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FDA Authorizes Fuller Vials for Moderna's COVID-19 Vaccine

The FDA authorized Moderna to add more coronavirus vaccine doses into its vials on Thursday, bumping the range up to between 11 to 15 doses that can be extracted.

Carolyn Crist

The FDA approved new vials from Moderna that can contain up to 15 doses, and the agency said the current 10-dose vials can safely extract up to 11 doses. "Ultimately, more vaccines getting to the public in a timely manner should help bring an end to the pandemic more rapidly," Peter Marks, MD, director of the FDA's Center for Biologics Evaluation and Research, said in a statement.

The move is anticipated to further increase U.S. vaccine supply in the coming weeks and could speed up Moderna's delivery timeline, according to *The New York Times.* Moderna has pledged to deliver 200 million doses by the end of May and 300 million by the end of July.

In anticipation of the FDA's approval, Moderna had already begun producing vials with more doses, the newspaper reported. The FDA told the company six weeks ago that it was in favor of increasing the number of doses. Moderna will begin shipping the 15-dose vials in the coming weeks, the company said in a statement on Thursday.

"We are committed to constantly learning and improving to facilitate easier administration of our COVID-19 vaccine for medical staff and accelerate immunization programs," Stéphane Bancel, the CEO of Moderna, said in the statement.

The FDA evaluated data from Moderna that showed how many doses could be safely extracted from the different vials and updated its fact sheet for health care providers to help frontline workers understand how many doses they can extract based on the type vial used.

Sources

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New York Times, "The F.D.A. authorizes fuller vials from Moderna, a boost to vaccine supplies."

Moderna, "Moderna Provides Storage Update & Announces the U.S. FDA Authorizes Up To 15-Doses Per Vial of its COVID-19 Vaccine."

https://bit.ly/3uBHMrn

Paleopharmaceuticals from Baltic amber might fight drug-resistant infections

For centuries, people in Baltic nations have used ancient amber for medicinal purposes.

Even today, infants are given amber necklaces that they chew to relieve teething pain, and people put pulverized amber in elixirs and ointments for its purported anti-inflammatory and anti-infective properties. Now, scientists have pinpointed compounds that help explain Baltic amber's therapeutic effects and that could lead to new medicines to combat antibiotic-resistant infections. The researchers will present their results today at the spring meeting of the American Chemical Society (ACS).

Baltic amber is not only beautiful, but also a potential source of new antibiotics. **Credit: Connor McDermott**

Each year in the U.S., at least 2.8 million people get antibiotic-resistant infections, leading to 35,000 deaths, according to the U.S. Centers for Disease Control and Prevention. "We knew from previous research that there were substances in Baltic amber that might lead to new antibiotics, but they had not been systematically explored," says Elizabeth Ambrose, Ph.D., who is the principal investigator of the project. "We have now extracted and identified several compounds in Baltic amber that show activity against gram-positive, antibiotic-resistant bacteria."

Ambrose's interest originally stemmed from her Baltic heritage.

While visiting family in Lithuania, she collected amber samples and heard stories about their medicinal uses. The Baltic Sea region contains the world's largest deposit of the material, which is fossilized resin formed about 44 million years ago. The resin oozed from now-extinct pines in the *Sciadopityaceae* family and acted as a defense against microorganisms such as bacteria and fungi, as well as herbivorous insects that would become trapped in the resin.

Ambrose and graduate student Connor McDermott, who are at the University of Minnesota, analyzed commercially available Baltic amber samples, in addition to some that Ambrose had collected. "One major challenge was preparing a homogeneous fine powder from the amber pebbles that could be extracted with solvents," McDermott explains. He used a tabletop jar rolling mill, in which the jar is filled with ceramic beads and amber pebbles and rotated on its side. Through trial and error, he determined the correct ratio of beads to pebbles to yield a semi-fine powder. Then, using various combinations of solvents and techniques, he filtered, concentrated and analyzed the amber powder extracts by gas chromatography-mass spectrometry (GC-MS).

Dozens of compounds were identified from the GC-MS spectra. The most interesting were abietic acid, dehydroabietic acid and palustric acid—20-carbon, three-ringed organic compounds with known biological activity. Because these compounds are difficult to purify, the researchers bought pure samples and sent them to a company that tested their activity against nine bacterial species, some of which are known to be antibiotic resistant.

"The most important finding is that these compounds are active against gram-positive bacteria, such as certain *Staphylococcus aureus* strains, but not gram-negative bacteria," McDermott says. Gram-positive bacteria have a less complex cell wall than gram-negative bacteria. "This implies that the composition of the bacterial membrane is important for the activity of the compounds," he says. McDermott also obtained a Japanese umbrella pine, the closest living species to the trees that produced the resin that became Baltic amber. He extracted resin from the needles and stem and identified sclarene, a molecule present in the extracts that could theoretically undergo chemical transformations to produce the bioactive compounds the researchers found in Baltic amber samples.

"We are excited to move forward with these results," Ambrose says. "Abietic acids and their derivatives are potentially an untapped source of new medicines, especially for treating infections caused by gram-positive bacteria, which are increasingly becoming resistant to known antibiotics."

https://bit.ly/3d4dKqe

Making cleaner, greener plastics from waste fish parts

Using fish oil, researchers have made a polyurethane-like material.

Polyurethanes, a type of plastic, are nearly everywhere—in shoes, clothes, refrigerators and construction materials. But these highly versatile materials can have a major downside. Derived from crude oil, toxic to synthesize, and slow to break down, conventional polyurethanes are not environmentally friendly. Today, researchers discuss devising what they say should be a safer, biodegradable alternative derived from fish waste—heads, bones, skin and guts—that would otherwise likely be discarded.

The researchers will present their results today at the spring meeting of the American Chemical Society (ACS).

If developed successfully, a fish-oil based polyurethane could help meet the immense need for more sustainable plastics, says Francesca Kerton, Ph.D., the project's principal investigator. "It is important that we start designing plastics with an end-of-life plan, whether it's chemical degradation that turns the material into carbon dioxide and water, or recycling and repurposing."

To make the new material, Kerton's team started out with oil

extracted from the remains of Atlantic salmon, after the fish were prepared for sale to consumers. "I find it interesting how we can make something useful, something that could even change the way plastics are made, from the garbage that people just throw out," says Mikhailey Wheeler, a graduate student who is presenting the work at the meeting. Both Kerton and Wheeler are at Memorial University of Newfoundland (Canada).

The conventional method for producing polyurethanes presents a number of environmental and safety problems. It requires crude oil, a non-renewable resource, and phosgene, a colorless and highly toxic gas. The synthesis generates isocyanates, potent respiratory irritants, and the final product does not readily break down in the environment. The limited biodegradation that does occur can release carcinogenic compounds. Meanwhile, demand for greener alternatives is growing. Previously, others have developed new polyurethanes using plant-derived oils to replace petroleum. However, these too come with a drawback: The crops, often soybeans, that produce the oil require land that could otherwise be used to grow food.

Leftover fish struck Kerton as a promising alternative. Salmon farming is a major industry for coastal Newfoundland, where her university is located. After the fish are processed, leftover parts are often discarded, but sometimes oil is extracted from them. Kerton and her colleagues developed a process for converting this fish oil into a polyurethane-like polymer. First, they add oxygen to the unsaturated oil in a controlled way to form epoxides, molecules similar to those in epoxy resin. After reacting these epoxides with carbon dioxide, they link the resulting molecules together with nitrogen-containing amines to form the new material.

But does the plastic smell fishy? "When we start the process with the fish oil, there is a faint kind of fish smell, but as we go through the steps, that smell disappears," Kerton says.

Kerton and her team described this method in a paper last August, and since then, Wheeler has been tweaking it. She has recently had some success swapping out the amine for amino acids, which simplifies the chemistry involved. And while the amine they used previously had to be derived from cashew nut shells, the amino acids already exist in nature. Wheeler's preliminary results suggest that histidine and asparagine could fill in for the amine by linking together the polymer's components.

In other experiments, they have begun examining how readily the new material would likely break down once its useful life is over. Wheeler soaked pieces of it in water, and to speed up the degradation for some pieces, she added lipase, an enzyme capable of breaking down fats like those in the fish oil. Under a microscope, she later saw microbial growth on all of the samples, even those that had been in plain water, an encouraging sign that the new material might biodegrade readily, Wheeler says.

Kerton and Wheeler plan to continue testing the effects of using an amino acid in the synthesis and studying how amenable the material is to the microbial growth that could hasten its breakdown. They also intend to study its physical properties to see how it might potentially be used in real world applications, such as in packaging or fibers for clothing.

More information: *Abstract title: Waste fish oil for the production of greener polyurethane materials*

https://bit.ly/39WHm71

Fireflies have a potential—protective 'musical armor' against bats

New study reveals: fireflies produce strong ultrasonic sounds that might deter bats

A new study at Tel Aviv University reveals a possible defense mechanism developed by fireflies for protection against bats that might prey on them. According to the study, fireflies produce

strong ultrasonic sounds—soundwaves that the human ear, and more importantly the fireflies themselves, cannot detect. The researchers hypothesize that these sounds are meant for the ears of bats, keeping them away from the poisonous fireflies, and thereby serving as a kind of 'musical armor.' The study was led by Prof. Yossi Yovel, Head of the Sagol School of Neuroscience, and a member of the School of Mechanical Engineering and the School of Zoology at the George S. Wise Faculty of Life Sciences. It was conducted in collaboration with the Vietnam Academy of Science and Technology (VAST). The paper was published in *iScience*.

Fireflies are known for their unique glow, used as a mating signal. Since their bodies contain poison, the light flashes probably also serve as an aposematic signal (a warning to potential predators). This signal is also the firefly's weakness, simply because it makes it an easy target for predators. Bats are among the fireflies' most prevalent potential predators, and some bats have poor vision, rendering the flashing signal ineffective. This led the researchers to check whether fireflies had some additional layer of protection against bats.

Prof. Yossi Yovel explains that the idea for this study came up accidentally, during a study that tracked bats' echolocation. "We were wandering around a tropical forest with microphones capable of recording bats' high frequencies, when suddenly, we detected unfamiliar sounds at similar frequencies, coming from fireflies," he recalls. "In-depth research using high-speed video revealed that the fireflies produce the sound by moving their wings, and that the fireflies themselves can't hear this frequency. Consequently we hypothesized that the sound is not intended for any internal communication within the species," adds Ksenia Krivoruchku, the Ph.D. student who led the study.

Following the accidental discovery, the team at Prof. Yovel's laboratory examined three different species of fireflies that are common in Vietnam (Curtos Luciola, Sclerotia) plus one Israeli species (Lampyroidea), and found that they all produce these unique ultrasonic sounds, but cannot hear them.

Can it be concluded that fireflies have developed a special defense mechanism specifically for bats? Prof. Yovel emphasizes that this claim was not proved in the study, but several features do point to this conclusion. First of all, the fact that the fireflies themselves can't hear the sound, while bats can both hear it and use it to find the fireflies—so it's more likely that it serves as a warning signal. Krivoruochku adds that the discovery of ultrasonic sounds in fireflies is in itself an important contribution to the study of predator-prey relations: "The idea of warning signals that the sender itself cannot detect is known from the world of plants but is quite rare among animals. Our discovery of the 'musical battle' between fireflies and bats may pave the way for further research, and possibly the discovery of a new defense mechanism developed by animals against potential predators."

More information: *Ksenia Krivoruchko et al, Fireflies produce ultrasonic clicks during flight as a potential aposematic anti-bat signal, iScience (2021).* *DOI: 10.1016/j.isci.2021.102194*

https://bit.ly/3wFLPEW

'Brain glue' helps repair circuitry in severe TBI

Reparative hydrogel mimics the composition and mechanics of the brain

At a cost of $38 billion a year, an estimated 5.3 million people are living with a permanent disability related to traumatic brain injury in the United States today, according to the Centers for Disease Control and Prevention. The physical, mental and financial toll of a TBI can be enormous, but new research from the University of Georgia provides promise.

In a new study, researchers at UGA's Regenerative Biosciences Center have demonstrated the long-term benefits of a hydrogel,

which they call "brain glue," for the treatment of traumatic brain injury. The new study provides evidence that not only does the gel protect against loss of brain tissue after a severe injury, but it also might aid in functional neural repair.

Brain damage following significant TBI commonly results in extensive tissue loss and long-term disability. There currently are no clinical treatments to prevent the resulting cognitive impairments or tissue loss.

Reported on March 5 in *Sciences Advances*, the new finding is the first to provide visual and functional evidence of the repair of brain neural circuits involved in reach-to-grasp movement in brain glue-implanted animals following severe TBI.

