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

COVID is here to stay: countries must decide how to adapt

The Omicron variant has laid bare the need to live with a disease that throws up an ever-changing set of challenges.

From a pandemic perspective, 2022 seemed poised to begin with a hefty dose of déjà vu, with COVID-19 cases on the rise in many countries in the lead-up to the new year. Meanwhile, a new coronavirus variant seemed poised to overwhelm health-care systems amid fears that vaccines — from first inoculations to boosters, depending on the country — could not be rolled out quickly enough to stem the impending tsunami of infections.

The welcome news that surges of the Omicron variant are associated with less severe disease in adults than are preceding variants of SARS-CoV-2 suggests that some of pandemic modellers' worst-case scenarios will not come to pass. But life has again been disrupted. Widespread absences due to coronavirus infections have left hospitals in many countries understaffed, forced schoolchildren to return to remote learning, and limited global mobility. And even if a relatively small percentage of those infected require hospitalization, sky-high infection rates across large populations mean that many people will still face life-threatening disease and long-term disability. This is particularly true for the unvaccinated — a group that includes a large proportion of the world's population, especially children.

For those who had hoped that 2021 would be the year that put the pandemic in the past tense, it was a harsh reminder that it is still very much present. Rather than laying plans to return to the 'normal' life we knew before the pandemic, 2022 is the year the world must come to terms with the fact that SARS-CoV-2 is here to stay.

Countries must decide how they will live with COVID-19 — and living with COVID-19 does not mean ignoring it. Each region must work out how to balance the deaths, disability and disruption caused by the virus with the financial and societal costs of measures used to try to control the virus, such as mask mandates and business closures. This balance will vary from one place to another, and with time, as more therapies and vaccines become available — and as new variants emerge.

The emergence of the Omicron variant last November highlighted the ongoing challenges of life with SARS-CoV-2. Some countries were already facing surges in the highly transmissible Delta variant, but vaccines and prior infection conferred relatively high levels of protection against Delta, particularly against severe disease. Many researchers — and a fair few politicians — hoped that future waves would be less disruptive, thanks to the build-up of immunity in populations that would keep viral circulation in check and protect most people from the severe manifestations of disease that drain health-care resources.

It was expected that mutations in the viral genome would slowly chip away at this immunity, particularly its ability to stop viral transmission. But Omicron dealt a swifter and more serious blow to immunity than predicted. It is now clear that SARS-CoV-2 reinfections are more common, and that some of the most widely used COVID-19 vaccines have faltered in the face of the variant. Existing vaccines, developed against an earlier variant, now require a booster to provide substantial levels of protection against infection.

But the news has not all been grim. Vaccines, particularly when boosted, still seem to provide substantial protection against severe disease and death. Early data from animal studies suggest that Omicron might generate a different pathology compared with previous variants, causing greater infection of the upper respiratory tract and less infection in the lungs. Data from several countries

suggest that the variant is associated with less severe disease, although whether this is due to the variant itself or widespread pre-existing immunity requires further study.

Countries have charted a variety of courses through the latest surge. Many with the resources have accelerated the distribution of vaccine boosters, but many others do not have this luxury. Some countries have reinstituted lockdowns, whereas others are holding back, waiting to see the extent to which climbing infection rates affect hospitals.

With infection rates soaring around the globe and many countries still unable to access adequate vaccine supplies, more SARS-CoV-2 variants of concern will continue to emerge. And, as Omicron has illustrated, the ability to predict what course those variants will take becomes more difficult as the complexities of viral evolution and pre-existing immunity complicate the models that have previously been used to anticipate the course of the pandemic. Now modellers need to factor in the effects of vaccines, previous infections, waning immunity over time, booster shots and viral variants — and, as the year progresses, they will also have to consider the impact of emerging antiviral treatments.

But what is clear is that the hope that vaccines and prior infection could generate herd immunity to COVID-19 — an unlikely possibility from the start — has all but disappeared. It is widely thought that SARS-CoV-2 will become endemic rather than extinct, with vaccines providing protection from severe disease and death, but not eradicating the virus.

As Omicron and other variants have shown, this only adds to the urgency with which vaccines must be distributed to countries that currently lack supplies. Efforts are under way to bolster vaccine production in countries such as South Africa, which have not historically been centres for vaccine manufacturing. These and other efforts to boost global access to vaccines remain in the best interests of all countries: devastating variants are particularly likely to emerge and seed blazing outbreaks in regions with low vaccination rates, and their spread will be further exacerbated where levels of testing and genomic surveillance are also low.

Fortunately, 2022 is poised to add to our defences against the pandemic. New vaccines — such as protein-based vaccines, which might cost less and have less-stringent storage requirements than mRNA vaccines currently do — will become more widely available. In December, the World Health Organization approved the long-awaited protein vaccine made by Novavax in Gaithersburg, Maryland, for emergency use. Ongoing clinical trials will establish whether upcoming vaccine candidates that target specific coronavirus variants, or that can be inhaled or taken orally rather than injected, will also be useful. Several nasal candidates are in clinical testing, including one from CanSino in Tianjin, China, and another developed by AstraZeneca in Cambridge, UK.

Meanwhile, new antiviral drugs, formulated in tablets that can be easily administered early in the course of infection to reduce the chance of serious disease and death, offer another approach against COVID-19. In the past few months, some countries have authorized the use of two such drugs: molnupiravir, made by Merck in Kenilworth, New Jersey, and Ridgeback Biotherapeutics in Miami, Florida; and Paxlovid, made by Pfizer, based in New York. Data from pivotal clinical trials of other candidates are expected in the coming year.

All of these will expand the world’s capacity to manage SARS-CoV-2 outbreaks. They are cause for hope and optimism, but with a hefty dose of realism: the virus will continue to circulate and change, and governments must continue to rely on the guidance and advice of scientists. We will not always be able to predict the virus’s path, and we must be ready to adapt with it.

*Nature **601**, 165 (2022) doi: https://doi.org/10.1038/d41586-022-00057-y*

https://bit.ly/3nqqRhc

T Cells From Common Colds Cross-Protect Against COVID-19 Infection

A new study, published in Nature Communications and led by Imperial College London researchers, provides the first evidence of a protective role for these T cells.

While previous studies have shown that T cells induced by other coronaviruses can recognize SARS-CoV-2, the new study examines for the first time how the presence of these T cells at the time of SARS-CoV-2 exposure influences whether someone becomes infected.

The researchers also say their findings provide a blueprint for a second-generation, universal vaccine that could prevent infection from current and future SARS-CoV-2 variants, including Omicron.

Dr. Rhia Kundu, first author of the study, from Imperial's National Heart & Lung Institute, says: "Being exposed to the SARS-CoV-2 virus doesn't always result in infection, and we've been keen to understand why. We found that high levels of pre-existing T cells, created by the body when infected with other human coronaviruses like the common cold, can protect against COVID-19 infection.

"While this is an important discovery, it is only one form of protection, and I would stress that no one should rely on this alone. Instead, the best way to protect yourself against COVID-19 is to be fully vaccinated, including getting your booster dose."

The study began in September 2020 when most people in the UK had neither been infected nor vaccinated against SARS-CoV-2. It included 52 people who lived with someone with PCR-confirmed SARS-CoV-2 infection and who had therefore been exposed to the virus. The participants did PCR tests at the outset and 4 and 7 days later, to determine if they developed an infection.

Blood samples from the 52 participants were taken within 1-6 days of them being exposed to the virus. This enabled the researchers to analyze the levels of pre-existing T cells induced by previous common cold coronavirus infections that also cross-recognize proteins of the SARS-CoV-2 virus.[1]

The researchers found that there were significantly higher levels of these cross-reactive T cells in the 26 people who did not become infected, compared to the 26 people who did become infected. These T cells targeted internal proteins within the SARS-CoV-2 virus, rather than the spike protein on the surface of the virus, to protect against infection.[2]

Current vaccines do not induce an immune response to these internal proteins. The researchers say that – alongside our existing effective spike protein-targeting vaccines – these internal proteins offer a new vaccine target that could provide long-lasting protection because T cell responses persist longer than antibody responses which wane within a few months of vaccination.

Professor Ajit Lalvani, senior author of the study and Director of the NIHR Respiratory Infections Health Protection Research Unit at Imperial, says: "Our study provides the clearest evidence to date that T cells induced by common cold coronaviruses play a protective role against SARS-CoV-2 infection. These T cells provide protection by attacking proteins within the virus, rather than the spike protein on its surface.

"The spike protein is under intense immune pressure from vaccine-induced antibody which drives evolution of vaccine escape mutants. In contrast, the internal proteins targeted by the protective T cells we identified mutate much less. Consequently, they are highly conserved between the various SARS-CoV-2 variants, including omicron. New vaccines that include these conserved, internal proteins would therefore induce broadly protective T cell responses that should protect against current and future SARS-CoV-2 variants."

The researchers note some limitations to their study, including that,

because it is small and 88% of participants were of white European ethnicity, it is not possible for them to model demographic factors.

Notes

1 These included external surface proteins (spike, membrane and envelope proteins) on the surface of the SARS-CoV-2 virus, and internal proteins, including nucleocapsid (which packages the virus' genetic material) and ORF1 (a part of SARS-CoV-2's replicative machinery).

2 The targeted internal proteins of SARS-CoV-2 included nucleocapsid and ORF1 only

Reference: "Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts" by Rhia Kundu, Janakan Sam Narean, Lulu Wang, Joseph Fenn, Timesh Pillay, Nieves Derqui Fernandez, Emily Conibear, Aleksandra Koycheva, Megan Davies, Mica Tolosa-Wright, Seran Hakki, Robert Varro, Eimear McDermott, Sarah Hammett, Jessica Cutajar, Ryan S. Thwaites, Eleanor Parker, Carolina Rosadas, Myra McClure, Richard Tedder, Graham P. Taylor, Jake Dunning and Ajit Lalvani, 10 January 2022, Nature Communications.
DOI: 10.1038/s41467-021-27674-x
The study was funded by the NIHR Health Protection Research Unit in Respiratory Infections and the Medical Research Council.

https://bit.ly/3nMI0uX

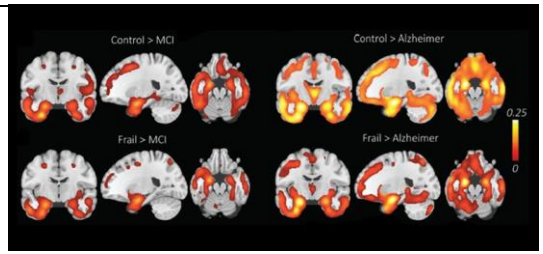
Cognitive Decline Is Not Always a Sign of Alzheimer's Disease

Some cognitively frail adults have impaired cognition but intact brain structure and function.

At the first sign of cognitive trouble, people often worry Alzheimer's disease is forthcoming. But poor cognition can be part of the spectrum of normality in older age, according to new research published in *JNeurosci*.

Kocagoncu et al. compared the brains of cognitively frail adults — people with reduced cognitive function who haven't noticed memory issues — to those of adults with a mild cognitive impairment (MCI) or Alzheimer's disease (AD) and healthy controls. They recruited healthy and cognitively frail adults from the Cambridge Centre for Ageing and Neuroscience study.

Researchers measured participants' cognition with a battery of tests, their brain structure with MRI, and their brain activity with EEG and MEG.



The brains of the cognitively frail more closely resemble the brains of healthy controls than those of adults with Alzheimer's disease or a mild cognitive impairment. **Credit: Kocagoncu et al., JNeurosci 2022**

Cognitively frail adults performed like adults with MCI on the cognitive tests — both worse than controls. But their brain structure and activity resembled those of the healthy controls: the atrophy in regions like the hippocampus typical in adults in AD did not appear in cognitively frail adults. Impaired cognition can be part of the range of normal aging and is not always an early sign of Alzheimer's disease. Cognitive frailty may instead hinge on lifestyle factors — many of which are reversible and modifiable — like physical activity, stress, education, and cardiovascular health.

