits prompted UofSC's Environmental Health & Disease Laboratory to investigate whether it could restore the altered gut microbiome/virome and alleviate other symptoms associated with GWI and similar conditions.

Saurabh Chatterjee, director of UofSC's Environmental & Disease Laboratory, identified how GWI-altered microbiomes produce endotoxins that pass through the thinned lining of the gut (i.e., leaky gut) and enter the bloodstream where they are circulated throughout the body, including the brain.

Andrographolide – a broad spectrum antibacterial, anti-viral and anti-inflammatory compound – could provide relief not only for chronic symptoms typically associated with the disease but may mitigate complications from and vulnerability to co-infections, such as COVID-19. The authors recommend that clinical trials with GWI veterans be conducted to better determine the efficacy of this course of treatment.

"The quest for identifying novel pathways of pathophysiology and to target them with compounds derived from natural products or botanicals remain a top priority for our research," Chatterjee says. "Punnag and Dipro exemplify the continuing quest of my lab to excel in achieving the mission of our department and the Arnold School of Public Health. The lab's collaborators nationwide and Dr. Lim's laboratory at Arizona State University are keys to these discoveries."

Reference: "Andrographolide Attenuates Gut-Brain-Axis Associated Pathology in Gulf War Illness by Modulating Bacteriome-Virome Associated Inflammation and Microglia-Neuron Proinflammatory Crosstalk" by Punnag Saha, Peter T. Skidmore, LaRinda A. Holland, Ayan Mondal, Dipro Bose, Ratanesh K. Seth, Kimberly Sullivan, Patricia A. Janulewicz, Ronnie Horner, Nancy Klimas, Mitzi Nagarkatti, Prakash Nagarkatti, Efrem S. Lim and Saurabh Chatterjee, 9 July 2021, Brain Sciences.

DOI: 10.3390/brainsci11070905

This study was supported by DoD-IIRFA Grant W81XWH1810374, VA Merit Award I01CX001923-01, NIH grant 2P20GM103641 to Saurabh Chatterjee, and NIH grant R00DK107923 to Efrem S. Lim. This work was supported in part by a Merit Review Award I01CX001923-01 from the United States (U.S.) Department of Veterans Affairs Clinical Sciences Research and Development Service.