"Our work provides a holistic view of what's going on in the recovery of the damaged region while the animal is accomplishing a specific reach-and-grasp task," said lead investigator Lohitash Karumbaiah, an associate professor in the University of Georgia's College of Agricultural and Environmental Sciences.

Created by Karumbaiah in 2017, brain glue was designed to mimic the structure and function of the meshwork of sugars that support brain cells. The gel contains key structures that bind to basic fibroblast growth factor and brain-derived neurotrophic factor, two protective protein factors that can enhance the survival and regrowth of brain cells after severe TBI.

In a prior short-term study, Karumbaiah and his team showed that brain glue significantly protected brain tissue from severe TBI damage. In this new research, to harness the neuroprotective capacity of the original, they further engineered the delivery surface of protective factors to help accelerate the regeneration and functional activity of brain cells. After 10 weeks, the results were apparent.

"Animal subjects that were implanted with the brain glue actually showed repair of severely damaged tissue of the brain," said Karumbaiah. "The animals also elicited a quicker recovery time compared to subjects without these materials."

To measure the glue's effectiveness, the team used a tissue-clearing method to make brain tissue optically transparent, which allowed them to visually capture the immediate response of cells in the reach-to-grasp circuit using a 3D imaging technique.

"Because of the tissue-clearing method, we were able to obtain a deeper view of the complex circuitry and recovery supported by brain glue," said Karumbaiah. "Using these methods along with conventional electrophysiological recordings, we were able to validate that brain glue supported the regeneration of functional neurons in the lesion cavity."

Karumbaiah pointed out that the RTG circuit is evolutionarily similar in rats and humans. "The modulation of this circuit in the rat could help speed up clinical translation of brain glue for humans," he said.

With support from UGA's Innovation Gateway, Karumbaiah has filed for a patent on the brain glue. He is also partnering with Parastoo Azadi, technical director of analytical services at the UGA Complex Carbohydrate Research Center, and GlycoMIP, a $23 million, National Science Foundation-funded Materials Innovation Platform, created to advance the field of glycomaterials through research and education.

"Doing the behavioral studies, the animal work and the molecular work sometimes takes a village," said Karumbaiah. "This research involved a whole cross-section of RBC undergraduate and graduate students, as well as faculty members from both UGA and Duke University."

The collaborative research effort provided five UGA RBC fellow undergraduates with an experiential learning opportunity and to publish their first paper. This is the first publication for Rameen Forghani, an aspiring M.D.-Ph.D. undergraduate working in the

Karumbaiah lab.

Forghani said the undergraduate team "learned how to collaborate on this project" and about the impact of moving lab research to patients who need treatment.

"My fellow undergraduates and I were empowered to take ownership of a piece of the project and see it through from the planning stages of data analysis to writing and being published," said Forghani. "As an aspiring, early-career physician-scientist, working on a project that has translational impact and directly addresses a very relevant clinical problem is very exciting to me."

Charles Latchoumane, research scientist in the Karumbaiah lab and first author on the study, divides his time between UGA and Lausanne, Switzerland, where he works at NeurRestore, a research center aimed at restoring lost neurological function for people suffering from Parkinson's disease or from neurological disorders following a head injury or stroke.

"This study has been four to five years in the making," said Latchoumane. "Our collaborative research is so painstakingly documented that, after you read about it, you have to believe there is new hope for severe victims of brain injury."

This work was supported by grants to Karumbaiah from the National Institutes of Health (RO1NS099596, R24GM137782), the Regenerative Engineering and Medicine Center seed grant program, and an Alliance for Regenerative Rehabilitation Research and Training technology development grant.

https://bit.ly/3d0Gdx1

This hydrogen fuel machine could be the ultimate guide to self-improvement

Harnesses sunlight into carbon-free hydrogen for fuel cells with twice the efficiency and stability of some previous technologies

Three years ago, scientists at the University of Michigan discovered an artificial photosynthesis device made of silicon and gallium nitride (Si/GaN) that harnesses sunlight into carbon-free hydrogen for fuel cells with twice the efficiency and stability of some previous technologies.

Now, scientists at the Department of Energy's (DOE's) Lawrence Berkeley National Laboratory (Berkeley Lab)—in collaboration with the University of Michigan and Lawrence Livermore National Laboratory (LLNL)—have uncovered a surprising, self-improving property in Si/GaN that contributes to the material's highly efficient and stable performance in converting light and water into carbon-free hydrogen. Their findings, reported in the journal *Nature Materials*, could help radically accelerate the commercialization of artificial photosynthesis technologies and hydrogen fuel cells.

"Our discovery is a real game-changer," said senior author Francesca Toma, a staff scientist in the Chemical Sciences Division at the Department of Energy's Lawrence Berkeley National Laboratory (Berkeley Lab). Usually, materials in solar fuels systems degrade, become less stable and thus produce hydrogen less efficiently, she said. "But we discovered an unusual property in Si/GaN that somehow enables it to become more efficient and stable. I've never seen such stability."

Previous artificial photosynthesis materials are either excellent light absorbers that lack durability; or they're durable materials that lack light-absorption efficiency.

But silicon and gallium nitride are abundant and cheap materials that are widely used as semiconductors in everyday electronics such as LEDs (light-emitting diodes) and solar cells, said co-author Zetian Mi, a professor of electrical and computer engineering at the University of Michigan who invented Si/GaN artificial photosynthesis devices a decade ago.

When Mi's Si/GaN device achieved a record-breaking 3 percent solar-to-hydrogen efficiency, he wondered how such ordinary materials could perform so extraordinarily well in an exotic artificial photosynthesis device—so he turned to Toma for help.

HydroGEN: Taking a Team Science approach to solar fuels

Mi had learned of Toma's expertise in advanced microscopy techniques for probing the nanoscale (billionths of a meter) properties of artificial photosynthesis materials through HydroGEN, a five-national lab consortium supported by the DOE's Hydrogen and Fuel Cell Technologies Office, and led by the National Renewable Energy Laboratory to facilitate collaborations between National Labs, academia, and industry for the development of advanced water-splitting materials. "These interactions of supporting industry and academia on advanced water-splitting materials with the capabilities of the National Labs are precisely why HydroGEN was formed—so that we can move the needle on clean hydrogen production technology," said Adam Weber, Berkeley Lab's Hydrogen and Fuel Cell Technologies Lab Program Manager and Co-Deputy Director of HydroGEN.

Toma and lead author Guosong Zeng, a postdoctoral scholar in Berkeley Lab's Chemical Sciences Division, suspected that GaN might be playing a role in the device's unusual potential for hydrogen production efficiency and stability.

To find out, Zeng carried out a photoconductive atomic force microscopy experiment at Toma's lab to test how GaN photocathodes could efficiently convert absorbed photons into electrons, and then recruit those free electrons to split water into hydrogen, before the material started to degrade and become less stable and efficient.

They expected to see a steep decline in the material's photon absorption efficiency and stability after just a few hours. To their astonishment, they observed a 2-3 orders of magnitude improvement in the material's photocurrent coming from tiny facets along the "sidewall" of the GaN grain, Zeng said. Even more perplexing was that the material had increased its efficiency over time, even though the overall surface of the material didn't change that much, Zeng said. "In other words, instead of getting worse, the material got better," he said.

To gather more clues, the researchers recruited scanning transmission electron microscopy (STEM) at the National Center for Electron Microscopy in Berkeley Lab's Molecular Foundry, and angle-dependent X-ray photon spectroscopy (XPS).

Those experiments revealed that a 1 nanometer layer mixed with gallium, nitrogen, and oxygen—or gallium oxynitride—had formed along some of the sidewalls. A chemical reaction had taken place, adding "active catalytic sites for hydrogen production reactions," Toma said.

Density functional theory (DFT) simulations carried out by co-authors Tadashi Ogitsu and Tuan Anh Pham at LLNL confirmed their observations. "By calculating the change of distribution of chemical species at specific parts of the material's surface, we successfully found a surface structure that correlates with the development of gallium oxynitride as a hydrogen evolution reaction site," Ogitsu said. "We hope that our findings and approach—a tightly integrated theory-experiments collaboration enabled by the HydroGEN consortium—will be used to further improve the renewable hydrogen production technologies."

Mi added: "We've been working on this material for over 10 years—we know it's stable and efficient. But this collaboration helped to identify the fundamental mechanisms behind why it gets more robust and efficient instead of degrading. The findings from this work will help us build more efficient artificial photosynthesis devices at a lower cost."

Looking ahead, Toma said that she and her team would like to test the Si/GaN photocathode in a water-splitting photoelectrochemical cell, and that Zeng will experiment with similar materials to get a better understanding of how nitrides contribute to stability in artificial photosynthesis devices—which is something they never thought would be possible.

"It was totally surprising," said Zeng. "It didn't make sense—but Pham's DFT calculations gave us the explanation we needed to validate our observations. Our findings will help us design even better artificial photosynthesis devices."

"This was an unprecedented network of collaboration between National Labs and a research university," said Toma. "The HydroGEN consortium brought us together—our work demonstrates how the National Labs' Team Science approach can help solve big problems that affect the entire world."

More information: *Development of a photoelectrochemically self-improving Si/GaN photocathode for efficient and durable H_2 production, Nature Materials (2021). dx.doi.org/10.1038/s41563-021-00965-w*

https://wb.md/3dGzl76

Endocrinologist Charged After Bomb-Making Supplies Found

An endocrinologist in Naples, Florida, faces multiple federal charges after police found homemade explosives and bomb-making supplies, as well as numerous illegal drugs, in his home.

Marcia Frellick

Police were executing a search warrant at the home of Christy Daniel Cugini, MD, 63, on March 30 when they found the items, according to Collier County Sheriff's Office (CCSO).

"An investigation continues and more charges could be brought," the sheriff's office said in a statement. As of April 1, Cugini was out on bond. His next court appearance is on April 26.

A search of his bedroom turned up marijuana, tramadol, oxycodone, and hydrocodone, the sheriff's office said. According to nbcmiami.com, police also found 560 grams of marijuana and $20,000 in cash and jewelry in a safe. "Some of the narcotics were in pill bottles with other people's names on them. Many of the substances were of trafficking quantities. The search also turned up numerous items of narcotic paraphernalia, including heat seal bags, a vacuum sealer, and a scale," the CCSO report said.

Charges against Cugini include narcotics trafficking; possession of marijuana with intent to sell/manufacture/deliver; possession of more than 20 grams of marijuana; possession of a controlled substance; and possession of narcotic paraphernalia, according to the report. He was also charged with nine counts of making/possessing a destructive device.

The CCSO bomb squad was brought in to investigate the homemade explosive devices and supplies, including potassium nitrate and ammonium nitrate which can be used as oxidizers, PVC pipe, and flash powders used in fireworks in Cugini's house and garage.

Newsweek reported that the bomb squad found six red cylindrical devices about 4 inches long, according to information reported in an affidavit from Collier County Officer Jeffrey Tayar. They may have been intended to be a hand-tossed improvised explosive device, Tayar wrote.

An officer also found three other devices made up of PVC pipe attached to a small wood square. A rifle round was inserted into the PVC pipe, Tayar's report said.

"The device could be placed on the ground in such a manner as to leave the rifle round facing up," Tayar reportedly wrote. "If downward pressure were applied on the tip of the round...the rifle round [would] discharge, launching the projectile portion of the round upward, presumably into the foot of the subject stepping on it." NBC News reported that deputies said Cugini appeared to live only with his young daughter.

He initially agreed to speak with deputies but then invoked his Miranda rights and stopped answering questions, NBC said. Cugini's profile has been removed from the Millennium Physician Group website.

His employer offered this statement to *Medscape Medical News* via

spokesperson Liza Fernandez: "We are shocked at the allegations regarding Dr Christy Cugini. He has been placed on administrative leave until further notice. Millennium is committed to cooperating with law enforcement and is conducting an internal investigation."

According to *US News & World Report,* Cugini is affiliated with NCH Baker Hospital. He received his medical degree from Ross University School of Medicine, now located in Barbados, and has been practicing for more than 20 years. *Medscape Medical News* attempted to contact Cugini but was unsuccessful.

https://bit.ly/3mvLcsI

Canada-wide ban on menthol cigarettes leads to significant increases in quitting among smokers

Study demonstrates the substantial benefits of banning menthol cigarettes

Bans on menthol cigarettes across Canada from 2016 to 2017 led to a significant increase in the number of smokers who attempted to quit, smokers who quit successfully, and lower rates of relapse among former smokers, according to a new research study from the International Tobacco Control Policy Evaluation Project (the ITC Project) at the University of Waterloo.

Menthol is the most common flavoring for cigarettes in many countries. Menthol creates a cooling sensation, which reduces the harshness of cigarette smoke. Because of this, menthol leads to increased experimentation and progression to regular smoking among new smokers, especially among youth.