Reference: "Neurophysiological and Brain Structural Markers of Cognitive Frailty Differ from Alzheimer's Disease" 10 January 2022, JNeurosci.
DOI: 10.1523/JNEUROSCI.0697-21.2021

https://nyti.ms/3A1QRxt

Uncovering Mysteries of Female Dolphin Sexual Anatomy

A close examination of 11 clitorises from common bottlenose dolphins suggests the female cetaceans experience pleasure during frequent sexual activity.

By Sabrina Imbler

Common bottlenose dolphins have sex frequently — very likely multiple times in a day. Copulation lasts only a few seconds, but social sex, which is used to maintain social bonds, can last much longer, happen more frequently and involve myriad heterosexual and homosexual pairings of dolphins and their body parts. Anything

is possible, and, as new research suggests, probably pleasurable for swimmers of both sexes.

According to a paper published on Monday in the journal Current Biology, female bottlenose dolphins most likely experience pleasure through their clitorises.

The findings come as little surprise to scientists who research these dolphins. “The only thing that surprises me is how long it has taken us as scientists to look at the basic reproductive anatomy,” Sarah Mesnick, an ecologist at NOAA Fisheries who was not involved with the research, said, speaking of the clitoris. She added, “It took a team of brilliant women,” referring to two of the authors.

“A lot of people assume that humans are unique in having sex for pleasure,” Justa Heinen-Kay, a researcher at the University of Minnesota who was not involved with the paper, wrote in an email. “This research challenges that notion.”

And learning more about the anatomy of marine mammals’ genitalia has clear implications for their survival, Dr. Mesnick said: “The more we know about the social behavior of these animals, the better we’re able to understand their evolution and help use that to manage and conserve them.”

Historically, researchers have focused on male genitalia, driven by prejudice toward male subjects, prejudice against female choice in sexual selection and the fact that it can be easier to study something that sticks out. “Female genitalia were assumed to be simple and uninteresting,” Dr. Heinen-Kay said. “But the more that researchers study female genitalia, the more we’re learning that this isn’t the case at all.” She added that this shift may be driven in part by the increasing number of women researchers.

Patricia Brennan, an evolutionary biologist at Mount Holyoke College and an author on the paper, wound up studying the dolphin clitoris by way of the dolphin vagina. She and Dara Orbach, a biologist at Texas A&M University and another author on the paper, previously revealed how female dolphins have intricately pleated vaginas that can handily stopper a penis. The internal anatomy grants the female agency in choosing which male’s sperm may fertilize her egg.

When Dr. Brennan and Dr. Orbach began researching dolphin vaginas together in 2016, they found themselves dissecting as many of these pleated pouches as they could get their hands on. The researchers put out a request to local stranding networks and received lumps of frozen tissue over the years from stranded cetaceans in varying states of decay.

As the researchers thawed the samples in a sink, the warming flesh often began to reek. “I’m really glad I’m a vegetarian because I think I would never be able to eat meat again,” Dr. Brennan said.

Like cultured oysters, every dissected dolphin vagina unfurled to reveal a kind of treasure: an unmistakable clitoris, the size of an AA battery and the color of spam. “You open it up and then there’s this giant clitoris right there,” Dr. Brennan said.

The researchers dissected the clitorises of 11 common bottlenose dolphins and ran tissue samples through a micro CT scanner. Their examination revealed a number of signs of a functional clitoris, including erectile tissue that could become turgid with blood. They also found a band of connective tissue surrounding the erectile tissue, which ensures the clitoris could engorge and keep its shape. And the clitoris changed shape as the dolphins reached adulthood, suggesting it has a function related to sexual maturity.

The CT scanner showed the clitoral tissue contained unusually large nerves — up to half a millimeter in diameter — and abundant free nerve endings just under the skin, increasing sensitivity. And the clitoral skin itself was a third of the thickness of neighboring genital skin, making it much easier to stimulate.

These observations provide “some nice suggestive evidence” that female dolphins feel pleasure responses to tactile stimulation, said

Brian Langerhans, an evolutionary biologist at North Carolina State University, who was not involved with the research. He added that more research was needed to prove the hypothesis.

But it is no easy feat to study dolphin sex experimentally in a lab, or in the wild. The physiological signs of pleasure associated with humans and other primates — vocalizing, grimacing, rolling eyes and panting — may look totally different in a dolphin. “Their bodies are so different from us, and their faces are so different from ours,” Dr. Brennan said. “How would we know?”

Dr. Langerhans and Dr. Mesnick both suggested the need for comparative research between other species of cetaceans. “Are they going to find the same kind of anatomy in species that are more solitary or open-ocean or deep-diving?” Dr. Mesnick wondered. For example, a pleasurable clitoris might be far less useful in a species where males and females interact less often.

Dr. Brennan hopes to study clitorises from across the animal kingdom — she already has an orca clitoris sitting in a jar in her lab. The white whale of marine clitorises may be the blue whale’s. “They’ve got the biggest everything,” Dr. Brennan said. “I would bet you a million dollars that they have a clitoris, and it’s probably huge.”

https://bit.ly/3KfnqFu

Did a large impact remix the Moon’s interior?

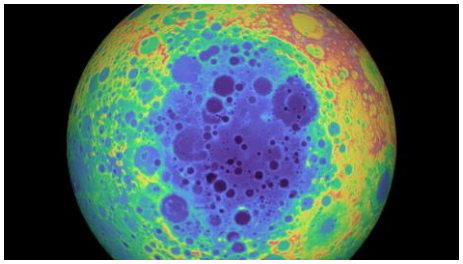
New model suggests a big impact roiled the Moon's interior, altered its volcanism.

John Timmer

As the Moon coalesced from the debris of an impact early in the Solar System's history, the steady stream of orbital impacts is thought to have formed a magma ocean, leaving the body liquid. That should have allowed its components to mix evenly, creating a roughly uniform body. But with the onset of space exploration, we were finally able to get our first good look at the far side of the Moon.

It turned out to look quite different from the side we were familiar with, with very little in the way of the dark regions, called mare, that dominate the side facing Earth.

These differences are also reflected in the chemical composition of the rocks on the different sides. If the whole Moon was once a well-mixed blob of magma, how did it end up with such a major difference between two of its faces? A new study links this difference to the Moon's largest impact crater.



Enlarge / The blue area is the basin formed by the largest impact on the Moon. Additional craters have formed by subsequent impacts.
NASA/GSFC/University of Arizona

A big crash

The South Pole-Aitken Basin is one of the largest impact craters in the Solar System, but again, we didn't realize it was there until after we put a craft in orbit around the Moon. All we can see from Earth are some of the ridges that are part of the outer crater wall. Most of the 2,500 kilometers of the crater itself extend into the far side of the Moon.

Clearly, the crater formed after the magma ocean period, based on the fact that its features solidified after the impact. But it's also very old, and it could have formed prior to many of the volcanic features we can see on the near side. Intriguingly, the largest concentration of volcanic mare are found in the north of the near side—roughly on the opposite side of the Moon from the impact itself. Could they be related?

It's clear that an impact of this size could have generated a lot of heat within the Moon and potentially influenced or even restarted convection of the materials there. But it's far less clear that this

would have produced volcanism so far from the site of impact.

To understand the situation better, a team of Chinese researchers built a model of the Moon's interior. This model combined software that could simulate the impact with models of the Moon's interior that could take into account the heating and additional material of the impact and the gravitational influence of the nearby Earth.

A big churn

As expected, the model shows that the heat derived from the impact does indeed restart convection within the interior of the Moon. But it doesn't restart evenly. That's because the body that created the crater also injects a lot of material into the interior of the Moon, and that material gradually spreads out from the site of impact in all directions. For a large portion of the Moon's interior, this disrupts organized convection.

This organized convection is what allows warmer, deep material to make its way to the surface and draws cooler material from the surface to the interior. The net result is that warm, deep material only makes its way closer to the surface on the side opposite the impact crater. On the Moon, this material also contains higher concentrations of radioactive isotopes, which will keep it warm for much longer, powering the extended period of volcanism that created the mare.

Not every impact will produce this sort of effect. If the angle of an impact is too shallow, the spread of material isn't wide enough to create a large asymmetry. And the details of the asymmetry are sensitive to the size of the impactor and the viscosity of the material it injects into the lunar interior.

Obviously, this sort of complicated mechanism requires a lot of things to go right, so researchers will probably want to recheck this work with independent convection models. And the authors of the study suggest that looking at the rocks near the Chang'e-5 landing site on the northern part of the near side may give us a greater sense of the composition of the materials that erupted there.

But as the authors note, there are several competing models to explain the asymmetry, so we'll have to wait for scientists to compare the models to see if there are any obvious differences in what they produce. And then we'll have to see if we can reasonably expect to get any relevant evidence from the Moon.

Nature Geoscience, 2022. DOI: 10.1038/s41561-021-00872-4 (About DOIs).

https://wb.md/3npf5wr

Olive Oil Intake Tied to Reduced Mortality

In an observational study of more than 90,000 US healthcare professionals, consuming even a small amount of olive oil was associated with reduced total mortality.

Marlene Busko

Compared to men and women who rarely or never consumed olive oil (the lowest intake), those who consumed greater than 0.5 tablespoon/day or more than 7 g/day (the highest intake) had a 19% lower mortality risk over a 28-year follow-up, starting from an average age of 56 years.

Moreover, compared to those with the lowest olive oil intake, those with the highest intake had a 19% lower cardiovascular disease (CVD) mortality, a 17% lower risk of dying from cancer, a 29% lower risk of dying from neurodegenerative disease, and an 18% lower risk of dying from respiratory disease during follow-up.

The researchers estimate that replacing 10 g/day of margarine, butter, mayonnaise, or dairy fat with the same amount of olive oil is associated with an 8% to 34% lower risk of death from various causes. The study by Marta Guasch-Ferré, PhD, and colleagues was published online January 10 in the *Journal of the American College of Cardiology*.

Results Support Plant-Based Dietary Fat Recommendations

"Our results support current dietary recommendations to increase

the intake of olive oil and other unsaturated vegetable oils in place of other fats to improve overall health and longevity," the researchers summarize.

However, "I wouldn't say that olive oil is the only way to help you live longer," Guasch-Ferré, a senior research scientist in the Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, cautioned in an interview with *theheart.org | Medscape Cardiology*.

"Other things are very important, such as not smoking, doing physical activity, etc, but one recommendation could be to try to eat more plant-based food including olive oil and healthy fat," she added, and to use it for cooking, salad dressing, and baking, and substitute it for saturated fat or animal fat, especially for cooking.

The study suggests that people should "consume a more plant-based diet and prioritize fatty acids such as olive oil because they have a better nutritional composition (high in phenols and antioxidants), instead of using butter or margarines or other animal fats that have been shown to have detrimental effects for health," she added, which is consistent with recommendations in the Dietary Guidelines for Americans.

"That said," Guasch-Ferré summarized, "replication is needed in other cohorts and populations to see if the results are similar."

In an accompanying editorial, Susanna C. Larsson, PhD, writes that "this was a well-designed study, with long-term follow-up and repeated measurements of dietary intake and other risk factors for diseases."

"However, the difference in olive oil consumption between those with the highest and those with the lowest/no olive oil consumption was very low (0.5 tablespoon) and a [12%] reduced mortality risk was observed already at a much lower intake (0.5 teaspoon, about 1.5 g/day) of olive oil," she noted in an email to *theheart.org | Medscape Cardiology*.

"It's a bit hard to believe that such a small amount could have an independent effect on mortality risk," Larsson, associate professor of epidemiology at the Karolinska Institutet, Stockholm, Sweden, cautioned. Like Guasch-Ferré, she noted that "just adding one or two teaspoons of olive oil to the diet each day will likely not change the risk of mortality."

Rather, "people may need to make larger changes in the whole diet, not focus on fat only. An overall healthier diet, rich in non-refined plant-based foods (vegetables, whole grains, nuts), low/no intake of processed foods, and a switch to healthier fat (eg, olive oil) is needed."

Importantly, "this study cannot say anything about causality, that is, whether it's olive oil specifically that reduces mortality risk or if there are many other beneficial factors that act together to reduce mortality rate among those with high olive oil consumption."

The researchers acknowledge this observational study limitation and that the findings may not be generalizable to other populations.

Novel Findings Regarding Alzheimer's and Respiratory Disease

Larsson highlights two novel findings of this study.

First, it showed a 27% reduction in risk of dementia-related mortality for those in the highest versus lowest category of olive oil consumption. "Considering the lack of preventive strategies for Alzheimer's disease and the high morbidity and mortality related to this disease, this finding, if confirmed, is of great public health importance," she said.

Second, the study reported an inverse association of olive oil consumption with risk of respiratory disease mortality. "Because residual confounding from smoking cannot be ruled out," Larsson said, "this finding is tentative and requires confirmation in a study that is less susceptible to confounding, such as a randomized trial."

And although the current study and previous studies have found

that consumption of olive oil may have health benefits, she identified several remaining questions.

"Are the associations causal or spurious?" she noted. Is olive oil consumption protective for certain cardiovascular diseases like stroke or atrial fibrillation only, as has been shown in other studies, or also for other major diseases and causes of death, she added. What is the amount of olive oil required for a protective effect?

Further, is the potential effect related to monounsaturated fatty acids (MUFAs) or phenolic compounds; that is, "is the protective effect confined to polyphenol-rich extra virgin olive oil or are refined olive oil and other vegetable oils as beneficial? More research is needed to address these questions," she concludes.

"Further studies are needed," the researchers agree, "to confirm the association of olive oil consumption with reduced mortality, clarify the mechanisms responsible, and quantify the dose/volume boundaries around this effect."

Virgin Olive Oil Has More Polyphenols

Olive oil, a key component of the Mediterranean diet, is high in MUFAs, especially oleic acid, as well as vitamin E and polyphenols, which contribute to its anti-inflammatory and antioxidant properties, the researchers explain.

Virgin olive oil, produced by mechanically pressing ripe olives, contains multiple bioactive and antioxidant components and has an acidity of < 1.5%. And extra-virgin olive oil is produced the same way but has a higher quality, more intense taste, and lower acidity (< 1%).

Refined or processed olive oil contains less phytochemicals, as some are lost during processing; it usually contains more than 80% refined oil, plus virgin oil added back to enhance flavor, and may also be labeled "pure" or "light." However, refined olive oil "still has a good amount of healthy fatty acids but less bioactive compounds," Guasch-Ferré noted.

Until now, no large prospective study has examined the link between olive oil intake and all-cause and cause-specific mortality in a US population, where olive oil consumption is limited compared with Mediterranean countries.

The researchers identified 60,582 women in the Nurses' Health Study and 31,801 men in the Health Professionals Follow-up Study who were free of CVD or cancer in 1990, the first year that food frequency questionnaires in these studies asked about olive oil.

Participants replied to questionnaires every 4 years that asked about use of olive oil (for salad dressing, baking, frying, sautéing, and spreading on bread), other vegetable oils (eg, corn, safflower, soybean, canola oil), margarine, butter, and dairy fat. The researchers averaged the consumption of these fats during the follow-up years.

From 1990 to 2019, the average consumption of olive oil increased from 1.6 g/day to 4 g/day. Margarine in the 1990s contained saturated fat and trans fats, whereas more recently margarine contains beneficial olive oil or vegetable fat, Guasch-Ferré noted.

Baseline olive oil consumption in this US population "differed remarkably" from that in the Spanish population in the PREDIMED (Prevención con Dieta Mediterránea) trial, which was, on average, 20 to 22 g/day of extra virgin olive oil and 16 to 18 g/day of refined/mixed olive oil, Larsson pointed out.

Because olive oil consumption was so low in this US study, the researchers did not distinguish between virgin/extra-virgin olive oil and refined/processed olive oil.

The participants were almost all White (99%) and were generally healthier than in the average US population; on average, they had a body mass index of 25.3 to 25.8 kg/m^2 and ate 4.8 to 7.2 fruits and vegetables/day.

Those with the highest olive oil consumption were more physically active, had a healthier diet, were more likely to have Southern

European or Mediterranean ancestry, and were less likely to smoke. During 28 years of follow-up, 36,856 participants died. The researchers classified the deaths into five categories: CVD, cancer, neurodegenerative disease (including Alzheimer's disease, Parkinson's disease, multiple sclerosis), respiratory disease (such as chronic obstructive pulmonary disease), and all other causes (including suicide, injury, infections, diabetes, and kidney disease).

After adjusting for multiple confounders, compared with participants who rarely or never consumed olive oil, those in the highest quartile for olive oil consumption had a decreased risk of death from all-causes (hazard ratio [HR], 0.81; 95% CI, 0.78 - 0.84) and from CVD (HR, 0.81; 95% CI, 0.75 - 0.87), cancer (HR, 0.83; 95% CI, 0.78 - 0.89), neurodegenerative disease (HR, 0.71; 95% CI, 0.64 - 0.78), and respiratory disease (HR, 0.82; 95% CI, 0.72 - 0.93). There was no decrease in mortality in models where the researchers substituted olive oil for vegetable oil, suggesting that vegetable oils may provide similar health benefits as olive oil.

The research was supported by grants from the National Institutes of Health. Guasch-Ferré was supported by the American Diabetes Association. Co-author Salas-Salvadó is partially supported by the Catalan Institution for Research and Advanced Studies and received the virgin olive oil that was used in the PREDIMED and PREDIMED-Plus studies from the Patrimonio Communal Olivalero and Hojiblanca (Málaga, Spain). The other study authors and Larsson have reported no relevant financial relationships.

J Am Coll Cardiol. Published online January 10, 2022. Abstract, Editorial

https://bit.ly/3GAHjMr

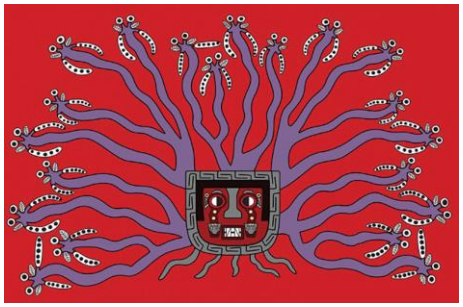
Drug-laced beer may have forged ancient Peruvian empire

Andean rulers may have fostered allegiance one feast at a time

By Andrew Curry

Between 500 and 1100 C.E., the highlands of Peru were home to a far-reaching empire known as the Wari. Like the Inca after them, the Wari managed to spread their culture over the vast distances and rugged terrain of the Andes Mountains. Now, new finds from a small site in Peru suggest the Wari may have forged political alliances by serving drug-laced beer to local elites at periodic parties, extending their empire one trippy feast at a time.

The idea that the Wari used hallucinogens for political maneuvering and not solitary religious rituals "makes a lot of sense," says University of North Carolina, Greensboro, archaeologist and Wari expert Donna Nash, who was not involved in the research.



Ancient Peru's Wari culture painted depictions of the vilca tree—and its hallucinogenic seed pods—on drinking vessels, like this motif from a site called Conchopata. **J. Ochatoma Paravicino/M. E. Biwar et. al., Antiquity (2021)**

Between 2013 and 2017, archaeologists excavating near Arequipa in southern Peru found evidence of a small Wari outpost, some 800 kilometers south of the capital at Huari. Called Quilcapampa today, the site was probably home to only 100 Wari at its peak—perhaps three extended families and a few others, plunked down in a remote, arid valley more than 200 kilometers from the nearest large Wari settlement.

Artifacts suggest the surrounding area was populated by locals who maintained their lifestyle after the Wari arrived in the middle of the ninth century. And though their outpost boasts typical Wari architectural styles and houses objects such as elaborately decorated drinking vessels, feathered ceremonial clothing, and stone tablets, it lacks any weapons that might signal a military presence. How could a small group of foreigners so far from home, researchers wondered, get locals to accept them and perhaps even recognize their authority?

Clues came from Quilcapampa's dry soil, which yielded hundreds

of thousands of dried plant remains. After spending months sorting them, Dickinson College archaeobotanist Matthew Biwer found 16 seeds from a hallucinogenic jungle plant called vilca.

Vilca seeds, which some Amazonian tribes still consume today, produce intense, incapacitating hallucinations akin to the psychedelic ayahuasca when pulverized and snorted. Archaeologists have documented thousands of years of vilca use as part of South American religious rituals, and vilca seed pods have been depicted on Wari drinking vessels. But the tree doesn't naturally grow near Quilcapampa, Biwer says. That fact—and the fact that the seeds were found only in the Wari compounds—suggests the vilca was imported by the Wari.

Why they brought the drug was another question. Consumed alone, vilca brings on intense, private hallucinations. However, when added to alcohol—particularly the fermented fruits of the molle tree—the seed's hallucinogenic compounds are diluted but remain active. "Instead of an abrupt out-of-body experience, you would have a more elongated high [that] you would be able to enjoy with other people," says Royal Ontario Museum archaeologist Justin Jennings, who led the excavation. "[The Wari] take something that is an antisocial drug and make it a social one."

Sure enough, the vilca at Quilcapampa was found near pits full of desiccated seeds from the berries of the molle tree, which had been soaked and fermented, presumably to make a strong beer known as chicha. That suggests vilca was a controlled substance, Jennings says. He and his colleagues also think it may have been used to make friends with the locals and influence regional elites, likely during exclusive feasts or parties. "The Wari are telling the locals, 'Bring the molle, and we're going to add the special sauce.'"

Rather than organizing grand public ceremonies or military invasions, the Wari may have built their empire one party at a time, the researchers theorize today in *Antiquity*. Artifacts from other Wari sites suggest they had a heady party culture: Much of their pottery is dedicated to beer brewing or serving. "Wari statecraft is happening on a smaller scale," Jennings says. "I see these as boozy family dinners, building social relationships one [feast] at a time." And because vilca was an exotic substance in Quilcapampa, a vilca-fueled party there would have been special, cementing the new arrivals' prestige.

The Quilcapampa finds could help reveal how Wari politics worked on a larger level, Nash says. "To find vilca at a smaller provincial site is interesting–and demonstrates not only that the high priest was using the drug, but that the use might have been more pervasive than we thought," she says.

Around 900 C.E., after just a few decades, the Quilcapampa settlement was abandoned. Breakdowns in long-distance trade meant the Wari there were cut off from their supply chains, and Jennings thinks their efforts to win over the locals eventually failed. The goodbye party was a rager, though. In one last, massive blowout, residents of the compounds spread smashed pottery, burned food, and left offerings on the clean floors of their houses. Then they blocked off doorways and abandoned the site, in a signature Wari farewell. *doi: 10.1126/science.ada0061*

https://bit.ly/3tsu3G3

Ankylosaur was sluggish and deaf

German and Austrian scientists took a closer look at the braincase of a dinosaur from Austria.

The group examined the fossil with a micro-CT and found surprising new details: it was sluggish and deaf. The respective study was recently published in the journal *Scientific Reports*.

Life reconstruction of the dinosaur Struthiosaurus austriacus from the Late Cretaceous of Austria. **Credit: Fabrizio De Rossi**

Ankylosaurs could grow up to eight meters in body length and represent a group of herbivorous dinosaurs also called 'living fortresses. Its body was cluttered with bony plates and spikes. The ankylosaurids sometimes possessed a club tail, while nodosaurids had elongated spikes on their necks and shoulders. However, some aspects of their lifestyle are still puzzling.