"Our study demonstrates the substantial benefits of banning menthol cigarettes," said Geoffrey T. Fong, Professor of Psychology and Public Health and Health Systems at Waterloo, and principal investigator of the ITC Project. "The enormous success of the Canadian menthol ban makes it even clearer now that the U.S. should finally ban menthol, which the tobacco industry has used for decades to attract new smokers and to keep many of them as customers, especially among the African-American community.

"The positive effects of the Canada menthol ban suggest that a U.S. menthol ban would lead to greater benefits since menthol cigarettes are much more popular in the U.S. From our findings, we estimate that banning menthol cigarettes in the U.S. would lead an additional 923,000 smokers to quit, including 230,000 African-American smokers."

The study conducted by Fong and his team examined the impact of menthol bans across seven Canadian provinces, covering 83 per cent of the Canadian population, which saw menthol cigarettes banned between August 2016 and October 2017. Canada was the one of the first countries to implement a ban on menthol cigarettes, and the first country where a menthol ban has been evaluated.

"The Canadian menthol ban did not lead to a high level of illicit menthol cigarette purchasing, which has been a concern by regulators considering a menthol ban," said Fong. "Fewer than 10 per cent of menthol smokers reported still smoking a menthol brand after the ban."

Scientific reviews conducted by the Tobacco Products Scientific Advisory Committee to the U.S. Food and Drug Administration (FDA), the FDA itself, and the World Health Organization have also concluded that banning menthol would have significant public health benefits.

The harms of menthol cigarettes in the U.S. have been much greater among African-Americans. Menthol cigarettes are smoked by 85 per cent of African-American smokers, over 2.8 times the percentage of menthols among white smokers.

A national sample of 1098 non-menthol and 138 menthol smokers participating in the ITC Canada Smoking and Vaping Survey were surveyed both before the menthol ban (in 2016) and after the menthol ban (in 2018).

The survey demonstrated three benefits of the Canadian menthol

ban. Menthol smokers were significantly more likely than non-menthol smokers to attempt to quit after the menthol ban (58.7 per cent vs. 49 per cent).

Daily menthol smokers were almost twice as likely than daily non-menthol smokers to quit after the menthol ban (21 per cent vs. 11.6 per cent).

Finally, those menthol smokers who had quit smoking before the menthol ban were significantly less likely than non-menthol smokers who had quit smoking to have relapsed back to smoking.

The study, Evaluating the impact of menthol cigarette bans on cessation and smoking behaviours in Canada: longitudinal findings from the Canadian arm of the 2016-2018 ITC Four Country Smoking and Vaping Surveys, was published today in the journal Tobacco Control.

https://wb.md/3fWWaXq

Star Trek Fan Has 26 COVID-19 Papers Retracted by Elsevier

An Elsevier journal has retracted more than two dozen Covid-19 papers by a researcher in Malta with a fondness for Star Trek after determining that the articles did not meet its standards for publication.

Retraction Watch Staff

The move comes several months after we reported that Hampton Gaddy, a student at the University of Oxford, had raised questions about more than 100 articles written by a pediatric cardiologist named Victor Grech. The papers appeared in *Early Human Development (EHD*), which Grech managed to turn into something of a vanity press — including for papers about how the lessons of Star Trek shed light on everything from the evolving role of nurses to the horrors of Nazi doctors.

As Gaddy pointed out to Elsevier last December, Grech has written at least 113 papers in *EHD*, 57 as sole author:

19 of these 113 articles focus on various aspects of the TV series Star Trek. They generally discuss topics within the series that are relevant to the field of medicine, but the extent of this stops at discussing the potrayals [sic] of doctors, 2 medical practices, 3 medical technology, 4 etc., in the series.1 Many of these articles were confusingly published in the category of 'Best practice guidelines' [BPGs].

The April issue of EHD has an editor's note addressing 17 of the "Star Trek BPG" papers. The note reads:

Upon publication of this BPG series, concerns were raised regarding its appropriateness for inclusion in a peer-reviewed academic journal. It is the Editor's judgement that this series of articles should not have been accepted for publication by the journal since it is not within its scope. The idea was to engage topics that the ordinary reader of Early Human Development might not normally come across – but could find interesting. The journal has re-designed its editorial and review workflow to ensure that this will not happen again in future.

However, only one of those, "Doctors in Star Trek: Reflections on the changing faces of future doctors," is now shown as retracted.

Returning to a realm where man *has* gone before, *EHD* has also withdrawn 26 papers by Grech about COVID-19. ("Withdrawn" is Elsevier's problematic term for retractions of papers that are online but have yet to appear in print.)

For example, Grech's article "Theoretical novel COVID-19 vaccination risk of rare and severe adverse events versus COVID-19 mortality," is withdrawn with the statement:

This article has been withdrawn at the request of the author(s) and/or editor. The Publisher apologizes for any inconvenience this may cause.

Grech — who in one fell swoop now joins our leaderboard of 30 authors with the most retractions in the world — told us, referring to the BPG series, that:

I abide by the editor's note.

Also on the list is "COVID-19 and potential global mortality – Revisited," which *EHD* published in May 2020 and which drew its conclusions in part from a controversial article by researchers at Imperial College London whose correction we reported on last

April. That notice reads:

The author has requested that Early Human Development retract this article. This article was based on very early data and reports from the World Health Organization and Ferguson et al. from which the article drew imprecise conclusions. We now have a far better, albeit still incomplete, understanding of COVID-19. The anticipated mortality will fortunately be far less than estimated in the paper itself.

The other retractions — which bring the total number of retracted COVID-19 papers above 100 for the first time — are:

Countering fake news in the COVID-19 era: The public's opinion on the role of an honest and reliable website
Malta tourism losses due to second wave of COVID-19
Novel research opportunities 2: An unfortunate small silver lining to COVID-19
The way in which COVID-19 changed behaviour on social media in Malta
Some health effects of global warming
Novel research opportunities: An unfortunate small silver lining to COVID-19
COVID-19: Combined supply-side and demand-side shocks, so lift restrictions (carefully) lest GPD declines ultimately kill more than COVID-19
COVID-19 is ageist, sexist, ruthless, dispassionate and opportunistic – Protecting our vulnerable
One of COVID-19's many costs: Malta's expenditure in consumables and non-consumables, a population-based study
Vaccine hesitancy among Maltese healthcare workers toward influenza and novel COVID-19 vaccination
COVID-19 related acute decline in paediatric admissions in Malta, a population-based study
COVID-19: The possible seasonal shape of things to come
Holidays over: A review of actual COVID-19 school outbreaks up to September 2020
The Spanish flu, COVID-19 and Malta's reactions: Contrasts and similarities
COVID-19: A global and continental overview of the second wave and its (relatively) attenuated case fatality ratio
Vaccine hesitancy in the University of Malta Faculties of Health Sciences, Dentistry and Medicine vis-à-vis influenza and novel COVID-19 vaccination
Vaccine hesitancy in Maltese family physicians and their trainees vis-à-vis influenza and novel COVID-19 vaccination
Needed: Less influenza vaccine hesitancy and less presenteeism among health care workers in the COVID-19 era
Sports and sportsmen as role models – or otherwise – in the COVID-19 era
COVID-19: Mathematical estimation of delay to deaths in relation to upsurges in positive rates
COVID-19, its novel vaccination and fake news – What a brew
To wear or not to wear? Adherence to face mask use during the COVID-19 and Spanish influenza pandemics
Sharp decline in acute and elective hospital attendances and admissions due to COVID-19 in Malta (Q1 2020) – A population-based study
Safe school reopening under COVID-19 restrictions – Measures implemented in San Andrea Independent School in Malta

Update, 2145 UTC, 3/31/21: The journal has also added an editor's note referring to 48 articles written by Grech, sometimes with co-authors, in a series called "Write A Scientific Paper," aka WASP:

Upon publication concerns were raised regarding the appropriateness for inclusion of several of the WASP BPGs in a peer-reviewed academic journal. It is the Editor's judgement that some of the papers in this series fall outside the journal's scope and should not have been accepted for publication. The idea was to provide an educational series of articles aimed at junior medical and nursing staff on the basic principles of writing a scientific paper. The journal has re-designed its editorial and review workflow to ensure that this will not happen again in future.

https://bit.ly/3dOyFNa

Meet 'Very Fast Death Factor' - The Algal Toxin Scientists Are Finding in Our Air

While some blue-green algae (or more accurately - cyanobacteria) are critical to us for their nitrogen-fixing abilities, others can also become dangerous pests of our own making.

Jacinta Bowler

Climate change and agricultural run-off are causing a once normal environmental process to spiral out of control more often, and a new study has shown that a particularly dangerous toxin produced by cyanobacteria is not just hitching a ride in water, but also in our air in some cases.

The toxin, called anatoxin-a (ATX) or Very Fast Death Factor (no, we're not kidding), does what it says on the tin - kills things fast. If you are unfortunate enough to be exposed it can cause a loss of coordination, paralysis, or death in humans and other animals.

"ATX is one of the more dangerous cyanotoxins produced by harmful algal blooms, which are becoming more predominant in lakes and ponds worldwide due to global warming and climate change," explains first author James Sutherland from the Nantucket Land Council.

ATX is produced by a range of cyanobacteria that bloom in warm, still, nutrient-rich water, and it can disrupt the rest of the ecosystem. In harmful algal blooms (HAB), the cyanobacteria lower the oxygen levels of the water and can sometimes produce toxins such as ATX. Then, once the bloom dies, the microbes that decompose the algae use even more oxygen, which can create mass fish die-offs and even dead zones.

Usually, when water authorities spot an algal bloom, they make sure that humans stay well clear of the water because of the danger that toxins such as ATX can cause. However, there's still been a number of hospitalizations, and many deaths of dogs and other animals from ingesting the water.

But researchers at the Nantucket Land Council wanted to know if the air surrounding the bloom was also dangerous.

"Although no previous studies have documented the capture of airborne ATX molecules or cyanobacteria cells containing ATX, we hypothesized that ATX could become airborne under certain environmental conditions," the team write in their new paper.

The team investigated Capaum Pond, a freshwater pound in Nantucket, Massachusetts, known for regular summer HABs.

They collected samples from the area between July to October 2019, both in the water itself, and the air around the edge of the pond.

ATX was found in quite high concentrations in the body of water - on one particular day - 11 September 2019 - the team recorded 21 nanograms per milliliter.

On that windy and foggy September day, the team also detected ATX in the air around the pond. They found an average concentration of 0.87 nanograms per filter, which corresponds to a potential airborne exposure of 0.16 nanograms per meter squared.

"People often recreate around these lakes and ponds with algal blooms without any awareness of the potential problems," said Sutherland. "Direct contact or inhalation of these cyanotoxins can present health risks for individuals, and we have reported a potential human health exposure not previously examined."

The team isn't sure yet how the toxin is ending up in the air, and aerosol exposure to ATX isn't well understood, so there's plenty more to investigate here.

The researchers suggest in the paper that perhaps the wind caused small droplets filled with ATX molecules, or even the cyanobacterial cells, to become airborne, and the fog helped the ATX stay in the air for longer.

In the meantime, best to stay away from bodies of water with algal blooms - especially on days with lots of wind or fog, lest you become an unwitting case study into the Very Fast Death Factor.

The research has been published in *Lake and Reservoir Management*.

https://bbc.in/328ZeqN

Breast cancer: New five-minute Phesgo treatment 'great'

A woman with breast cancer has said becoming one of the first in England to be given a new five-minute treatment for the disease "feels amazing".

A newly-approved remedy combines two treatments into a single injection, cutting the time needed to administer it by about two-and-a-half hours. Paula Lamb was prescribed it by her "delighted" consultant at Merseyside's Clatterbridge Cancer Centre (CCC).

The 51-year-old said it was "great" the treatment was now so quick.

CCC said the treatment, known as Phesgo, combines two others - ***pertuzumab*** and ***trastuzumab*** - that are usually given separately as intravenous infusions into a single injection into the thigh.

Ms Lamb, from Newton-le-Willows, was diagnosed with breast cancer in 2014 and had been spending about two hours in hospital every three weeks. After receiving the remedy at a CCC clinic in St Helens, she said it felt "amazing to be one of the first people to receive this treatment through this NHS scheme".

'Keeping patients safe'

She said she had received both medication, along with chemotherapy, since her diagnosis and it was "great that I can now get the same drugs in one injection that only takes a few minutes".

"It did sting a little, but then it was fine," she added. "Now I'm free to go off and do what I want, rather than being sat here for a few

hours."

Consultant medical oncologist Dr Helen Innes said the centre was "always looking at how we can enhance care and make it more convenient for patients".

NHS national clinical director for cancer Peter Johnson said the treatment would be offered to patients with HER2-positive breast cancer across the country. As a result, about 15% of all breast cancer patients will be offered the remedy, either by itself or alongside chemotherapy.

He added that the NHS had "continued to adopt new treatments rapidly throughout the pandemic to improve cancer care for patients" and Phesgo was "the latest in a series of changes which have meant the NHS has been able to deliver vital cancer treatment while keeping patients safe from Covid".

https://bit.ly/2PPaNRu

Why Our Brains Miss Opportunities to Improve Through Subtraction

If, as the saying goes, less is more, why do we humans overdo so much?

By Jennifer McManamay

In a new paper featured on the cover of the journal Nature, University of Virginia researchers explain why people rarely look at a situation, object or idea that needs improving — in all kinds of contexts — and think to remove something as a solution. Instead, we almost always add some element, whether it helps or not.

The team's findings suggest a fundamental reason that people struggle with overwhelming schedules, that institutions bog down in proliferating red tape, and, of particular interest to researchers, that humanity is exhausting the planet's resources.

"It happens in engineering design, which is my main interest," said Leidy Klotz, Copenhaver Associate Professor in the Department of Engineering Systems and Environment and co-director of the Convergent Behavioral Science Initiative. "But it also happens in writing, cooking and everything else — just think about your own work and you will see it. The first thing that comes to our minds is, what can we add to make it better. Our paper shows we do this to our detriment, even when the only right answer is to subtract. Even with financial incentive, we still don't think to take away."

Klotz, whose research explores the overlaps between engineering and behavioral science, teamed with three colleagues from the Batten School of Leadership and Public Policy on the interdisciplinary research that shows just how additive we are by nature. Batten public policy and psychology faculty, assistant professor Gabrielle Adams and associate professor Benjamin Converse, and former Batten postdoctoral researcher Andrew Hales, collaborated with Klotz on a series of observational studies and experiments to study the phenomenon.

When considering two broad possibilities for why people systematically default to addition — either they generate ideas for both possibilities and disproportionately discard subtractive solutions or they overlook subtractive ideas altogether — the researchers focused on the latter.

"Additive ideas come to mind quickly and easily, but subtractive ideas require more cognitive effort," Converse said. "Because people are often moving fast and working with the first ideas that come to mind, they end up accepting additive solutions without considering subtraction at all."

The researchers think there may be a self-reinforcing effect.

"The more often people rely on additive strategies, the more cognitively accessible they become," Adams said. "Over time, the habit of looking for additive ideas may get stronger and stronger, and in the long run, we end up missing out on many opportunities to improve the world by subtraction."

Klotz has a book that takes a wider view of the topic, "Subtract:

The Untapped Science of Less," coming out a week after the Nature paper. Although the timing is coincidence, both the paper and book are products of the interdisciplinary and collaborative research environment at UVA, he said.

"It's an incredibly interesting finding, and I think our research has tremendous implications across contexts, but especially in engineering to improve how we design technology to benefit humanity," Klotz said.

https://bit.ly/3mznJad

New Lyme disease test distinguishes between early and late-stage disease

New test targets genetic sequences in Lyme-causing bacteria and is highly sensitive, detecting just one bacterial cell in a blood sample

For those who live in an area blighted by ticks, the threat of Lyme disease can cast a shadow over the joy of spring and summer. These blood-sucking arachnids can transmit bacteria into the bloodstream of their unsuspecting host, causing the disease. Early treatment is essential, but current tests are not usually sensitive enough to detect the disease in early-stage patients. A recent study in open-access journal *Frontiers in Microbiology* reveals a new test for Lyme disease, which is the first to reliably distinguish between early- and late-stage patients. The test detects a genetic sequence left by a virus that resides in Lyme-causing bacteria, and can detect just one bacterial cell in a small blood sample.

As the most common tick-borne infection, Lyme disease affects nearly 500,000 people in the U.S. every year. Symptoms include fever, fatigue, joint pain, and a distinctive 'bullseye' rash, but if left untreated, the disease can cause paralysis and even death. As such, early diagnosis is important, but difficult.

"Early diagnosis of Lyme disease is absolutely vital in reducing suffering, because early Lyme can be treated, but late Lyme is very difficult to treat," explained Dr Jinyu Shan of the University of Leicester, lead author on the study. "Current tests cannot typically detect the low numbers of bacteria in early-stage patient blood samples. Our goal was to design a highly sensitive test to help doctors to identify Lyme disease as early as possible."

Shan's test is based on polymerase chain reaction, or PCR, which works by amplifying small amounts of specific genetic material so that it can be detected. To date, this technique has not been particularly useful in detecting Lyme-causing bacteria in the blood. Such bacteria often lurk in tissues, and may not be present in the blood in large numbers. Additionally, many of the genetic sequences targeted by PCR have only a single copy within each cell, making it difficult to find and amplify enough for detection.

Shan and his colleagues realized that there is another potential PCR target in Lyme-causing bacteria. These targets are called prophages, and are a genetic sequence that was inserted into the bacteria by a virus. Happily, such genetic material can escape the bacteria and is therefore more likely to be detectable in the blood, and multiple copies are present in individual bacterial cells.

The researchers assessed their new prophage-targeted test by adding small amounts of Lyme-causing bacteria to blood samples. They found that the test was very sensitive, detecting just one bacterial cell in 0.3 mL of blood. This suggests that the test is sensitive enough for use with human samples, as people infected with Lyme-causing bacteria typically have between 1 and 100 bacterial cells per mL of blood.

Based on these promising results, the researchers used their PCR test to analyze blood samples from healthy volunteers and patients with either early-stage or late-stage Lyme disease. Strikingly, the test could successfully distinguish healthy, early-stage and late-stage Lyme disease samples, and is the first technology to successfully achieve this. "The test could also be very useful in

rapidly ruling out someone with suspected Lyme disease," said Shan.

The technique may also be applicable to diagnostic tests for other bacterial infections, if researchers can identify suitable prophage sequences for such bacteria. The technology will need further development before it is suitable for clinical use, but the researchers have already begun the groundwork for this. "We are currently working with a commercial partner, and investigating regulatory issues and the potential for a clinical trial for this technology," said Shan.

https://wb.md/3mBWCLu

Coffee Could Be the Secret Weapon Against NAFLD

"I do recommend at least two to three cups of coffee per day for my patients with NAFLD"

Bruce Jancin

Treatment of obesity through exercise and diet is unquestionably the foundation of care for patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). But drinking at least several cups of coffee a day makes for additional powerful medicine, said Manal F. Abdelmalek, MD, MPH, at the Gastroenterology Updates, IBD, Liver Disease Conference.

"I do recommend at least two to three cups of coffee per day for my patients with NAFLD," said Abdelmalek, professor of medicine and a gastroenterologist at Duke University, Durham, N.C.

Her thinking on this recommendation has been influenced by a meta-analysis of 16 studies including more than 3,000 coffee drinkers and 132,000 nonconsumers; the meta-analysis concluded that coffee drinkers were 39% less likely to develop cirrhosis. There was evidence of a dose-response effect: Consumers of two or more cups daily had a 47% reduction in the risk of cirrhosis, compared with the nondrinkers, while more modest consumption was associated with a 34% reduction. Moreover, the investigators found that coffee consumption was also associated with a 27% reduction in the likelihood of developing advanced hepatic fibrosis, compared with that of non–coffee drinkers.

"What's even more provocative is the evidence that coffee decreases risk of hepatocellular carcinoma," the gastroenterologist said.

She highlighted a U.K. meta-analysis of 18 cohort studies with 2.27 million participants and 2,905 cases, along with 8 case-control studies featuring a collective 1,825 cases and 4,652 controls. The investigators reported that drinking at least two cups of coffee per day was associated with a 35% reduction in the risk of hepatocellular carcinoma independent of a patient's stage of liver disease or the presence or absence of high alcohol consumption, smoking, obesity, type 2 diabetes, or hepatitis B or C infection.

"This is very impressive data and certainly not something you should ignore," according to Abdelmalek.

There is also "fairly strong" data that coffee reduces the risk of developing type 2 diabetes, she continued. The mechanism of these benefits is unclear.

"It's not known if it's caffeine or some other constituent of the bean; a phenol, for example. The story behind tea is not as compelling as for coffee, so it may be something beyond caffeine," according to Abdelmalek.

Session moderator Norah A. Terrault, MD, MPH, noted that drinking at least two cups of coffee per day has also been associated with reduced risk of cirrhosis in patients with hepatitis B or hepatitis C infection. So she too is on board the coffee express.

"I'm also a big proponent of recommending coffee. We take so much away from the patients, it's nice to give them back something, right?" said Terrault, professor of medicine and chief of gastroenterology and liver diseases at the University of Southern California, Los Angeles.

Diet and Exercise

Most of the major gastroenterology professional societies emphasize in their practice guidelines for NAFLD that diet and routine physical activity are mandatory. If sustained, these lifestyle modifications can improve NASH and hepatic fibrosis, as well as reduce the risk of portal hypertension and liver cancer. Abdelmalek counsels her patients to aim for at least 150 minutes per week of moderate or vigorous aerobic and/or resistance exercise. She doesn't care about the exercise intensity or type, noting that what she considers to be "a beautifully done intervention trial" in 220 patients over the course of 12 months concluded that both moderate and vigorous exercise achieved a significant reduction in intrahepatic triglyceride content.

"Tailor exercise to what patients can do, what they enjoy, and what they can sustain," she advised.

She identifies and addresses all modifiable risk factors for NAFLD, including hypertension, diabetes, abdominal obesity, smoking, excessive alcohol intake, obstructive sleep apnea, and an unhealthy diet high in fat, red meat, and fructose.

"The primary message I tell my patients interested in dieting is: I want you to find the right approach for you. There is no right or wrong answer. For some of my patients, it's intermittent fasting and having their first meal at 2 or 3 o'clock in the afternoon. For others it's a Weight Watchers approach, or a Mediterranean diet, or it's high protein. The bottom line of my approach is a gravitation away from excess carbohydrates and fats, and beyond that if I can achieve weight loss through caloric restriction or intermittent fasting, I try to tailor that to my patients' preferences. I do send them to nutritionists," the gastroenterologist said.

A 7%-10% weight loss has been shown to result in resolution of NASH in 64%-90% of patients. However, only about 10% of patients who achieve clinically meaningful weight loss short term are able to maintain it at 1 year, so ongoing follow-up is essential.

At present there is no FDA-approved therapy for NAFLD/NASH. Beyond diet and exercise – and coffee – there is the option of antiobesity weight-loss drug therapy, which is about as effective as successful lifestyle modification, and bariatric surgery, which is dramatically effective. French surgeons recently reported in a prospective single-center study of 180 severely obese patients with NASH who underwent bariatric surgery that, at 5 years' follow-up, 84% of them had resolution of NASH with no worsening of liver fibrosis. Indeed, 63% of patients with mild fibrosis at baseline experienced complete resolution of their fibrosis at follow-up, as did 46% of those with more severe baseline bridging fibrosis.

Abdelmalek reported having no financial conflicts of interest regarding her presentation.

https://bit.ly/3a1fLS9

Manual workers face twice the risk of developing ALS

Scientists discover that the majority of ALS patients had a blue-collar job

ALS is a progressive neurological disease that attacks the nerves that interact with the body's muscles. The disease typically leads to complete paralysis of the body, robbing patients of their ability to walk, speak, eat and breathe.

Researchers studied ALS patients and healthy elderly volunteers living in Malta who took part in an ongoing study aiming at identifying genetic and environmental risk factors. Malta is a sovereign microstate in the middle of the Mediterranean Sea, and is home to a geographically and culturally isolated population. Recently, Maltese ALS patients were found to have a unique genetic makeup compared to their European counterparts.

In this study, based on demographic data collected over a four-year period, the researchers found that manual workers were twice as likely to develop ALS. Indeed, close to two thirds of ALS patients

reported a blue-collar job as their main occupation during their entire career.

"We have long known that Italian football players, American National Football League players and military serviceman have an increased risk of ALS compared to the general population. A common thread running through these professions is sustained or strenuous physical exertion. Our study supports this notion," said the study's lead researcher Dr Ruben J. Cauchi, PhD, a senior lecturer at the University of Malta's School of Medicine and lead investigator at the University of Malta's Centre for Molecular Medicine and Biobanking.

Despite the fact that Malta does not have professional football players nor an elite military service, the study found that sweat-inducing jobs including those in construction and carpentry were associated with a higher ALS risk. Patients in these occupations were more prone to develop bulbar-onset ALS, a form of the disease in which speech or swallowing problems appear before muscle weakness in the limbs. Patients with bulbar-onset ALS fare worse than those with limb-onset.