While many dinosaurs likely lived in groups, at least some ankylosaurs seemed to prefer a lonesome life because of an inferior sense of hearing. That's what the scientists from the universities of Greifswald and Vienna concluded when they examined the braincase of the Austrian dinosaur with a high-resolution computer tomograph to produce a digital three-dimensional cast.

Fossil braincases, which once housed the brain and other neurosensory tissues, are rare but important for science because these structures can provide insights into the lifestyle of a given animal. For example, the inner ears can hint to auditory capacities and skull orientation.

Struthiosaurus austriacus is a comparably small nodosaurid from the Late Cretaceous (80 Ma) of Austria and comes from a locality near Muthmannsdorf, south of Vienna. The fossil remains of this dinosaur already belonged to the collection of the Institute for Paleontology in Vienna in the 19th century. For their study, Marco Schade (University of Greifswald), Cathrin Pfaff (University of Vienna) and their colleagues examined the tiny (50 mm) braincase to reveal new details of the anatomy and lifestyle of Struthiosaurus austriacus. With these data, it was possible to learn more about its sense of equilibrium and hearing.

The results of this study show that Struthiosaurus' brain was very similar to the brains of its close relatives. For example, the flocculus, an evolutionary old part of the brain, was very small. The flocculus is important for the fixation of the eyes during motions of the head, neck and whole body, which can be very useful if such an animal was trying to target potential competitors or aggressors. "In contrast to its North American relative Euoplocephalus, which had a tail club and a clear flocculus on the brain cast, Struthiosaurus austriacus may have rather relied on its body armor for protection," says Marco Schade. Together with the form of the semicircular canals in the inner ear, this hints towards an exceptionally sluggish lifestyle of this Austrian plant eater. Furthermore, the scientists found the—so far—shortest lagena of any dinosaur. The lagena is the part of the inner ear where hearing takes place and its size can help to infer auditory capacities. This study delivers new insights into the evolutionary history of dinosaurs and their world, in which Europe was largely submerged in the ocean.

More information: *Marco Schade et al, Neuroanatomy of the nodosaurid Struthiosaurus austriacus (Dinosauria: Thyreophora) supports potential ecological differentiations within Ankylosauria, Scientific Reports (2022). DOI: 10.1038/s41598-021-03599-9*

https://bit.ly/3tsZpfw

How Much Did the Moon Heat Young Earth?

Tidal heating may have raised the surface temperature of early Earth and triggered global volcanism, a new study says.

by Jure Japelj

The Moon used to orbit Earth 10–15 times closer than it does today. Orbiting even closer than geosynchronous satellites, our only natural satellite exerted a strong gravitational pull on our planet, deformed it, and heated its interior.

A recent study published in *Paläontologische Zeitschrift* suggested that such tidal heating generated considerable heat for about a hundred million years after the formation of the Moon. The heat could have directly increased the surface temperature of early Earth by several degrees. Indirectly, the process may have further heated the surface by triggering global volcanic activity and thus enriched the atmosphere with greenhouse gases.

Never-Ending Dance of a Planet and Its Moon

The Moon formed much closer to Earth than it is now, and it has

been drifting away ever since.

About 4.5 billion years ago, a Mars-sized body likely collided with Earth. The collision propelled molten debris into orbit around Earth, and over time the wreckage coalesced into the Moon. Although scientists have largely accepted the giant impact theory of lunar origin, debates about the timing of the impact and the mechanisms that led to the formation of the Moon are ongoing. What is clear is that the Moon formed much closer to Earth than it is now, and it has been drifting away ever since.

Paradoxically, the Moon and Earth are growing apart due to gravity. The Moon's gravity exerts a stronger pull on the part of Earth that faces it (as opposed to the antipodes), stretching the planet into a slightly oblong, bulged shape. These tidal forces are the primary cause of tides on Earth. That would be the end of the story if it weren't for the fact that Earth rotates on its axis faster than the Moon orbits the planet. As a result of this discrepancy, the planet puts on the brakes while the Moon speeds up in its orbit, slowly drifting away.

Tidal forces contribute to heating in Earth's interior. "The tides generate friction, and friction leads to heat," explained René Heller, a scientist at the Max Planck Institute for Solar System Research and a lecturer at the University of Göttingen in Germany.

Tidal heating is not a significant phenomenon on Earth now, but conditions were different billions of years ago. Previous works found that tidal heating was relevant for a few million years after the formation of the Moon. Heller and colleagues suggest that the period of significant heating lasted about a hundred million years.

"The energy that would have been dissipated in the Earth, according to the authors, is of the order of magnitude of the heat content of the Earth," said Tilman Spohn, a professor and executive director of the International Space Science Institute in Switzerland. Spohn was not involved in the study. "If you release it at once, you would double [Earth's] internal temperature." (Both Spohn and the researchers noted that such a release would not be sudden.)

Warming Up Early Earth

The new research also contributes to one of the most famous problems in astrophysics. Tidal heating could have raised the temperature on early Earth by a few degrees and therefore played a minor but not irrelevant role in solving the so-called faint young Sun paradox. Evidence has suggested that Earth harbored liquid water as far back as 4.4 billion years ago. That observation is difficult to reconcile with our understanding of the evolution of the Sun, whose energy output at the time was about 30% lower than it is today. For decades, scientists have been trying to model various atmospheric conditions to keep early Earth from becoming a snowball. "There are theories that try to solve the faint young Sun paradox which ignore tidal heating entirely and just focus on the Earth's atmosphere," said Heller. "The truth will need to combine all these effects."

"Maybe we should reconsider the early evolution of the Earth-Moon system."

Furthermore, tidal heating likely triggered global volcanism. We need only to look at Jupiter's moon Io to see the effect playing out in real time. Thanks to enormous tidal stresses that melt the moon's interior, Io is the most volcanically active body in the solar system. Similar volcanic activity on early Earth would release greenhouse gases into the atmosphere.

All studies addressing the faint young Sun paradox have to contend with sparse geological records of early Earth, however. "The mineral zircon is almost the only record we have for early Earth," warned Junjie Dong, a graduate student at Harvard University who was not involved with the recent study. "The evidence for liquid water on the surface is based on isotopic records in zircons, and there are still people who dispute that interpretation."

Regardless, the researchers said the concept of tidal heating of early Earth should not be brushed aside. “I would take [the study] as a reminder or suggestion that maybe we should reconsider the early evolution of the Earth-Moon system,” said Spohn. The next step would be to construct a more detailed model by considering the evolution of the Moon’s orbit, tidal heating of the Moon itself, and a thorough treatment of Earth’s internal structure.

https://bit.ly/3tvz3tt

Cannabinoids From Hemp Prevent COVID-19 Coronavirus From Entering Human Cells

Hemp compounds show the ability to prevent SARS-CoV-2 from entering human cells

Hemp compounds identified by Oregon State University research via a chemical screening technique invented at OSU show the ability to prevent the virus that causes COVID-19 from entering human cells.

Findings of the study led by Richard van Breemen, a researcher with Oregon State’s Global Hemp Innovation Center, College of Pharmacy, and Linus Pauling Institute, were published on January 10, 2022, in the *Journal of Natural Products.*

Hemp, known scientifically as Cannabis sativa, is a source of fiber, food, and animal feed, and multiple hemp extracts and compounds are added to cosmetics, body lotions, dietary supplements, and food, van Breemen said.

Van Breemen and collaborators, including scientists at Oregon Health & Science University, found that a pair of cannabinoid acids bind to the SARS-CoV-2 spike protein, blocking a critical step in the process the virus uses to infect people.

The compounds are cannabigerolic acid, or CBGA, and cannabidiolic acid, CBDA, and the spike protein is the same drug target used in COVID-19 vaccines and antibody therapy. A drug target is any molecule critical to the process a disease follows, meaning its disruption can thwart infection or disease progression.

“These cannabinoid acids are abundant in hemp and in many hemp extracts,” van Breemen said. “They are not controlled substances like THC, the psychoactive ingredient in marijuana, and have a good safety profile in humans. And our research showed the hemp compounds were equally effective against variants of SARS-CoV-2, including variant B.1.1.7, which was first detected in the United Kingdom, and variant B.1.351, first detected in South Africa.”

Those two variants are also known the alpha and beta variant, respectively.

Characterized by crown-like protrusions on its outer surface, SARS-CoV-2 features RNA strands that encode its four main structural proteins – spike, envelope, membrane, and nucleocapsid – as well as 16 nonstructural proteins and several “accessory” proteins, van Breemen said.

“Any part of the infection and replication cycle is a potential target for antiviral intervention, and the connection of the spike protein’s receptor binding domain to the human cell surface receptor ACE2 is a critical step in that cycle,” he said. “That means cell entry inhibitors, like the acids from hemp, could be used to prevent SARS-CoV-2 infection and also to shorten infections by preventing virus particles from infecting human cells. They bind to the spike proteins so those proteins can’t bind to the ACE2 enzyme, which is abundant on the outer membrane of endothelial cells in the lungs and other organs.”

Using compounds that block virus-receptor interaction has been helpful for patients with other viral infections, he notes, including HIV-1 and hepatitis.

Van Breemen, Ruth Muchiro of the College of Pharmacy and Linus Pauling Institute and five scientists from OHSU identified the two cannabinoid acids via a mass spectrometry-based screening technique invented in van Breemen’s laboratory. Van Breemen’s

team screened a range of botanicals used as dietary supplements including red clover, wild yam, hops and three species of licorice.

An earlier paper in the *Journal of the American Society for Mass Spectrometry* described tailoring the novel method, affinity selection mass spectrometry, to finding drugs that would target the SARS-CoV-2 spike protein.

In the later research, lab tests showed that cannabigerolic acid and cannabidiolic acid prevented infection of human epithelial cells by the coronavirus spike protein and prevented entry of SARS-CoV-2 into cells.

"These compounds can be taken orally and have a long history of safe use in humans," van Breemen said. "They have the potential to prevent as well as treat infection by SARS-CoV-2. CBDA and CBGA are produced by the hemp plant as precursors to CBD and CBG, which are familiar to many consumers. However, they are different from the acids and are not contained in hemp products."

Van Breemen explains that affinity selection mass spectrometery, which he abbreviates to AS-MS, involves incubating a drug target like the SARS-CoV-2 spike protein with a mixture of possible ligands – things that might bind to it – such as a botanical extract, in this case hemp extract.

The ligand-receptor complexes are then filtered from the non-binding molecules using one of several methods.

"We identified several cannabinoid ligands and ranked them by affinity to the spike protein," van Breemen said. "The two cannabinoids with the highest affinities for the spike protein were CBDA and CGBA, and they were confirmed to block infection.

"One of the primary concerns in the pandemic is the spread of variants, of which there are many, and B.1.1.7 and B.1.351 are among the most widespread and concerning," he added. "These variants are well known for evading antibodies against early lineage SARS-CoV-2, which is obviously concerning given that current vaccination strategies rely on the early lineage spike protein as an antigen. Our data show CBDA and CBGA are effective against the two variants we looked at, and we hope that trend will extend to other existing and future variants."

Van Breemen said resistant variants could still arise amid widespread use of cannabinoids but that the combination of vaccination and CBDA/CBGA treatment should make for a much more challenging environment for SARS-CoV-2.

"Our earlier research reported on the discovery of another compound, one from licorice, that binds to the spike protein too," he said. "However, we did not test that compound, licochalcone A, for activity against the live virus yet. We need new funding for that."