The setting up of a national ALS Registry and Biobank at the University of Malta in 2017, with the aim of identifying and tracking ALS patients and healthy volunteers, was key for this discovery. Right now, the research team is studying the interplay between genetics and environmental exposures in causing ALS in patients.

Study co-authors are Maia Farrugia Wismayer, Rebecca Borg, Dr Andrew Farrugia Wismayer, Dr Karl Bonavia and Prof Neville Vassallo from the University of Malta; Dr Malcolm Vella from Mater Dei Hospital; and, Dr Adrian Pace from Karin Grech and Gozo General Hospitals.

The study was funded by the University of Malta Research Excellence Fund, an Endeavour Scholarship (part-financed by the European Social Fund), a Malta Council for Science & Technology Internationalisation Partnership Award, ALS Malta Foundation and the University of Malta's Research Trust (RIDT).

https://bit.ly/3uDMO6D

2 recent studies sequence DNA from the earliest Homo sapiens in Eurasia

One study includes DNA from the son of Neanderthal and Homo sapiens parents.

Kiona N. Smith

Hajdinjak et al. 2020

DNA from the earliest *Homo sapiens* in Europe adds more detail to the story of our species' expansion into Eurasia—and our complicated 5,000-year relationship with Neanderthals.

The earliest traces of our species in Eurasia are a lower molar and a few fragments of bone from Bacho Kiro Cave in Bulgaria, dating to between 46,000 and 42,000 years old. A recent paper describes DNA from those fossils, as well as a 42,000- to 37,000-year-old jawbone from the Oase site in Romania. The results suggest that the early waves of *Homo sapiens* in Eurasia included several genetically distinct groups, only some of which eventually passed their genes on to modern people. Most of those early Eurasians mingled with Neanderthals fairly often.

Paleolithic and ready to mingle

Neanderthals had lived in Europe and Asia for at least 350,000 years (and had a complicated population history of their own) when the first groups of *Homo sapiens* expanded northward from eastern Africa and the Levant. Today, many populations of modern humans still carry tiny fragments of Neanderthal DNA in our genomes as souvenirs from the mingling of two hominin species 45,000 years ago. But we still don't know much about how often Neanderthals and *Homo sapiens* got together during the few millennia when they shared a continent.

When Max Planck Institute for Evolutionary Anthropology geneticist Mateja Hajdinjak and her colleagues sequenced DNA from the *Homo sapiens* bones at Bacho Kiro Cave in Bulgaria, one lower molar and a small scrap of bone were all that remained of a man who died at the site around 45,900 years ago. But that's enough to get us genetic data these days. His genome contained fragments of the Neanderthal versions of some genes, which had been split up and rearranged in a way that suggested they'd been passed down through about six generations. In other words, one of his great-great-great-great grandparents was a Neanderthal.

Two other pieces of bone at Bacho Kiro Cave were the sole remains of two men who died around 45,000 to 42,000 years ago, and both of them had Neanderthal ancestors seven generations back. Meanwhile, at the Oase site in Romania, DNA from a man who died between 42,000 and 37,000 years ago revealed that one of his direct relatives—a parent or grandparent—was a Neanderthal.

That's a rare glimpse of a specific, very human story: direct evidence that a Neanderthal and a *Homo sapiens* had sex and produced a child. A tooth from Denisova Cave in the Altai Mountains of Siberia tells a similar story about a Neanderthal, a Denisovan, and their daughter 90,000 years ago. Those moments are rare in a genetic and archaeological record, which usually only reveals big, sweeping population trends. While we don't have direct *evidence* of individual relationships—whatever form they took, and whatever they meant to the people involved—the relationships themselves probably were anything but rare.

"It is striking that all four of the European individuals who overlapped in time with late Neanderthals and from whom genome-wide data have been retrieved had close Neanderthal relatives in their family histories," wrote Hajdinjak and her colleagues in their paper. "This suggests that mixing between Neanderthals and the first modern humans that arrived into Europe was perhaps more common than is often assumed."

Neanderthal deserts

If Neanderthals and *Homo sapiens* were really having sex—and offspring—that often, it may sound like modern people with European and Asian ancestry should be carrying around a lot more Neanderthal DNA. But on average, it's only about two percent. But Hajdinjak's study suggests that most Neanderthal genes got weeded out by the process of natural selection very quickly. Within just a few generations, the three men from Bacho Kiro Cave only had between 3.0 and 3.8 percent Neanderthal DNA.

In modern people, Neanderthal DNA is scattered throughout the genome, but Neanderthal versions of genes are more common in some parts of the genome than others. And in some areas, called "Neanderthal deserts," there are no Neanderthal genes. When Hajdinjak and her colleagues examined the DNA from the three Bacho Kiro men and the one from Oase, they found that although a few Neanderthal alleles still lingered in those sections of the genome, the "Neanderthal deserts" were already starting to form. In other words, the *Homo sapiens* versions of certain genes offered such an evolutionary advantage that they had already out-competed the Neanderthal versions within just a few generations.

In fact, a younger bone fragment from Bacho Kiro dating to around 35,000 years ago came from a person who had just 1.9 percent Neanderthal DNA, similar to the levels seen in most modern non-African people. However, Hajdinjak and her colleagues acknowledged that "additional individuals with recent Neanderthal ancestry will be needed to fully resolve this question."

A complicated relationship history

Before this pair of recent studies, we had DNA from just three individuals older than 45,000 years. Now we have DNA from seven, and that drastically improves our view. Still, as always in archaeology, the more data we get, the more questions we can ask.

And there are some questions we may never be able to answer. When *Homo sapiens* and Neanderthals had offspring, were those pairings the result of illicit relationships, intergroup marriages, or something more violent? It's hard to imagine what kind of archaeological evidence could provide those details, and the genetic evidence records only the bare biological facts. But because people have always been people, the answer is likely "all of the above, at different times and places."

Another recent study supports the suggestion that the story wasn't the same everywhere. DNA from the bones of a 45,000-year-old member of our species, from the Ust'Ishim site in Siberia, suggested that this person's most recent Neanderthal ancestor was 80 to 95 generations back in the family tree.

And when anthropologist Kay Prüfer, also of the Max Planck Institute, sequenced the DNA of a woman who died at Zlatý kůň in the Czech Republic, her mitochondrial DNA (DNA outside the cell nucleus that is passed directly from mother to child) suggested that she was about 43,000 years old. And based on the length of the segments of Neanderthal DNA in her nuclear genome, her last Neanderthal ancestor lived about 64 to 80 generations before she did. This could mean that interactions varied as different groups of humans and Neanderthals moved around and potentially interacted in different ways.

Who's related to whom?

The DNA from both recent studies sheds some light on how those different groups moved around and how some of them are related to groups of modern people in central and eastern Asia. Both Hajdinjak and her colleagues and Prüfer and her colleagues compared DNA from their specimens to genomes from other ancient and modern people, looking to see how many alleles they shared in common and using computer modeling to see how they might be related.

In Prüfer and her colleagues' study, the woman from Zlatý kůň belonged to a group of people who apparently didn't contribute much to the ancestry of later Eurasian people. And DNA from Oase 1, the son of a Neanderthal and a *Homo sapiens*, suggested that his population also hadn't "contributed detectably to later populations." In other words, he was part of a lineage that had died out.

On the other hand, the earliest known *Homo sapiens* remains in Europe, at Bacho Kiro Cave, belonged to a group that shared noticeably more alleles with modern people in eastern and central Asia than with the people now living in Bulgaria (or anywhere else in Europe or western Asia). The Bacho Kiro population also seems to have been related to another group, which included the ancestors of a 40,000-year-old person unearthed at Tianyuan, in China.

That "provides evidence that there was at least some continuity between the earliest modern humans in Europe and later people in Eurasia," as Hajdinjak and her colleagues put it, but it's also clear that several of the first *Homo sapiens* groups to reach Europe eventually faded away without leaving much of a genetic mark.

The tooth and bone fragments at Bacho Kiro Cave were found buried in a layer of sediment that also contained the remains of a culture known to archaeologists as the Initial Upper Paleolithic. Based on a common style of making stone tools, Initial Upper Paleolithic, or IUP, artifacts have turned up at sites from central and eastern Europe all the way to Mongolia, and it's possible that some may be waiting to be discovered even further east.

Archaeologists are still debating whether the IUP spans such a wide area because one group of people managed to spread that far or because ideas spread between groups. But both archaeological and genetic evidence now suggest connections between the first *Homo sapiens* to gain a foothold in Europe and those who lived in Asia just a few thousand years later.

Nature, 2021 DOI: 10.1038/s41586-021-03335-3 (About DOIs).

https://bit.ly/39ZEq9w

An amyloid link between Parkinson's disease and melanoma

For 50 years, doctors have recognized that Parkinson's disease patients are more likely to develop melanoma

Washington - On the surface, Parkinson's disease -- a neurodegenerative disorder -- and melanoma -- a type of skin cancer -- do not appear to have much in common. However, for nearly 50 years, doctors have recognized that Parkinson's disease patients are more likely to develop melanoma than the general population. Now, scientists report a molecular link between the two diseases in the form of protein aggregates known as amyloids.

The researchers will present their results today at the spring meeting of the American Chemical Society (ACS). ACS Spring 2021 is being held online April 5-30. Live sessions will be hosted April 5-16, and on-demand and networking content will continue through April 30. The meeting features nearly 9,000 presentations on a wide range of science topics.

"Several studies have shown that melanoma occurs two to six times more frequently in the Parkinson's population than the healthy population," says Dexter Dean, Ph.D., a postdoctoral fellow at the National Heart, Lung, and Blood Institute (NHLBI), who is presenting the work at the meeting. "What's more, the protein involved in Parkinson's disease, α-synuclein, is elevated in melanoma cells."

In Parkinson's disease, α-synuclein forms amyloid deposits that are thought to kill dopamine-producing neurons in the brain, causing symptoms such as tremor, slow movements and dementia. While intense research has focused on the effects of α-synuclein in the brain, much less is known about its presence or activities in other tissues. However, scientists have evidence that the amyloid-forming protein is expressed more in melanoma cells than in healthy skin. Furthermore, higher levels of α-synuclein in melanocytes (the skin cells that give rise to melanoma) correlate with reduced pigment, or melanin, production. Melanin protects skin from damage by the sun's ultraviolet rays.

Jennifer Lee, Ph.D., Dean's postdoctoral advisor at NHLBI, part of the National Institutes of Health, had previously studied another amyloid-forming protein called premelanosomal protein (Pmel). "Most people know that amyloids are involved in diseases, such as Parkinson's and Alzheimer's, but it's less well-known that some amyloids, like Pmel, actually serve a useful function," Lee says. In healthy melanocytes, Pmel forms amyloid fibrils that act as scaffolds to store melanin in melanosomes (the organelle where the pigment is produced, stored and transported). "Because both α-synuclein and Pmel are expressed in melanoma cells, we wondered if these two amyloid proteins could interact, and whether this interaction could be relevant to the correlation between Parkinson's disease and melanoma," Lee says.

To investigate whether α-synuclein and Pmel could interact, the researchers used microscopy and western blotting to show that the two proteins both resided in the melanosomes of human melanoma cells. When Dean added preformed α-synuclein amyloid to a test tube containing the amyloid-forming region of Pmel (known as the repeat, or RPT, domain), the α-synuclein fibrils stimulated Pmel to aggregate and form a twisted fibril structure that the protein does not normally adopt on its own.

Because α-synuclein in melanoma cells may also be found in its soluble, or non-amyloid, form, the researchers performed other in vitro experiments in which they added soluble α-synuclein to the Pmel RPT domain. In this case, α-synuclein inhibited Pmel's ability to self-aggregate and form amyloid in a concentration-dependent manner. They traced this activity to the first 60 amino acids of α-synuclein.

"We now have preliminary data that suggest an amyloid from one protein can 'seed' or template amyloid from another, and in the soluble form, α-synuclein prevents Pmel aggregation." Lee says. "Therefore, we think that both forms of α-synuclein could diminish melanin biosynthesis -- the amyloid form by causing Pmel to form an unusual twisted structure, and the soluble form by stopping Pmel from aggregating like it should." Loss of skin pigmentation could contribute to the increased melanoma risk in Parkinson's disease patients, the researchers say.

"I think we're just at the tip of the iceberg of appreciating what α-synuclein might be doing in melanoma," Dean says. "In future experiments, I'm really interested in understanding more about what α-synuclein is doing to promote melanoma proliferation, in addition to this interaction with Pmel."

The researchers acknowledge funding from the National Institutes of Health Intramural Research Program.

https://bit.ly/3s9o30q

IU School of Medicine researchers develop blood test for depression, bipolar disorder

Promising blood test aimed at a precision medicine approach to treatment

Indianapolis--Worldwide, 1 in 4 people will suffer from a depressive episode in their lifetime. While current diagnosis and treatment approaches are largely trial and error, a breakthrough study by Indiana University School of Medicine researchers sheds new light on the biological basis of mood disorders, and offers a promising blood test aimed at a precision medicine approach to treatment.