Reference: "Cannabinoids Block Cellular Entry of SARS-CoV-2 and the Emerging Variants" by Richard B. van Breemen, Ruth N. Muchiri, Timothy A. Bates, Jules B. Weinstein, Hans C. Leier, Scotland Farley and Fikadu G. Tafesse, 10 January 2022, Journal of Natural Products. DOI: 10.1021/acs.jnatprod.1c00946

Timothy Bates, Jules Weinstein, Hans Leier, Scotland Farley and Fikadu Tafesse of OHSU also contributed to the cannabinoid study.

https://wb.md/3A2b0U3

Make Room for Mavericks Among Us

Mainstream medicine is the best route for most people and conditions, most of the time. But we must make room for maverick medicine as well.

George D. Lundberg, MD

Be not the first by whom the new is tried,
Nor yet the last to lay the old aside. – Alexander Pope

Do you know "truth"? I don't, but I sure do like to search for it. I see mainstream medicine as that developed and espoused by the "establishment." That is — forgive the alphabet soup — the AAMC, LCME, ACGME, ACCME, the medical education industry, NIH, CDC (and all state and county health departments), AHRQ, FDA, USPSTF, FSMB (and all state licensing boards), AHA, AAHC, UCA, MGMA, AMA (and all specialty and state medical societies),

ANA, CMS, the health insurance industry, the HR benefits industry, PhRMA, NLM, the medical publishing industry, medical marketing and advertising, and assorted others. This is a rich, self-sustaining, propagating mega-behemoth, fully capable of producing-consuming-spending 18% of the US gross domestic product, approximately $4 trillion, or $12,000/person/year, and best characterized by Warren Buffett as an unbeatable economic tapeworm.

Mainstream medicine — peer-reviewed, guideline-based, bureaucracy-approved, insurance-controlled, medically crowdsourced, conventional wisdom medicine — is by and large a good thing, albeit expensive, and is the best route for most people and conditions, most of the time. Randomized, controlled, blinded (when possible) clinical trials with numbers large enough to assert statistical power must remain the gold standard.

But we must make room for maverick medicine as well. Many diseases and possible treatments do not present with sufficient numbers for large-scale trials, so we need alternative ways to evaluate them.

The value of patient autonomy is fiercely defended by many, and rightfully so. Take charge of your life; after all, it is your life. However, with respect to your health, this is best done with a trusted physician with whom you share decision-making.

The value of physician autonomy is likewise fiercely defended by many, and rightfully so. Medical education (undergrad, graduate, continuing) is worth much, as are degrees, licenses, certification, and staff privileging.

I see maverick medicine as essential as contrarian challenges to complacency or regimentation. Like serious investigative journalism, we should always be asking questions, challenging dogma, puncturing bloated myths, and seeking and reporting truth.

My favorite medical maverick is not an American. He is GP Malcolm Kendrick of Scotland, who publishes a widely read blog — acerbic, witty, sarcastic, devilish, bombastic, invasive, irreverent, insulting, based on fundamental basic science principles like chemistry, mathematics, physiology, anatomy, plus a keen sense of history, clinical experience, and total intolerance of haughty BS. One recent column lambasted a major UK agency (NICE, the UK National Institute for Health and Care Excellence) that (I thought) holds worldwide respect.

But the best medical maverick may be the elegantly educated physician, also greatly experienced in real-world medicine, with the zeal of an investigative journalist, huge savvy on how to gather information, and laser-focused on critical thinking. This maverick has no government or industry ties to constrain or conflict, is truly independent, driven by truth-finding and telling, and practicing rapid information throughput dissemination. I am *not* describing artificial intelligence (although maybe someday). I refer to public media physician journalists such as Vin Gupta and Leana Wen, and angry critic Vinay Prasad.

Medscape columnist and Yale professor F. Perry Wilson; daily newsletter writer Dr Bill Bestermann; and my favorite COVID blogger, Dr Susan Levenstein and her Stethoscope on Rome are among the best at living out, critically analyzing, and broadly disseminating the rapidly moving fronts of medical information that beg for instant interpretation. Valued physicians like these can be both mainstream and maverick simultaneously.

There are a lot of physicians out there who don't know from nothing, for whom science seems an unknown never-never land. I lay that learning deficit on the US medical education system, which grants a "professional" degree, MD, rather than an "academic" degree, PhD. Rote memorizing of vast information is emphasized in many medical schools.

There may be a "science of medicine," but really medical science is

more an amalgamation of many other solid sciences as applied to human health and disease. A person will not learn the critical thinking necessary for scientific understanding without dedicated and guided study.

Two of the generally most trustworthy guideposts for evidence-based medicine are US Food and Drug Administration (FDA) approval of a drug or device and approval for its specific uses. Once the Centers for Medicare & Medicaid Services (CMS) and other insurance payers also approve payment for a given product or service, it can usually be considered reliable.

Infallible, the FDA is not; witness the current Aduhelm debacle. So far, CMS has not announced a coverage decision for Aduhelm. Many physicians and medical organizations have announced that they have no plan to prescribe the agent, which may or may not have slight effects on a biomarker and none on brain function.

Mainstream medicine has gotten plenty of things very wrong historically, even in the 20th and 21st centuries. Sometimes non-MD mavericks are essential in noting where some of the failures may lie and in pointing to a different direction. I like to think that I have played on all sides of this serious circus over the decades.

Publications on topics such as these represent maverick opportunities:

* Cancer as a metabolic (not gene-based) disease, by biology professor Thomas Seyfried
* Registry-based virtual trials to screen for therapies, by podiatrist Al Musella
* Topical hydrogen peroxide for premalignant lesions, by oncology journalist Ron Piana
* Physicist Gary Taubes and the case against sugar
* My own fingernail surgery for seborrheic keratoses
* Dr Bill Bestermann on coronary artery calcium scores way back in 2007
* Remarkable results in well-performed n-of-1 clinical trials
* Entrepreneur Marty Tenenbaum, PhD, as a long-term metastatic melanoma survivor and an outlier in a "failed" early clinical trial of immunotherapy

Individual clinical observations must be considered anecdotes and the results not generalized until they can be validated in some way. I gag at hearing the word "ivermectin," the poster-child drug of the physician who had "a case" and erroneously projected it to be generalizable by extrapolation bias.

Make no mistake, there are legions of physician-kooks out there; just read some of the physician comments on Medscape to find an abundance, even a plethora, of physicians who would "not recognize good science if it punched them in the mouth" (to plagiarize Mike Tyson).

Beware of the true loonies, the politics-over-science bunch, the word-of-mouth rumors made ubiquitous by some active users of social media; the folks who recognize that an untruth, or better yet a half-truth, no matter how egregious and provably false, if repeated often enough in enough places by enough sources for a long enough period of time will come to be known as "true" by some, even by many. Members of the healing professions are not immune to the gaslighting phenomenon.

That's my opinion. I'm Dr George Lundberg, at large at Medscape.

George Lundberg, MD, is contributing editor at Cancer Commons, president of the Lundberg Institute, executive advisor at Cureus, and a clinical professor of pathology at Northwestern University. Previously, he served as editor-in-chief of JAMA *(including 10 specialty journals),* American Medical News, *and Medscape.*

https://bit.ly/34YnKQt

Study challenges evolutionary theory that DNA mutations are random

Studying the genome of thale cress, a small flowering weed, led to a new understanding about DNA mutations.

A simple roadside weed may hold the key to understanding and predicting DNA mutation, according to new research from University of California, Davis, and the Max Planck Institute for Developmental Biology in Germany.

The findings, published January 12 in the journal *Nature*, radically

change our understanding of evolution and could one day help researchers breed better crops or even help humans fight cancer.

Mutations occur when DNA is damaged and left unrepaired, creating a new variation. The scientists wanted to know if mutation was purely random or something deeper. What they found was unexpected.

"We always thought of mutation as basically random across the genome," said Grey Monroe, an assistant professor in the UC Davis Department of Plant Sciences who is lead author on the paper. "It turns out that mutation is very non-random and it's non-random in a way that benefits the plant. It's a totally new way of thinking about mutation."

Researchers spent three years sequencing the DNA of hundreds of *Arabidopsis thaliana*, or thale cress, a small, flowering weed considered the "lab rat among plants" because of its relatively small genome comprising around 120 million base pairs. Humans, by comparison, have roughly 3 billion base pairs.

"It's a model organism for genetics," Monroe said.

Lab-grown plants yield many variations

Work began at Max Planck Institute where researchers grew specimens in a protected lab environment, which allowed plants with defects that may not have survived in nature be able to survive in a controlled space.

Sequencing of those hundreds of *Arabidopsis thaliana* plants revealed more than 1 million mutations. Within those mutations a nonrandom pattern was revealed, counter to what was expected.

"At first glance, what we found seemed to contradict established theory that initial mutations are entirely random and that only natural selection determines which mutations are observed in organisms," said Detlef Weigel, scientific director at Max Planck Institute and senior author on the study.

Instead of randomness they found patches of the genome with low mutation rates. In those patches, they were surprised to discover an over-representation of essential genes, such as those involved in cell growth and gene expression.

"These are the really important regions of the genome," Monroe said. "The areas that are the most biologically important are the ones being protected from mutation."

The areas are also sensitive to the harmful effects of new mutations. "DNA damage repair seems therefore to be particularly effective in these regions," Weigel added.

Plant evolved to protect itself

The scientists found that the way DNA was wrapped around different types of proteins was a good predictor of whether a gene would mutate or not. "It means we can predict which genes are more likely to mutate than others and it gives us a good idea of what's going on," Weigel said.

The findings add a surprising twist to Charles Darwin's theory of evolution by natural selection because it reveals that the plant has evolved to protect its genes from mutation to ensure survival.

"The plant has evolved a way to protect its most important places from mutation," Weigel said. "This is exciting because we could even use these discoveries to think about how to protect human genes from mutation."

Future uses

Knowing why some regions of the genome mutate more than others could help breeders who rely on genetic variation to develop better crops. Scientists could also use the information to better predict or develop new treatments for diseases like cancer that are caused by mutation.

"Our discoveries yield a more complete account of the forces driving patterns of natural variation; they should inspire new avenues of theoretical and practical research on the role of mutation in evolution," the paper concludes.

Co-authors from UC Davis include Daniel Kliebenstein, Mariele Lensink, Marie Klein, from the Department of Plant Sciences. Researchers from the Carnegie Institution for Science, Stanford University, Westfield State University, University of Montpellier, Uppsala University, College of Charleston, and South Dakota State University contributed to the research.

More information: *Detlef Weigel, Mutation bias reflects natural selection in Arabidopsis thaliana, Nature (2022). DOI: 10.1038/s41586-021-04269-6. www.nature.com/articles/s41586-021-04269-6*

https://bbc.in/3A34CvW

Covid in pregnancy linked to birth-related complications

A new study has linked Covid-19 to complications during pregnancy.

Scottish researchers found that women who catch the virus near the end of pregnancy were more vulnerable to birth-related complications. They are more likely to suffer them than women who catch Covid in early pregnancy or not at all.

The researchers say getting vaccinated is crucial to protect pregnant women and their babies from life-threatening complications.

The latest findings come from the Covid in Pregnancy Study (Cops), which carried out research across Scotland to learn about the incidence and outcomes of Covid-19 infection and vaccination in pregnancy. It is one of the first national studies of pregnancy and Covid.

The research team included scientists from the Universities of Edinburgh, Glasgow, Aberdeen, Strathclyde, and St Andrews along with Public Health Scotland (PHS) and and Victoria University of Wellington in New Zealand.

They found that preterm births, stillbirths and newborn deaths were more common among women who had the virus 28 days, or less, before their delivery date. The majority of complications occurred in unvaccinated women.

The results, which have been published in Nature Medicine, come after recent data showed 98% of pregnant women admitted to UK intensive care units with coronavirus symptoms were unvaccinated.

Researchers are now calling for measures to increase vaccine uptake in pregnant women.

The study analysed data relating to all pregnant women in Scotland. It included more than 87,000 women who were pregnant between the start of vaccination uptake in December 2020 and October 2021.

Vaccination uptake was lower in pregnant women during the study period, compared with women aged 18 to 44 in the general population. Just 32% of women who gave birth in October 2021 were fully vaccinated, compared with 77% of the general female population aged 18 to 44.

All of the women whose babies died had not been vaccinated against Covid at the time of infection, though experts stressed that it is not possible to say if the virus contributed directly to the deaths or preterm births as they did not have access to detailed clinical records for individual women.

'This reassures me I did the right thing'

Nyree Mairs from Broxburn found out she was pregnant in January 2021. After suffering from seven miscarriages she was understandably worried about the effect of both the virus and the vaccine on her pregnancy.

She told the BBC: "I was quite confused at the start but when the government rolled out the vaccine for pregnant women, I sought more advice from my consultant and my midwife. I read reports which had been released at that point and findings from US studies, and that helped me make my decision.

She was anxious due to her past losses: "Having a baby in my 40s is a miracle and we didn't think it was going to happen," she said.

"I got good advice and I had to make an informed decision. I had also read sad stories about mums who had suffered losses and become really ill with Covid and their babies were really sick. That made my decision for me.

"This is so important and that's why I got the vaccination done."

Hearing the results of the study reinforced that her decision was the right one. She said: "I have a son here who is absolutely perfect, nothing wrong with him and he is healthy. I feel really sad for people who didn't get it done and maybe had complications and I am just glad the information is out there for people. I'd advise people to get it. My son and I have been fine, and I have even had my booster now."

Cops co-lead Dr Sarah Stock, of the University of Edinburgh's Usher Institute, who is also a consultant obstetrician, said: "Our data adds to the evidence that vaccination in pregnancy does not increase the risk of complications in pregnancy, but Covid-19 does.

"Vaccination in pregnancy is crucial to protect women and babies from preventable, life-threatening complications of Covid."

The team also looked at data on extended perinatal deaths, which is defined as the death of a baby in the womb after 24 weeks of pregnancy, or in the first 28 days after birth. They found that the extended perinatal death rate among babies born within 28 days of their mother developing Covid was 23 per 1,000 births.

This was compared to the background perinatal mortality rate, the rate for all babies born in Scotland regardless of whether their mother had previously had Covid or been vaccinated, which was six per 1000 births during the pandemic.

Some 17% of babies born within 28 days of their mother developing Covid were delivered prematurely - more than three weeks before their due date - compared to a background preterm birth rate of 8%. A total of 4,950 cases of Covid-19 have been confirmed during pregnancy since the start of the vaccination programme, with 77% of these cases in unvaccinated women.

Complication rates in women vaccinated during pregnancy were found to be very similar to background rates, which experts said gave further reassurance on the safety of vaccination during pregnancy.

Cops co-lead, Dr Rachael Wood, a consultant in public health medicine with Public Health Scotland, said: "It is clear that vaccination is the safest and most effective way for pregnant women to protect themselves and their babies from severe Covid-19 disease."

The Scottish government's deputy chief medical officer Prof Nicola Steedman said: "This is an incredibly important piece of research, what it goes to show is Covid is that dangerous for pregnant women both for themselves and for their babies.

"There is really strong evidence now that Covid has much greater risks for pregnant women if they get it later in pregnancy and that vaccination is protective, so my message would be please if you have hesitated before and you are pregnant, please please get the vaccination for your own protection and for the protection of your baby."

Last week, the Scottish government deferred fertility treatment for all patients who are not fully vaccinated - unless they are waiting to become eligible for a booster.

It said the decision was based on uncertainty about how pregnant women were affected by the Omicron variant amid rising cases.

https://bit.ly/3rnaFaL

There's a Hidden Mathematical 'Law' in The Sand Megaripples Found All Over Earth

Wherever there is sand and an atmosphere, prevailing winds may whip the grains into undulating shapes, pleasing to the eye with their calming repetition.

David Nield

Certain sand waves, with wavelengths between 30 centimeters (almost 12 inches) and several meters (around 30 feet), are known as megaripples: they're between ordinary beach ripples and full dunes in size, and we've seen them not just on Earth, but even on

other planets such as Mars, well known for its all-encompassing dust storms.

Aside from their size, a key characteristic of these middle-ground ripples is the grain size involved – a surface of coarse grains over an interior of much finer material. Yet this mix of grains is never the same, and nor are the winds that blow across the sand to create the ripples in the first place.

Now researchers have discovered a surprising mathematical feature of megaripples: Dividing the diameter of the coarsest grains in the mix with the diameter of the smallest grains always equals a similar number – something that hasn't been spotted before across several decades of research.

In the future, this number could be used to categorize different types of ripples and which particular grain transport processes formed them, the study authors conclude.

"We found that a characteristic signature of grain-scale transport is encoded in the grain-size distributions (GSDs) that co-evolve with megaripples," write the researchers in their published paper.

Transverse aeolian ridges, a type of megaripple seen on Mars. **(NASA/JPL-Caltech/Univ. of Arizona)**

"Our compilation of original and literature data firmly establishes the accuracy and robustness of the theoretical prediction across a wide range of geographic locations and prevailing environmental conditions."

As winds whip across the sand, megaripples are caused by fine grains kicking up coarser ones. Traveling at different rates, the coarse grains collect on the crests of the ripples, while the fine grains usually settle in the troughs.

Samples were studied from megaripple fields in Israel, China, Namibia, India, Jordan, Antarctica and New Mexico in the US. Further analysis was added from observations made on Mars and in a lab wind tunnel.

"A comprehensive collection of terrestrial and extraterrestrial data, covering a wide range of geographical sources and environmental conditions, supports the accuracy and robustness of this unexpected theoretical finding," write the researchers.

What also sets megaripples apart is that they're more fragile than smaller sand ripples and larger dunes, and more susceptible to the whims of shifting wind patterns – if the wind gets too strong, the mechanisms creating the megaripples get overpowered.

The researchers suggest that their calculations could also be used to predict when this will happen, and even to look back at past weather and climate conditions based on the sediment left behind by previous megaripples.

The findings even apply beyond Earth: they could give us a better understanding of how megaripples are created on planets such as Mars, and the sort of atmospheric conditions required to produce them rather than other types of sand waves.

"If we were able to use prevailing atmospheric conditions to explain the origin and migration of terrestrial and extraterrestrial sand waves, this would be an important step," says theoretical physicist Katharina Tholen, from Leipzig University. "It might then be possible to evaluate the sand structures we are currently observing, for example on Mars or in fossils and remote locations on Earth, as complex archives of past climatic conditions."

The research has been published in *Nature Communications*.

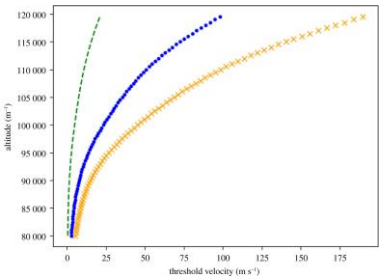
https://bit.ly/3tEqXi2

Model suggests vertical winds could push bacteria to an altitude beyond 120km

Strong vertical winds in the upper atmosphere could push bacteria higher than 120 km

by Bob Yirka , Phys.org

A pair of researchers at The Higgs Centre for Theoretical Physics in the U.K. has found evidence suggesting that strong vertical winds in the upper atmosphere could push bacteria higher than 120 km. In their paper published in *Proceedings of the Royal Society A*, Arjun Berera and Daniel Brener describe a model that shows how strong winds might behave in the upper reaches of the atmosphere.



***Threshold velocity equation (2.13) for three different test particles. Standard dust test particle of density 1000 kg m^{-3}, height and radius of a nanometre with a mass of ~3×10^{-24}kg (green dash). Virus-sized test particle of density 196 kg m^{-3}, thickness 109 nm (H1N1 virus from [65]) (blue dot). Small bacteria or bacteria organelle-sized test particle of density 2000 kg m^{-3}, height 40 nm, radius ~2 μm ~2 μm and mass 10^{-15}kg (orange cross).* Credit: DOI: 10.1098/rspa.2021.0626**

For many years, the scientific community believed that Earth's biosphere extended to approximately 75 km above the surface. More recent research has suggested that it might be higher than that—possibly as high as 120 km. This is because samples of bacteria have been found at these elevations. Bafflingly, astronauts aboard the ISS, which orbits at over 400 km, found bacteria clinging to the outside of the structure. Prior research has also shown that there are strong vertical winds blowing around in both the upper mesosphere and thermosphere. In this new effort, the researchers wondered if such strong winds, which have been measured at up to 100 m s^{-1}, could be blowing bacteria higher than previously thought. To find out, they created a model to simulate conditions in the upper atmosphere.

To make their model, the researchers added data from known sources such as measurements of wind speeds and data describing the size and weight of bacteria.

The simulations showed that bacteria could easily be carried up to elevations as high as 120 km—but because of limited data, that was the extent of the findings. But the researchers also noted that at such altitudes, the momentum of the bacteria carried by the wind could propel them much higher. They theorize that bacteria from the surface could be carried high enough to be impacted by space dust, which, they note, moves fast enough to carry it into space—and perhaps, to other planets. They note if their assumptions are correct, the same sort of activity could have occurred on Mars—bacteria there could have been blown here to Earth.

More information: *A. Berera et al, On the force of vertical winds in the upper atmosphere: consequences for small biological particles, Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences (2022). DOI: 10.1098/rspa.2021.0626*

https://bit.ly/3FKfm3L

Two decades of soldiers' medical records implicate common virus in multiple sclerosis

Vaccines under development against Epstein-Barr virus might prevent rare, devastating disease

By Jocelyn Kaiser

One hundred and fifty years after a French neurologist first recognized a case of multiple sclerosis (MS) in a young woman with an unusual tremor, the cause of this devastating disease remains elusive. Now, a study that combed data from regular blood tests of 10 million U.S. soldiers has found the strongest evidence yet that infection with a common virus, Epstein-Barr virus (EBV), dramatically increases a person's chances of developing the rare disease.

The work leaves many questions, such as why MS only affects about one in 1000 people even though nearly everyone will contract EBV in their lifetime. Still, "It provides probably the best evidence that can currently be obtained for a major pathogenic role of EBV in MS," says neurologist Hans Lassmann of the Medical University of Vienna, who was not involved in the study.

The study authors hope it will spur the development of a vaccine against EBV. The virus has been linked to several cancers and causes mononucleosis, and early vaccine testing is underway. Researchers then want to test whether vaccinating young people against EBV prevents MS.

MS develops when immune cells go awry and attack the myelin sheaths that insulate nerve fibers in the spinal cord and brain. The result is vision problems, pain, weakness, and numbness that can come and go, but worsen over time. Infusions of antibodies that deplete B cells, a type of white blood cell, can curb relapses. But the disease has no cure.

A combination of genetics—the disease often runs in families—and environmental triggers such as viruses is the likely cause. EBV, a herpesvirus that infects most people by adolescence and then lies latent in B cells throughout life, has long been a prime suspect. People who have had mono are at higher risk for MS. But although 99% of MS patients have had an EBV infection, 95% of those without MS have, too, making it difficult to pin down the virus' effects.

Ideally, researchers would track a group of young people who haven't yet been infected by EBV to see whether those who contract the infection are more likely to develop MS than those who don't. A team led by physician and epidemiologist Alberto Ascherio of the Harvard T.H. Chan School of Public Health found a clever way to do that. They probed a medical records database of 10 million active duty U.S. military personnel who enlisted between 1993 and 2013 and gave a blood sample every other year for HIV testing.

Eventually, 955 soldiers developed MS. Of the 801 with sufficient blood samples, 35 were negative for EBV in their first blood test; all but one became EBV positive during the study before developing MS on average 5 years later. By comparison, only half of 107 MS-free study participants used as controls became EBV positive during the same period, the researchers report today in *Science*. That means an EBV infection multiplies a person's risk of MS 32-fold, comparable to the increase in risk of getting lung cancer from heavy smoking, Ascherio says.