Led by Alexander B. Niculescu, MD, PhD, Professor of Psychiatry at IU School of Medicine, the study was published today in the high impact journal *Molecular Psychiatry* . The work builds on previous research conducted by Niculescu and his colleagues into blood biomarkers that track suicidality as well as pain, post-traumatic stress disorder and Alzheimer's disease.

"We have pioneered the area of precision medicine in psychiatry over the last two decades, particularly over the last 10 years. This study represents a current state-of-the-art outcome of our efforts," said Niculescu. "This is part of our effort to bring psychiatry from the 19th century into the 21st century. To help it become like other contemporary fields such as oncology. Ultimately, the mission is to save and improve lives."

The team's work describes the development of a blood test, composed of RNA biomarkers, that can distinguish how severe a patient's depression is, the risk of them developing severe depression in the future, and the risk of future bipolar disorder (manic-depressive illness). The test also informs tailored medication choices for patients.

This comprehensive study took place over four years, with over 300 participants recruited primarily from the patient population at the Richard L. Roudebush VA Medical Center in Indianapolis. The team used a careful four-step approach of discovery, prioritization, validation and testing.

First, the participants were followed over time, with researchers observing them in both high and low mood states--each time recording what changed in terms of the biological markers (biomarkers) in their blood between the two states.

Next, Niculescu's team utilized large databases developed from all previous studies in the field, to cross-validate and prioritize their findings. From here, researchers validated the top 26 candidate biomarkers in independent cohorts of clinically severe people with depression or mania. Last, the biomarkers were tested in additional independent cohorts to determine how strong they were at predicting who is ill, and who will become ill in the future.

From this approach, researchers were then able to demonstrate how to match patients with medications--even finding a new potential

medication to treat depression.

"Through this work, we wanted to develop blood tests for depression and for bipolar disorder, to distinguish between the two, and to match people to the right treatments," said Niculescu. "Blood biomarkers are emerging as important tools in disorders where subjective self-report by an individual, or a clinical impression of a health care professional, are not always reliable. These blood tests can open the door to precise, personalized matching with medications, and objective monitoring of response to treatment."

In addition to the diagnostic and therapeutic advances discovered in their latest study, Niculescu's team found that mood disorders are underlined by circadian clock genes--the genes that regulate seasonal, day-night and sleep-wake cycles. "That explains why some patients get worse with seasonal changes, and the sleep alterations that occur in mood disorders," said Niculescu.

According to Niculescu, the work done by his team has opened the door for their findings to be translated into clinical practice, as well as help with new drug development. Focusing on collaboration with pharmaceutical companies and other doctors in a push to start applying some of their tools and discoveries in real-world scenarios, Niculescu said he believes the work being done by his team is vital in improving the quality of life for countless patients.

"Blood biomarkers offer real-world clinical practice advantages. The brain cannot be easily biopsied in live individuals, so we've worked hard over the years to identify blood biomarkers for neuropsychiatric disorders," said Niculescu. "Given the fact that 1 in 4 people will have a clinical mood disorder episode in their lifetime, the need for and importance of efforts such as ours cannot be overstated."

This research was supported by the National Institutes of Health under Award Number 1DP20D007363 and R01mh117431 and a VA Merit Award 2I01CX000139. The content is solely the responsibility of Indiana University School of Medicine and does not necessarily represent the official views of the National Institutes of Health or the VA.

https://bit.ly/2QarIOj

Our ancestors left Africa both with and without modern brains

The genus Homo originated with a brain that still had ape-like features.

John Timmer

One of the remarkably intact Dmanisi skulls at the time of its discovery. **Guy Bar-Oz**

We have an extensive collection of fossils from the lineages that produced us humans. A large number of *Australopithecus* and early *Homo* skeletons track the transition to bipedal walking and the appearance of features that mark our present anatomy.

But it's much harder to figure out what led to the mental capabilities—complex language, the near-constant use of tools, and so on—that help set humans apart.

Much harder—but not entirely impossible. Remains of skulls can help us figure out the likely cranial capacity of extinct species. And the brain actually leaves its mark on the interior of skulls, allowing some aspects of the brain's anatomy to be pieced together. Now, an international team has done this sort of analysis on a set of *Homo erectus* from a critical point in our species' past. They have found that some earlier brain species persisted well into the history of our genus *Homo*, but that didn't stop those ancestors from migrating out of Africa.

Reconstructing brains

How do you figure out what a brain once looked like? You need a reasonably intact skull, which is relatively rare, given the fragility of the bones. Once the skull is reconstructed, it's possible to make

what's called an "endocast" of the interior of the skull, capturing the details of its features, including where it conformed to the underlying brain. In some cases, endocasts form naturally during the deposition of material around a fossil. They could also be made after discovery and now can be done virtually thanks to our ability to scan and reconstruct 3D volumes.

Obviously, there's a lot going on in the brain that isn't near its interface with the skull, and endocasts aren't going to be able to tell us about those changes. But if you look at endocasts of the brains of humans and our closest simian relatives, there are some clear diagnostic differences. One of the more significant ones is in an area called Broca's cap, which is associated with language abilities.

Lots of endocasts have been made over the years, and they show a pretty clear pattern. Early relatives like Australopiths retained the ape-like arrangement of the forebrain. More recent ancestors, like *Homo erectus*, had an arrangement that looked much more like what we have today. This led to the assumption that the modern arrangement evolved at the same time as our genus *Homo* appeared.

The new work extends our collection of endocasts to some critical skeletons: the Dmanisi hominins, which date to about 1.8 million years ago and were discovered in the Republic of Georgia. These are generally classified as members of *Homo erectus*, but they retain enough features of earlier species that this label remains controversial. The Dmanisi skeletons are interpreted as indications that *Homo erectus* expanded out of Africa very early, perhaps while its features were still in flux.

Redrawing the tree

The results are pretty clear: all five Dmanisi skulls show the earlier pattern of brain structure. That has a number of significant implications. It clearly means that the present-day brain structure did not originate with the genus *Homo* but only evolved after we'd been around for nearly a million years. In addition, the Dmanisi skeletons were found with a variety of stone tools, so we can infer that the modern brain structure wasn't a prerequisite for their development.

Finally, it also shows that our ancestors didn't need the present-day brain structure in order to spread far beyond their point of origin in Africa. In fact, it suggests that the relationship between our brains and migrations is extremely complicated because previous data, when incorporated into this analysis, indicates that the modern arrangement of the brain was in place by 1.5 million years ago—and appeared almost contemporaneously from Africa to Southeast Asia.

This suggests that our ancestors left Africa in multiple waves, some not separated by very much time, at least in evolutionary terms. And before this critical time period, the size of the brain (as opposed to its arrangement) was increasing gradually and steadily. (Albeit with some severe outliers like the Indonesian hobbits and *Homo naledi*, which were small-brained but very recent.)

Complicating matters further, the researchers note that there were much larger changes going on in facial morphology during this time, probably driven largely by diet. But there's no clear correlation between what was going on with the face and jaw and what was happening with the brain structure.

So while the new study clarifies a lot of questions and overturns a major assumption, there are limits to how much it can tell us. Although the brain region looked at here is associated with language, there's no way to tell if its appearance correlated with the use of language. Tool technologies changed at around the same time as the transition between brain structures, but it's impossible to tell if the two were related. And we can only guess at the selective pressures that drove the changes in the brain. But one thing is clear: our ancestors' ability and desire to roam the world was present long before our current brain structure was in place.

Science, 2021. DOI: 10.1126/science.aaz0032 (About DOIs).

https://bit.ly/3d8iCLc

Brain disease transmitted by tick bites may be treatable

A new study describes antibodies capable of neutralizing the virus transmitted by tick bites

Tick-borne encephalitis is a disease just as nasty as it sounds. Once bitten by an infected tick, some people develop flu-like symptoms that resolve quietly but leave behind rampant neurological disease--brain swelling, memory loss, and cognitive decline. Cases are on the rise in Central Europe and Russia with some 10,000 incidents reported each year. Vaccines can provide protection, but only for a limited time. There is no cure.

The castor bean tick, which is prevalent throughout Europe, can cause both Lyme disease and tick-borne encephalitis. **Laboratory of Molecular Immunology at The Rockefeller University**

Now a new study describes antibodies capable of neutralizing the virus transmitted by tick bites. These so-called broadly neutralizing antibodies have shown promise in preventing TBE in mice and could inform the development of better vaccines for humans. Further, preliminary results suggest that the antibodies may not only prevent tick-borne encephalitis but even treat the condition, as well as the related Powassan virus emerging in the United States.

Lead author Marianna Agudelo and colleagues in the laboratory of Rockefeller's Michel C. Nussenzweig examined nearly 800 antibodies obtained from individuals who had recovered from TBE or had been vaccinated to prevent infection. The most potent antibodies, designated VH3-48, turned out to be best suited to fend off future infections. They found that VH3-48 neutralized lab-grown varieties of the TBE virus, as well other tick-borne illnesses including the Langat, Louping ill, Omsk hemorrhagic fever, Kyasanur forest disease, and Powassan viruses.

The researchers also showed that these powerful antibodies are not common; in fact, most of the antibodies produced by humans exposed to TBE virus are of inferior quality, with the coveted VH3-48 antibodies making only occasional appearances. Moreover, vaccinated patients in the study did not manage to develop any VH3-48 antibodies at all. "You'd expect the most prevalent antibodies to be the absolute best, but that is not what we found in TBE," Agudelo says. "This may explain how the virus tricks the immune system, misdirecting it into producing inferior antibodies."

The discovery of VH3-48 provides hope for a more effective TBE vaccine. Current vaccines require three doses spaced over two years and only provide about five years of protection before a booster shot is required. Next-generation vaccines built around coaxing the body into producing the rare VH3-48 antibody could be more potent, require fewer booster shots, and also prove protective against a number of tick-borne viruses.

"A vaccine like this would not just be more elegant, but also better focused," says Michel C. Nussenzweig, the Zanvil A. Cohn and Ralph M. Steinman Professor and head of the Laboratory of Molecular Immunology at Rockefeller. "Now that we have the structures of these antibodies, we know what to target in order to design more effective vaccines."

Broadly neutralizing antibodies may also provide the first specific treatment for TBE. Nussenzweig, Agudelo, and colleagues found that mice infected with TBE recover after receiving antibody therapy, although it remains to be seen if this finding will translate to humans.

"The next step is a clinical trial with the antibodies," Nussenzweig says, "perhaps in Europe where there are many cases, to see whether we can ameliorate the symptoms of those suffering from encephalitis."

https://bit.ly/3s4af7l

Living fossils: Microbe discovered in evolutionary stasis for millions of years

New research led by Bigelow Laboratory for Ocean Sciences has revealed that a group of microbes, Candidatus Desulforudis audaxviator, have been at an evolutionary standstill for millions of years.

It's like something out of science fiction. Research led by Bigelow Laboratory for Ocean Sciences has revealed that a group of microbes, which feed off chemical reactions triggered by radioactivity, have been at an evolutionary standstill for millions of years.

The discovery could have significant implications for biotechnology applications and scientific understanding of microbial evolution.

"This discovery shows that we must be careful when making assumptions about the speed of evolution and how we interpret the tree of life," said Eric Becraft, the lead author on the paper. "It is possible that some organisms go into an evolutionary full-sprint, while others slow to a crawl, challenging the establishment of reliable molecular timelines."

Becraft, now an assistant professor of biology at the University of Northern Alabama, completed the research as part of his postdoctoral work at Bigelow Laboratory and recently published it in the Nature publishing group's *ISME Journal*.

The microbe, Candidatus Desulforudis audaxviator, was first discovered in 2008 by a team of scientists, led by Tullis Onstott, a co-author on the new study. Found in a South African gold mine almost two miles beneath the Earth's surface, the microbes acquire the energy they need from chemical reactions caused by the natural radioactive decay in minerals. They inhabit water-filled cavities inside rocks in a completely independent ecosystem, free from reliance on sunlight or any other organisms.

Because of their unique biology and isolation, the authors of the new study wanted to understand how the microbes evolved. They searched other environmental samples from deep underground and discovered Candidatus Desulforudis audaxviator in Siberia and California, as well as in several additional mines in South Africa. Since each environment was chemically different, these discoveries gave the researchers a unique opportunity to look for differences that have emerged between the populations over their millions of years of evolution.

"We wanted to use that information to understand how they evolved and what kind of environmental conditions lead to what kind of genetic adaptations," said Bigelow Laboratory Senior Research Scientist Ramunas Stepanauskas, the corresponding author on the paper and Becraft's postdoctoral advisor.