None of the other common viruses Ascherio and his team tested for showed an effect. To bolster their case, they showed that people who eventually developed MS had a rise in levels of a protein linked to neural degradation after their EBV infection. Ascherio believes the study clinches the case. "How do you explain the fact that you don't get MS unless you get EBV? There is no other alternative explanation," he says.

Others are cautious. The new evidence is "very exciting," but "it's still an association," says Jeffrey Cohen, a virologist at the National Institute of Allergy and Infectious Diseases. And the study doesn't explain why most people who get EBV don't develop MS, says neurologist Emmanuelle Waubant of the University of California, San Francisco. "Clearly other fuses have to be lit for the trigger to result in the disease," says Stanford University neuroimmunologist Lawrence Steinman, who co-authored a Perspective on the paper.

Also dissatisfying is the lack of a known mechanism for how EBV might cause the immune attack. Some researchers suspect EBV transforms B cells so they become pathogenic; others, including Steinman, suggest an EBV protein resembles a neural protein and teaches the immune system to attack nerves.

An EBV vaccine could help researchers prove the virus has a causal role by vaccinating a large cohort of young people at high risk for MS because of family history. Experimental evidence that a vaccine prevents cases would "tick the final box," says neurologist Gavin Giovannoni of Queen Mary University of London, who is working with the MS patient community to design such a study.

Several years ago, GlaxoSmithKline developed a vaccine based on

an EBV envelope protein but abandoned it after a trial showed it reduced the incidence of mono but didn't prevent EBV infections.

Two new candidate vaccines now in early clinical trials could be more potent. One developed by Cohen displays the same EBV protein on nanoparticles. Another from Moderna contains messenger RNA that instructs cells to make four different EBV proteins.

Vaccine expert Larry Corey of the Fred Hutchinson Cancer Research Center cautions that despite the potential public health benefits, there's no guarantee a company will take an EBV vaccine through licensing. Still, the new evidence firming up the role of EBV in MS "should make the risk benefit of that investment much greater," he says.

https://bit.ly/3rndRTN

Research Shows 1 in 10 People May Still Be Infectious for COVID After 10 Days

One in 10 people may have clinically relevant levels of potentially infectious SARS-CoV-2 past the 10 day quarantine period, according to new research.

One in 10 people may have clinically relevant levels of potentially infectious SARS-CoV-2 past the 10 day quarantine period, according to new research.

The study, led by the University of Exeter and funded by Animal Free Research UK, used a newly adapted test which can detect whether the virus was potentially still active. It was applied to samples from 176 people in Exeter who had tested positive on standard PCR tests.

The study, published in the *International Journal of Infectious Diseases* found that 13 percent of people still exhibited clinically-relevant levels of virus after 10 days, meaning they could potentially still be infectious. Some people retained these levels for up to 68 days. The authors believe this new test should be applied in settings where people are vulnerable, to stop the spread of COVID-19.

Professor Lorna Harries, of the University of Exeter Medical School, oversaw the study. She said: "While this is a relatively small study, our results suggest that potentially active virus may sometimes persist beyond a 10 day period, and could pose a potential risk of onward transmission. Furthermore, there was nothing clinically remarkable about these people, which means we wouldn't be able to predict who they are".

Conventional PCR tests work by testing for the presence of viral fragments. While they can tell if someone has recently had the virus, they cannot detect whether it is still active, and the person is infectious. The test used in the latest study however gives a positive result only when the virus is active and potentially capable of onward transmission.

Lead author Merlin Davies, of the University of Exeter Medical School, said: "In some settings, such as people returning to care homes after illness, People continuing to be infectious after ten days could pose a serious public health risk. We may need to ensure people in those setting have a negative active virus test to ensure people are no longer infectious. We now want to conduct larger trials to investigate this further."

Animal Free Research UK CEO, Carla Owen, said: "The University of Exeter team's discovery is exciting and potentially very important. Once more, it shows how focusing exclusively on human biology during medical research can produce results that are more reliable and more likely to benefit humans and animals.

"Pioneering animal free work is providing the best chance of not only defeating Covid 19 but also finding better treatments for all human diseases. "The results also send a loud and clear message to the Government to better fund modern medical research and make the UK a world leader in cutting edge, kinder science."

The research is a collaboration between the University of Exeter Medical School, the Royal Devon & Exeter NHS Foundation Trust, and the NIHR Exeter Clinical Research Facility.

Reference: "Persistence of clinically-relevant levels of SARS-CoV2 envelope gene subgenomic RNAs in non-immunocompromised individuals" by Merlin Davies, Laura R Bramwell, Nicola Jeffery, Ben Bunce, Ben P Lee, Bridget Knight, Cressida Auckland, Jane AH Masoli and Lorna W Harries, 7 December 2021, International Journal of Infectious Diseases. DOI: 10.1016/j.ijid.2021.12.312

https://bit.ly/3Ib0IUw

Compost is a major source of pathogenic aspergillus spores

Fourteen percent of Aspergillus fumigatus isolates cultured from garden soils were resistant to an agricultural triazole antifungal drug, tebuconazole.

Tebuconazole resistance confers resistance to medical triazoles that are used to treat aspergillosis, a lung infection that can be serious, which results from inhalation of *A. fumigatus* spores. The research is published in *Applied and Environmental Microbiology*, a journal of the American Society for Microbiology.

In the study, which was lead author Jennifer Shelton's Ph.D. thesis, she and her collaborators found that compost and compost-enriched soils contain high concentrations of *A. fumigatus* spores.

"The research suggests that handling compost presents a public health risk when individuals are exposed to large numbers of aerosolized spores and raises questions of whether compost bags should carry additional health warnings, whether compost should be sterilized before shipping, and whether individuals should be advised to wear face masks when handling compost," said Shelton.

A novel aspect of this study is that the soil samples—509 of them—were collected from their gardens by 249 citizen scientists whom Shelton enlisted in this effort via social media and through the Aspergillosis Trust, a charity raising awareness of the problem. The samples were all collected on the same day, June 21, 2019. From these, the investigators cultured 5,174 isolates of *A. fumigatus*. Many of these *A. fumigatus* isolates contained polymorphisms in the cyp51A gene, which is frequently associated with triazole-resistance. Soil samples containing compost were significantly more likely to grow tebuconazole-resistant *A. fumigatus* strains than those that did not, and compost samples grew significantly higher numbers of *A. fumigatus* than other soil samples.

The study was motivated by a growing number of cases caused by triazole resistant *A. fumigatus* spores in the UK, said Shelton, who conducted the research at Imperial College London and UK Centre for Ecology and Hydrology.

"An estimated 185,000-plus people in the UK live with aspergillosis, with conditions ranging from severe hypersensitization, "fungal asthma," and chronic colonization or invasion of the lungs that can disseminate to other organs including the brain," said Shelton. "Chronic forms of aspergillosis are life-limiting and difficult to treat, and invasive infections have mortality rates of between 40 and 70 percent, and higher if infected with triazole resistant *A. fumigatus*."

People normally inhale spores from the environment, including those of *A. fumigatus*. Those with weak immunity, due to immune-suppressing drugs, conditions such as diabetes or rheumatoid arthritis, or lung damage from infection by tuberculosis, COVID-19, severe influenza or smoking, are especially vulnerable, but even those without predisposing conditions can develop aspergillosis if they inhale sufficient numbers of spores.

"Our research suggests that handling compost and compost-enriched soils exposes individuals to large numbers of spores and that behavioral changes on their part, and action taken by the composting industry could reduce these exposures," said Shelton.

More information: *Jennifer M. G. Shelton et al, Citizen-science surveillance of triazole-resistant Aspergillus fumigatus in UK residential garden soils, Applied and Environmental Microbiology (2022). DOI: 10.1128/AEM.02061-21*

https://bit.ly/34P080h

Pioneering Test Reliably Predicts the Spread or Return of Deadly Skin Cancer

New test developed as mechanism of skin cancer growth understood.

A pioneering test that reliably predicts the spread or return of the most deadly form of skin cancer has been developed by a team of Newcastle scientists and clinicians. The technological advance came as they made a scientific breakthrough in understanding the mechanism of skin cancer growth.

Led by Professor Penny Lovat at Newcastle University, UK, in association with the University spin out company AMLo Biosciences, the test offers reassurance for patients diagnosed with an early stage melanoma.

By applying the test – called AMBLor® – to the standard biopsy of the primary melanoma on its removal, patients who are at low risk of the disease reoccurring or spreading can be identified.

With the support of the National Institute for Health Research (NIHR) to develop the provision and working with AMLo Biosciences, a referral service is now available where sections from a patient's melanoma can be posted to a lab for analysis.

The test identifies a patient's true risk of disease progression and provides anyone diagnosed with a non-ulcerated early stage melanoma – accounting for around 75% of all new diagnoses – more accurate information about the risk of the disease spreading.

Now the scientists have demonstrated the mechanism in the skin which underpins the test, publishing the research in the *British Journal of Dermatology*.

Melanoma growth

Melanoma is increasing worldwide and every year more than 16,000 people in the UK and 96,000 people in the US are diagnosed with the cancer.

In the new research, the authors explain how early stage melanomas at risk of spreading secrete a growth factor, TGFß2 which causes the reduction, or downregulation, of the proteins AMBRA1 and Loricrin – both of which are found in the skin overlaying the tumor. The growth factor TGFß2 also causes the loss of claudin-1 leading to loss of the integrity of the skin and facilitating ulceration.

Senior author Professor Penny Lovat, Professor of Cellular Dermatology and Oncology at Newcastle University and Chief Scientific Officer at AMLo Biosciences explains: "Like mortar and bricks holding together a wall, AMBRA1, Loricrin and Claudin 1 are all proteins key to maintaining the integrity of the upper layer of the skin. When these proteins are lost gaps develop – like the mortar crumbling away in the wall. This allows the tumor to spread and ultimately ulcerate which we know is a process associated with higher risk tumors. "Our new understanding of this biological mechanism underpins the test we have available."

Cory Inglis, 49, lives on the South Coast and AMBLor®is about to be used on his standard biopsy after a diagnosis of a melanoma on his back. He explained: "When you sit down with a dermatologist after the initial excision, you hear that it wasn't a mole, it was a melanoma. You are in a state of fear. It's overwhelming. At that moment a lot of the information that is provided is in very impenetrable, technical language. You ask yourself, what does it mean for me? To be able to have a test like this which provides you with result of the melanoma being low or at risk can help your medical team communicate the information in a way that is comprehensible, and importantly to help them to make the right subsequent decisions for you.

"A test, like AMBLor® which tells you that your tumor is genuinely low risk helps significantly with the anxiety of an already very stressful situation.

"Patients will understand what a low risk result means. If the result

is at risk, it completely justifies the significant number of interactions that you will have with the dermatology team over a five year period. I don't see any downside in providing the dermatology team with more information about your melanoma."

Professor Penny Lovat added: "Our test offers a personalized prognosis as it more accurately predicts if your skin cancer is unlikely to spread. This test will aid clinicians to identify genuinely low risk patients diagnosed with an early stage melanoma and to reduce the number of follow up appointments for those identified as low risk, saving NHS time and money."

Phil Brady, Chief Operating Officer, British Skin Foundation said: "The British Skin Foundation is proud to support Prof Penny Lovat's ground-breaking melanoma research. The development of the AMBLor test can alleviate stress and anxiety for patients caused by this potentially deadly skin cancer, whilst increasing efficiency and reducing costs to the NHS."

Professor Nick Levell, Consultant Dermatologist & British Skin Foundation spokesperson who has not been involved in the research said: "This is excellent news. This new test for melanoma will help many people with skin cancer. People at low risk can be reassured and will not have to attend hospital so often for check-ups. This British Skin Foundation co-funded research is an important step forward in making care after melanoma more personal."

Currently, primary tumors are removed by surgery and pathologists study the biopsy under the microscope to determine the stage the skin cancer is at and the risk of it spreading (metastasis). Even if defined as low risk, the patient is followed up in clinic for as long as five years – and it is these patients that the test is able to identify.

The AMBRA1 and loricrin test is accredited by UKAS and is already available through a private referral service from the spin out company, AMBLo Biosciences. The test involves tissue sections from the standard biopsy being sent in the post to the lab for analysis. The Newcastle team have also submitted an application for the test to be made available on the NHS.

Reference: "Melanoma secretion of TGFß-2 leads to loss of epidermal AMBRA1 threatening epidermal integrity and facilitating tumour ulceration" by I. Cosgarea, A.T. McConnell, T. Ewen,D. Tang, D.S. Hill, M. Anagnostou, M. Elias,R.A. Ellis, A. Murray, L.C. Spender, P. Giglio, M. Gagliardi, A. Greenwood, M. Piacentini, G.J. Inman, G.M. Fimia, M. Corazzari, J.L. Armstrong and P.E. Lovat, 13 November 2021, British Journal of Dermatology. DOI: 10.1111/bjd.20889

https://bit.ly/34X4anB

New Links Discovered Between Brain Cell Development and Psychiatric Disorders – "Major Step Forward"

Cardiff University study is 'major step forward' in hunt for developmental origins of schizophrenia and other psychiatric disorders.

Scientists from Cardiff University have discovered new links between the breakdown in brain cell development and the risk of schizophrenia and other psychiatric disorders.

Genetic risk factors are known to disrupt brain development in a number of these disorders, but little is known about which aspects of this process are affected.

This research is the first time that genetic disruption of specific cell processes crucial to brain development has been linked to disease risk in a wide range of psychiatric disorders.

The findings are published today (January 14, 2022) in the journal *Nature Communications.*

The study was jointly led by Dr. Andrew Pocklington from the Division of Psychological Medicine and Clinical Neurosciences at Cardiff University and Dr. Eunju Jenny Shin from the Neuroscience and Mental Health Research Institute at Cardiff University and now at Keele University.

Dr. Pocklington said: "Genetic factors play a significant role in determining a person's risk of developing psychiatric disorders.

Uncovering biological processes impacted by these genetic risk factors is a major step towards understanding the causes of disease."

Dr. Shin said: "To truly understand the root causes of psychiatric disorders, we focused on studying the development of brain cells. The knowledge gained through this approach may ultimately help guide the development of novel therapies or help explain why some individuals respond to some treatments but not others."

The scientists studied the birth and early development of human brain cells – a process known as neurogenesis – in vitro using human pluripotent stem cells.

They identified several sets of genes that are switched on during neurogenesis – both in vitro and in human fetal brain – with each set appearing to play a distinct functional role. The researchers showed that genetic risk factors contributing to schizophrenia and other psychiatric disorders were highly concentrated in these sets.

Dr. Shin said: "In vitro experiments showed that when activation of these sets is disrupted, the shape, movement and electrical activity of developing brain cells is altered, linking changes in these properties to disease."

Disorders linked to disruption of these genes included both early onset conditions (developmental delay, autism, and ADHD) and, more surprisingly, conditions with a later onset (bipolar disorder, major depression) for which disruption of early brain development is not generally thought to play a large role.

This raises the question of whether some of these genes – which are first switched on long before birth – remain active later in life and contribute to mature brain function, where they can potentially be targeted therapeutically.

Dr. Pocklington said: "Previous studies have shown that genes active in mature brain cells are enriched for common genetic variants contributing to schizophrenia. Much of this enrichment was captured by the early developmental gene sets, which seem to contain a greater burden of common genetic risk factors.

"This suggests that some biological pathways first switched on in the early prenatal brain may remain active in later life, with genetic variation in these pathways contributing to disease by disrupting both development and mature brain function."

Further work is needed to map out the full range of developmental processes disrupted in different psychiatric disorders and explore their longer-term effects on the brain.

Dr. Shin said: "Although much remains to be uncovered, our findings provide valuable insight into the developmental origins of psychiatric disorders such as schizophrenia."

Reference *"Transcriptional programs regulating neuronal differentiation are disrupted in DLG2 knockout human embryonic stem cells and enriched for schizophrenia and related disorders risk variants" by Bret Sanders, Daniel D'Andrea, Mark O. Collins, Elliott Rees, Tom G. J. Steward, Ying Zhu, Gareth Chapman, Sophie E. Legge, Antonio F. Pardiñas, Adrian J. Harwood, William P. Gray, Michael C. O'Donovan, Michael J. Owen, Adam C. Errington, Derek J. Blake, Daniel J. Whitcomb, Andrew J. Pocklington and Eunju Shin, 14 January 2022, Nature Communications. DOI: 10.1038/s41467-021-27601-0*

https://bit.ly/3qzetql

Phosphorene nanoribbons find their first use in a solar cell just 3 years after discovery

Phosphorene nanoribbons – a promising material synthesised just three years ago – have already found their first application, in a perovskite solar cell.[1]

By Fernando Gomollón-Bel

'It is impressive that such excellent results have come through [the] pipeline so rapidly,' comments David Lewis from the University of Manchester, UK, who was not involved in the study.

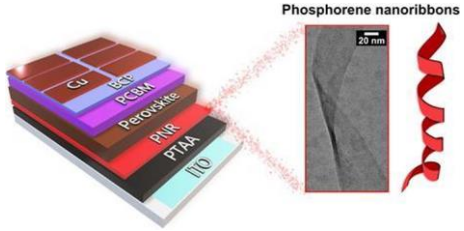
Phosphorene is a monolayer material obtained by exfoliating black phosphorus crystals. Nanoribbons made from phosphorene are an atom thick layer, however unlike 2D sheets they're only tens of atoms wide, explains Chris Howard from University College

London, UK, co-author on this paper. Howard's team first isolated and characterised these structures in 2019.[2] 'Our work was motivated by hundreds of theory papers predicting extraordinary properties for phosphorene nanoribbons,' he says. Some of these potential applications include fast-charging batteries, quicker transistors and more efficient optoelectronic devices for high-speed telecommunications.

Howard's team, in collaboration with solar cell experts at Imperial College London, UK, has now enhanced the performance of perovskite devices using phosphorene nanoribbons. 'We simply add [them] between the semiconducting polymer and the perovskite absorber layers,' explains Tom Macdonald from Imperial, who led the study.

Perovskite solar cells separate positive and negative charge carriers after absorbing light, explains Lewis. This leads to the generation of electrical currents. Semiconductors like phosphorene nanoribbons enhance the extraction of positive charges or holes. 'The addition of phosphorene nanoribbons provides a favourable energy alignment between the [layers], allowing a more effective avenue for hole extraction,' explains Macdonald.

The 'incredibly high mobility' of phosphorene also boosts performance. Improving the efficiency of hole extraction 'provides a new strategy to improve the overall efficiency of these devices', Lewis adds. 'The authors show this unambiguously with a nice suite of experiments.'



Inverted perovskite solar cell device stack with phosphorene nanoribbons (PNR) sandwiched between poly(triarylamine) (PTAA) and the perovskite (BC, bathocuproine; fullerene derivative, PCBM and indium tin oxide, ITO)
Source: © Thomas J Macdonald, Thomas Webb and Vaso Tileli

The researchers added the extra layer of phosphorene nanoribbons using spin-coating, a standard technique in perovskite solar cell production. This is an 'advantage of the simple processability of phosphorene nanoribbons in solution', explains Macdonald. This process involves separating the individual phosphorene layers from crystalline black phosphorus and adding a lithium salt in a solvent, explains Lewis. 'This means a myriad of opportunities for scale-up, [as] you could make large batches of the material,' he adds. Macdonald says that 'scale-up is certainly part of our future plans'.

Researchers now expect many applications beyond solar cells. 'The future is very bright for phosphorene nanoribbons in optoelectronics,' says Macdonald. Lewis agrees and says the 'really exciting part' is how just a very thin layer of phosphorene nanoribbons yields 'dramatic improvements'. '[We] will see many applications using this interlayer engineering approach in other devices,' he adds.

Macdonald confirms that they're already exploring the possibilities of phosphorene nanoribbons in light-emitting diodes and batteries, among other things. 'This [is] only the tip of the iceberg.'

References

*1 TJ Macdonald et al, J. Am. Chem. Soc., 2021, **143**, 21549 (DOI: 10.1021/jacs.1c08905)*
*2 MC Watts et al, Nature, 2019, **568**, 216 (DOI: 10.1038/s41586-019-1074-x)*

https://bit.ly/3qxexXn

Shkreli's infamous 4,000% price hike gets him a lifetime pharma ban

New York's attorney general celebrated with Wu-Tang Clan references.

Beth Mole

A federal court on Friday banned convicted fraudster Martin Shkreli from ever working in the pharmaceutical industry again in any capacity and ordered him to pay back $64.6 million in profits from his infamous scheme that raised the price of the life-saving

drug Daraprim more than 4,000 percent.

US District Judge Denise Cote issued the lifetime ban after finding that Shkreli engaged in anticompetitive practices to protect the monopoly profits of Daraprim.

According to a lawsuit filed by the Federal Trade Commission and seven states—New York, California, Illinois, North Carolina, Ohio, Pennsylvania, and Virginia—Shkreli, his former pharmaceutical company Vyera (formerly Turing), and former Vyera CEO Kevin Mulleady created a "web of anticompetitive restrictions to box out the competition" in 2015 after they bought the rights to Daraprim.

Daraprim is a cheap, decades-old anti-parasitic drug used to treat toxoplasmosis, which often sickens people with compromised immune systems (such as AIDS patients) and can be deadly to newborns. Shkreli and Mulleady allegedly set up a complex scheme that kept the drug out of the hands of competitors, restricted suppliers from selling critical drug ingredients to competitors, and blocked the release of sales data that would reveal the market size to competitors.

Meanwhile, Shkreli and Mulleady abruptly hiked the list price of Daraprim by more than 4,000 percent, from $17.50 to $750 per tablet.

A better tomorrow

In Cote's ruling Friday, she concluded that Shkreli "was the mastermind of [Vyera's] illegal conduct and the person principally responsible for it throughout the years." His lifetime ban and the order to pay $64.6 million in disgorgement "serves the interests of justice," she wrote.

In a press release Friday, New York Attorney General Letitia James celebrated the ruling with some Wu-Tang Clan references.

"'Envy, greed, lust, and hate,' don't just 'separate,' but they obviously motivated Mr. Shkreli and his partner to illegally jack up the price of a life-saving drug as Americans' lives hung in the balance," Attorney General James said, referencing lyrics from Wu-Tang Clan's *A Better Tomorrow*.

"But Americans can rest easy because Martin Shkreli is a pharma bro no more… The rich and powerful don't get to play by their own set of rules, so it seems that cash doesn't rule everything around Mr. Shkreli," Attorney General James continued.

Friday's ruling follows a settlement announced last month in which Vyera and its parent company, Phoenixus, agreed to pay up to $40 million to victims of the Daraprim scheme. The settlement also required the companies to make Daraprim available to competitors at cost and barred them from entering into any similar scheme for 10 years. Mulleady was banned from the pharmaceutical industry for seven years.

Shkreli is currently serving a seven-year prison sentence from a 2017 securities fraud conviction related to two hedge funds he ran prior to the Daraprim scheme. Following his fraud conviction, he was ordered to forfeit $7.36 million in assets, including the sole copy of the Wu-Tang album *Once Upon a Time in Shaolin*, which he bought in 2015 at auction from Wu-Tang member RZA for $2 million.