"We thought of the microbes as though they were inhabitants of isolated islands, like the finches that Darwin studied in the Galapagos."

Using advanced tools that allow scientists to read the genetic blueprints of individual cells, the researchers examined the genomes of 126 microbes obtained from three continents. Surprisingly, they all turned out to be almost identical.

"It was shocking," Stepanauskas said. "They had the same makeup, and so we started scratching our heads."

Scientists found no evidence that the microbes can travel long distances, survive on the surface, or live long in the presence of oxygen. So, once researchers determined that there was no possibility the samples were cross-contaminated during research, plausible explanations dwindled.

"The best explanation we have at the moment is that these microbes did not change much since their physical locations separated during the breakup of supercontinent Pangaea, about 175 million years

ago," Stepanauskas said. "They appear to be living fossils from those days. That sounds quite crazy and goes against the contemporary understanding of microbial evolution."

What this means for the pace of microbial evolution, which often happens at a much more accelerated rate, is surprising. Many well-studied bacteria, such as E. coli, have been found to evolve in only a few years in response to environmental changes, such as exposure to antibiotics.

Stepanauskas and his colleagues hypothesize the standstill evolution they discovered is due to the microbe's powerful protections against mutation, which have essentially locked their genetic code. If the researchers are correct, this would be a rare feature with potentially valuable benefits.

Microbial enzymes that create copies of DNA molecules, called DNA polymerases, are widely used in biotechnology. Enzymes with high fidelity, or the ability to recreate themselves with little differences between the copy and the original, are especially valuable.

"There's a high demand for DNA polymerases that don't make many mistakes," Stepanauskas said. "Such enzymes may be useful for DNA sequencing, diagnostic tests, and gene therapy."

Beyond potential applications, the results of this study could have far-reaching implications and change the way scientists think about microbial genetics and the pace of their evolution.

"These findings are a powerful reminder that the various microbial branches we observe on the tree of life may differ vastly in the time since their last common ancestor," Becraft said.

"Understanding this is critical to understanding the history of life on Earth."

More information: *Eric D. Becraft et al, Evolutionary stasis of a deep subsurface microbial lineage, The ISME Journal (2021).* *DOI: 10.1038/s41396-021-00965-3*

https://wb.md/3dPtP29

Common COVID Vaccine Administration Errors to Watch For

We must take care to minimize errors in vaccine administration.

Sarah F. Schillie, MD, MPH, MBA; Jennifer Buzzell, MS; Christina A. Nelson, MD, MPH; Sarah Kidd, MD, MPH; Katherine R. Shealy, MPH; Sarah Reagan-Steiner, MD, MPH

In December 2020, the US Food and Drug Administration approved Emergency Use Authorizations (EUAs) for the Pfizer-BioNTech and Moderna COVID-19 vaccines. As of March 20, 2021, more than 120 million COVID-19 vaccine doses have been administered to people in the United States. As we work toward expanding COVID-19 vaccination further, however, we must take care to minimize errors in vaccine administration.

Proper vaccine administration is necessary to ensure vaccine effectiveness, achieve optimal vaccine-induced protection, avoid safety implications, and assure confidence in the COVID-19 vaccination program. Since the launch of vaccination efforts on December 14, 2020, the Centers for Disease Control and Prevention (CDC) has received more than 300 inquiries through the CDC inquiry response services (eg, CDC-INFO, NIP-INFO) seeking guidance for managing an mRNA COVID-19 vaccine administration error that had occurred.

The most common error type described in inquiries (Table), representing more than one third of inquiries, was administration of a lower-than-authorized dose (eg, the needle disconnecting from the syringe, resulting in vaccine spillage). Other frequent error types queried included administration to someone younger than the authorized age (18.5% of inquiries) and administration by a route other than intramuscular (IM) (12.3% of inquiries).

These inquiries probably underestimate the actual number of COVID-19 vaccine administration errors and might not capture all

inquiries CDC received.

Table. COVID-19 Vaccine Administration Error Inquiries Received by CDC, December 14, 2020, to February 28, 2021

Error type	Example	Number (%) of topics across inquires received (N = 324)[a]
Administration by the incorrect route	Subcutaneous administration	40 (12.3%)
Administration at an incorrect anatomic site	Administration into shoulder bursa; administration in the gluteal muscle of the buttock	33 (10.2%)
Higher-than-authorized dose volume administered	Administration of undiluted vaccine	11 (3.4%)
Lower-than-authorized dose volume administered	Dose leaked out of syringe; recipient pulled away and dose leaked out	114 (35.2%)
Administration to someone younger than the authorized age	Administration to person aged < 16 years (Pfizer-BioNTech) or < 18 years (Moderna)	60 (18.5%)
Administration of a mixed-product series	First and second doses from different manufacturer	16 (4.9%)
Administration of a second dose earlier than the 4-day grace period	Second dose administered < 17 days (Pfizer-BioNTech) or < 24 days (Moderna) after the first dose	21 (6.5%)
Dose administered after improper storage and handling	Temperature excursion; more than allowed time after first vial puncture; use after beyond use date	15 (4.6%)
Other	Incorrect diluent; incorrect needle length; expired syringe	14 (4.3%)

[a]Some inquiries represent errors affecting more than one vaccine recipient (eg, at a mass vaccination clinic).

The interim clinical considerations for the use of currently authorized COVID-19 vaccines contain guidance for managing vaccine administration errors. For most errors, CDC does not recommend repeating the dose. For dosage errors in which less than half the dose was administered, as well as errors in which only diluent was administered, CDC recommends repeating the dose as soon as possible in the opposite arm. CDC refers inquiries about errors related to improper storage and handling or use of an incorrect diluent to the vaccine manufacturer for guidance.

Errors Reducing Vaccine Effectiveness

Some vaccine administration errors might reduce vaccine effectiveness. Although data for mRNA COVID-19 vaccines are lacking, IM vaccine administration in general (compared with subcutaneous administration) optimizes immunogenicity and minimizes local adverse reactions. Subcutaneous fat has poor vascularity, leading to slow mobilization and antigen processing for some other vaccines administered subcutaneously.

When some vaccines (ie, hepatitis B, human papillomavirus, or influenza vaccines) are inadvertently administered subcutaneously, readministration by the IM route is recommended. However, it is not necessary to readminister vaccine doses intended for subcutaneous administration (eg, MMR or varicella vaccines) that were inadvertently administered by the IM route because immune response is unlikely to be affected.

Errors Affecting Safety

The safety implications of many COVID-19 vaccine administration errors remain unknown (eg, administration to someone younger than the authorized age or administration of a second dose earlier than the 4-day grace period). Shoulder injury related to vaccine administration (SIRVA) is a recognized consequence of unintentional injection of a vaccine into the tissues and structures lying underneath the deltoid muscle of the shoulder. It is an injury to the musculoskeletal structures of the shoulder, including

ligaments, bursa, and tendons. SIRVA is thought to occur from unintended injection of vaccine or trauma from the needle into or around the underlying bursa of the shoulder.

Signs and symptoms of SIRVA include shoulder pain and decreased range of motion, hypothesized to be caused by an inflammatory reaction in the shoulder joint. SIRVA is preventable with correct recognition of anatomical landmarks and proper IM vaccine administration techniques.

As outlined in the EUA Fact Sheet for Healthcare Providers, vaccination providers are required to report vaccine administration errors — whether they are associated with an adverse event or not — to the Vaccine Adverse Event Reporting System. Vaccination providers should assess how the error occurred and take steps to prevent future errors.

Millions more doses of COVID-19 vaccines will be administered over the next few months. Although this report covers the time period when mRNA COVID-19 vaccines were administered, errors might occur with administration of other COVID-19 vaccine types, such as the newly authorized Janssen (Johnson & Johnson) viral vector vaccine.

Errors related to COVID-19 vaccine administration might result in reduced vaccine effectiveness and safety implications. A limited vaccine supply and strained vaccination provider workforce might preclude readministration of incorrectly administered doses. To prevent COVID-19 vaccine administration errors, providers should be aware of the EUA Fact Sheet for Healthcare Providers, Advisory Committee on Immunization Practices (ACIP) recommendations, and CDC's interim clinical considerations for COVID-19 vaccination (see the Resources section). Given the importance of vaccinating as many Americans as quickly and safely as possible, it is critical to prevent waste and make every dose count.

Resources

COVID-19 ACIP Vaccine Recommendations
Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States
Vaccine Information for Healthcare Professionals
ACIP General Best Practice Guidelines for Immunization
List of Adverse Events Providers Are Required to Report to VAERS
Pfizer-BioNTech EUA Fact Sheet for Vaccination Providers
Moderna EUA Fact Sheet for Vaccination Providers
Janssen COVID-19 Vaccine (Johnson & Johnson) EUA Fact Sheet for Vaccination Providers

https://bit.ly/2Qb7kNd

Chronic Pain Could Have a Unique Genetic Basis in Women

A sweeping meta-analysis of data from the United Kingdom Biobank has found a different genetic basis for chronic pain in women compared to men.

Carly Cassella

The results are still preliminary, but to date, this is one of the largest genetic studies on chronic pain to analyze the female and male sex separately."Our study highlights the importance of considering sex as a biological variable and showed subtle but interesting sex differences in the genetics of chronic pain," says population geneticist Keira Johnston from the University of Glasgow in Scotland.

Chronic pain conditions are among the most prevalent, disabling, and expensive conditions in public health. In the United States, chronic pain affects more people than heart disease, diabetes, and cancer combined, and yet it receives a fraction of the overall funding.

Even when studies are done, they often overlook underlying sex differences, and that's a huge and detrimental oversight. Compared to men, women are far more likely to develop multiple chronic pain disorders, and yet historically, 80 percent of all pain studies have been conducted on male mice or male humans. This means we

know very little about how and why females are suffering more and what treatments can help them best.

While there are probably multiple biological and psychosocial processes in this sex discrepancy, the current genome-wide study suggests there's a genetic factor in the mix, too.

Comparing gene variants associated with chronic pain in 209,093 women and 178,556 men from the UK Biobank, researchers have attempted to find at least part of the answer in our biology.

In the end, researchers found 31 genes associated with chronic pain in women and 37 genes associated with chronic pain in men with barely any overlap. The authors admit some of the differences here might stem from their lower male sample size, but the results are nonetheless intriguing.

When researchers tested the expression of all these genetic variants across various tissues from mice and humans, they noticed the vast majority were active in a cluster of nerves within the spinal cord, known as the dorsal root ganglion, which transmits messages from the body to the brain. Several genes in the male-only or female-only list were associated with psychiatric issues or immune function, but only one gene, known as DCC, was in both lists.

DCC encodes for a receptor that binds with a protein crucial for the development of the nervous system, especially the dopaminergic system; as well as being a reward center, the latter has recently been connected to pain modulation in the body.

DCC is also thought to be a risk gene for the pathology of depression, and DCC mutations appear in those with congenital mirror movement disorder, which results in movements on one side of the body being replicated on the other side.

How exactly DCC is connected to chronic pain remains unclear, but the authors say their results support several theories "of strong nervous system and immune involvement in chronic pain in both sexes", which they hope will be used to develop better treatments in the future.

If chronic pain is more strongly associated with immune function in women, for instance, the side-effects of immune-targeting drugs may be very different to men. On the other hand, treatments such as chronic opioid use might also have different outcomes. Opioids are known to adversely affect immune function, which suggests they could make things worse and not better for women in chronic pain.

For right now at least, these are just ideas. Way more pain research needs to be done and far more of it needs to be conducted among women before we can really begin to understand the real sex discrepancies at play and what we can do about it.

"All of these lines of evidence, together, suggest putative central and peripheral neuronal roles for some of these genes, many of which have not been historically well studied in the field of chronic pain," the authors conclude.

The study was published in PLOS Genetics.

https://bit.ly/3uCjWvw

Immune-stimulating drug before surgery shows promise in early-stage pancreatic cancer

For the first time, researchers led by SU2C "Dream Team" show how CD40 agonist drives an immune response to hard-to-penetrate tumors

Philadelphia--Giving early-stage pancreatic cancer patients a CD40 immune-stimulating drug helped jumpstart a T cell attack to the notoriously stubborn tumor microenvironment before surgery and other treatments, according to a new study from researchers in the **Abramson Cancer Center (ACC) at the University of Pennsylvania**. Changing the microenvironment from so-called T cell "poor" to T cell "rich" with a CD40 agonist earlier could help slow eventual progression of the disease and prevent cancer from spreading in more patients.

The data--which included 16 patients treated with the CD40 agonist

selicrelumab--was presented today by **Katelyn T. Byrne, PhD**, an instructor of Medicine in the division of Hematology-Oncology in the Perelman School of Medicine at the University of Pennsylvania, during a plenary session at the American Association for Cancer Research annual meeting (Abstract #CT005).

"Many patients with early-stage disease undergo surgery and adjuvant chemotherapy. But it's often not enough to slow or stop the cancer," Byrne said. "Our data supports the idea that you can do interventions up front to activate a targeted immune response at the tumor site--which was unheard of five years ago for pancreatic cancer--even before you take it out."

The purpose of CD40 agonists is to help "push the gas" on the immune system both by activating antigen-presenting cells, such as dendritic cells, to "prime" T cells and by enhancing immune-independent destruction of the tumor site. The therapies have mostly been investigated in patients with metastatic pancreatic cancer patients in combination with other therapies, such as chemotherapy or other immunotherapies. This is the first time the drug has been shown to drive an immune response in early-stage patients both at the tumor site and systemically--which mirrors what researchers found in their mouse studies.

The phase 1b clinical trial was conducted at four sites, including the ACC, Fred Hutchinson Cancer Research Center at the University of Washington, Case Western Reserve University, and Johns Hopkins University.

Sixteen patients were treated with selicrelumab before surgery. Of those patients, 15 underwent surgery and received adjuvant chemotherapy and a CD40 agonist. Data collected from those patients' tumors and responses were compared to data from controls (patients who did not receive the CD40 agonist before surgery) treated at Oregon Health and Science University and Dana Farber Cancer Institute.

Multiplex imaging of immune responses revealed major differences between the two groups. Eighty-two percent of tumors in patients who received the CD40 agonist before surgery were T-cell enriched, compared to 37 percent of untreated tumors and 23 percent chemotherapy or chemoradiation-treated tumors. Selicrelumab tumors also had less tumor-associated fibrosis (bundles of tissue that prevent T cells and traditional therapies from penetrating tumors), and antigen-presenting cells known as dendritic cells were more mature.

In the treatment group, disease-free survival was 13.8 months and median overall survival was 23.4 months, with eight patients alive at a median of 20 months after surgery.

"This is a first step in building a backbone for immunotherapy interventions in pancreatic cancer," Byrne said.

Based on these findings, researchers are now investigating how other therapies combined with CD40 could help strengthen the immune response even further in pancreatic cancer patients before surgery.

"We're starting to turn the tide," said **Robert H. Vonderheide, MD, DPhil**, director of the ACC and senior author. "This latest study adds to growing evidence that therapies such as CD40 before surgery can trigger an immune response in patients, which is the biggest hurdle we've faced. We're excited to see how the next-generation of CD40 trials will take us even closer to better treatments."

https://nyti.ms/3s60SnH

Blood Clots Linked to AstraZeneca Vaccine Stem From Rare Antibody Reaction

New studies from Germany and Norway examined cases involving mostly younger people who developed serious and sometimes fatal blood disorders.

By Denise Grady

New research has identified unusual antibodies that appear to have caused, in rare cases, serious and sometimes fatal blood clots in people who received the Covid vaccine made by AstraZeneca.

Exactly why the rare reactions to the vaccine occurred is still a mystery.

Scientific teams from Germany and Norway found that people who developed the clots after vaccination had produced antibodies that activated their platelets, a blood component involved in clotting. The new reports add extensive details to what the researchers have already stated publicly about the blood disorder.

Younger people appear more susceptible than older ones, but researchers say no pre-existing health conditions are known to predispose people to the rare reaction. That is worrisome, they say, because there is no way to tell if an individual is at high risk.

Reports of the clots have already led a number of countries to limit AstraZeneca's vaccine to older people, or to stop using it entirely.

These cases have dealt a crushing blow to global efforts to halt the pandemic, because the AstraZeneca shot — easy to store and relatively cheap — has been a mainstay of vaccination programs in more than 100 countries.

The European Medicines Agency, the regulator for the European Union, has emphasized repeatedly that the clotting disorder is rare, and that the vaccine's benefits far outweigh its risks. But when a side effect has the potential to be devastating or fatal — like the blood clots in the brain linked to this vaccine — some regulators and segments of the public are finding that the risk is unacceptable, even if it is extremely rare.

As of Sunday, European regulators had received reports of 222 cases of the rare blood-clotting problem in Britain and the 30-nation European Economic Area (the European Union plus Iceland, Norway and Liechtenstein). They said that about 34 million people had received the AstraZeneca vaccine in those countries, and that the clotting problems were appearing at a rate of about one in 100,000 recipients.

European regulators said that as of March 22, they had carried out detailed reviews of 86 cases, 18 of which had been fatal.

The safety bar for vaccines is set high, because they are given to healthy people. The seemingly greater vulnerability of younger people to the clotting disorder is of particular concern, because their risk of severe illness from Covid itself is lower than that in older people. Those differences suggest that overall, compared to older people, younger people may have less to gain and more to lose from the AstraZeneca vaccine.

Germany, the Netherlands, the Philippines, Portugal and Spain have recommended that the AstraZeneca vaccine be given only to people over 60. Canada and France have limited it to those over 55; Australia, over 50; Belgium, over 56. Britain, where the vaccine was developed, has been its staunchest defender, but announced on Wednesday that it would begin offering alternative shots to people under 30.

The University of Oxford, which developed the vaccine with AstraZeneca, said on Tuesday that it had suspended a two-month-old trial of the vaccine in children and teenagers in Britain while it waits for regulatory guidance.

Cameroon, the Democratic Republic of Congo, Denmark and Norway have stopped using the vaccine.

Full vaccination with the AstraZeneca vaccine requires two doses, but regulators in France and Germany have recommended that people under 55 who have had one dose get a different vaccine for their second shot.

The AstraZeneca vaccine is not authorized for use in the United States, but the company has said it plans to apply to the Food and Drug Administration for permission for emergency use. The agency declined on Friday to comment on the rare clotting disorder.

On Wednesday, the European Medicines Agency said that the vaccine's labeling should be revised to include listing the clotting disorder as a "very rare" side effect of the vaccine.

In a statement on its website, AstraZeneca said it was "actively collaborating with the regulators to implement these changes to the product information and is already working to understand the individual cases, epidemiology and possible mechanisms that could explain these extremely rare events."

The two new studies were published by The New England Journal of Medicine. One from Germany described 11 patients, including nine women ages 22 to 49. From five to 16 days after vaccination, they were found to have one or more clots. Nine had cerebral venous thrombosis, a clot blocking a vein that drains blood from the brain. Some had clots in their lungs, abdomen or other areas. Six of the 11 died, one from a brain hemorrhage.

Although most of the patients were female, it is not known whether women are more vulnerable than men. Many health care workers in Germany are women, and they were among the first to be vaccinated. One patient had pre-existing conditions that affected clotting. During a news briefing on Friday, Dr. Andreas Greinacher, an author of the report, said those conditions most likely played only a minor role in the reaction that occurred after vaccination.

He also said it was a "likely possibility" that the people who developed the clotting disorder had some rare, unknown biological traits — what he called "individual co-factors" — that predisposed their immune systems to make powerful, misdirected antibodies in response to the vaccine. He called that "good news" for the general population, who do not have the co-factors.

There is "clear evidence" that the AstraZeneca vaccine in rare cases leads the body to make antibodies that activate platelets, and that those antibodies are causing blood clots, Dr. Greinacher said.

But, he added: "We have no way to predict who will develop these antibodies."

So far, his laboratory has identified only about 40 cases, of 1.4 million people in Germany who have received the vaccine. If the vaccine alone were causing the problem, without individual co-factors, there would be many, many more cases, Dr. Greinacher said.

He called the deaths in young people "tragic," but noted that the numbers were small. "Not vaccinating will bring many, many more people with severe complications than vaccination," Dr. Greinacher warned. All of the first 11 patients in his study, as well as 17 others with clots after vaccination whose blood was tested, had the antibodies known to activate platelets.

The antibodies led to a condition called thrombotic thrombocytopenia, which caused both clotting and abnormal bleeding. The researchers suggested naming the newly identified version in these patients "vaccine-induced immune thrombotic thrombocytopenia," or VITT.

Various theories have been offered by scientists as to what touches off the immune reaction. The AstraZeneca vaccine employs a chimpanzee adenovirus to carry DNA into recipients to spark an immune response against the coronavirus. Laboratory studies have suggested that the chimp virus or the DNA might cause the problem. Some researchers have suggested that bleeding from the injection, mixed with the vaccine, might put platelets in the cross-hairs of the immune system.

Dr. Greinacher called the theories plausible but unproven.

The article described specialized blood tests that can be used to diagnose the disorder, and distinguish it from other, more common clotting problems not related to the vaccine. The research team suggested treatment with a blood product called intravenous immune globulin, which is used to treat various immune disorders. Dr. Greinacher likened the treatment to putting out a fire.

Drugs called anti-coagulants, or blood thinners, can also be administered. But the researchers recommended against prescribing a commonly used one, heparin — because the vaccine-related condition is very similar to a severe reaction that occurs, rarely, in people given heparin.

The second report, from Norway, described five patients, one male and four female health care workers ages 32 to 54, who had clots and bleeding from seven to 10 days after receiving the AstraZeneca vaccine. Four had severe clots in the brain, and three died. Severe headaches were among their early symptoms. Like the German patients, all had high levels of antibodies that could activate platelets.

The team from Norway also recommended treatment with intravenous immune globulin. The researchers said the disorder was rare, but “a new phenomenon with devastating effects for otherwise healthy young adults,” and they suggested that it may be more common than previous studies of the AstraZeneca vaccine had indicated.

On Friday, European regulators also said they were reviewing reports of a few blood clot cases that occurred in people who had received the Johnson and Johnson vaccine. In the United States, federal agencies are investigating reports of a different type of unusual blood disorder involving a precipitous drop in platelets that emerged in a few dozen people who had received either the Pfizer-BioNTech or Moderna vaccines.

Benjamin Mueller and Melissa Eddy contributed.

https://bit.ly/3q48QeE

One COVID-19 Strain May 'Break Through' Pfizer Vaccine, Early Results Show

The South African coronavirus variant is better at "breaking through" the defenses of the Pfizer/BioNTech vaccine than other forms of the virus, Israeli experts said Sunday.

However, one of the authors told AFP that while the study showed the variant to be relatively successful in infecting vaccinated people, it did not provide any data on whether it could generate serious illness among vaccinees.

The study by Tel Aviv University and Clalit Health Services, Israel's largest healthcare provider, compared 400 unvaccinated people infected with COVID-19 to 400 partially or fully vaccinated people who also had the virus.

According to the study, published as a draft on Saturday and currently being peer reviewed, the South African variant accounted for less than one percent of coronavirus cases in Israel.

But, among the 150 people in the study who were fully vaccinated and had COVID-19, "the prevalence rate (of the South African variant) was eight times higher than the rate in the unvaccinated (individuals)," the study said. "This means that the Pfizer-BioNtech vaccine, though highly protective, probably does not provide the same level of protection against the South African (B.1.351) variant of the coronavirus," the study added.

"The South African variant is able, to some extent, to break through the vaccine's protection," said professor Adi Stern of Tel Aviv University's Shmunis School of Biomedicine and Cancer Research, one of the study's authors.

Stern told AFP Sunday the study did not assess whether the fully vaccinated Israelis with the South African variant - eight people in total - developed serious illness. "Since we found a very small number of vaccinees infected with B.1.351, it is statistically meaningless to report disease outcomes," he said.

Preventative measures

Two studies published in February in the *New England Journal of Medicine* conducted by principal vaccine manufacturers Pfizer/BioNTech and Moderna showed that the presence of antibodies after vaccination was less pronounced in people exposed

to the South African variant, indicating diminished protection.
The Israeli study was the first real-world assessment of the South African variant's ability to bypass a vaccine.
Israel's vaccination campaign has seen 5.3 million people receive a first dose, while 4.9 million, or 53 percent of the population, have had two shots.
An earlier study by Clalit on 1.2 million Israelis found that the Pfizer/BioNTech jab gave 94 percent protection against COVID-19.
Following the successful vaccination rollout, Israel has eased many of its restrictions but various measures remain in place including mask-wearing and a "green passport" system that grants access to certain sites only to those vaccinated.
Ran Balicer of Clalit, one of the study's authors, told AFP the results could help inform states on how best to ease restrictions.
Balicer said inoculations, plus mask-wearing and other safety measures had still likely helped limit the spread of the South African variant, despite its apparent ability to break through the Pfizer/BioNTech vaccine.
A combination of all these factors "are most likely... preventing the virus strains, including the South African one, from spreading" significantly in Israel, he said.
"As we taper down the non-pharmaceutical interventions, we must do so gradually to ensure we do not cross a threshold that would enable these variants to spread."