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Exposure to Chemical from Babies Linked to Aggression

A study finds that the odorless compound hexadecanal, or HEX, increases aggressive behavior in women but has a calming effect on men.

Chloe Tenn

Pheromones famously trigger the olfactory system in animals, and have been linked to mating and aggressive behavior. For example, compounds in mouse urine can induce male mice to fight each other, and a rabbit mother will attack her own offspring if she smells a different female rabbit, according to *Science*. However, the presence of pheromones in humans has not been confirmed. In a study published in *Science Advances* on November 19, scientists identified a compound known as hexadecanal that seems to increase aggression in women who smell it but suppress aggression in men.

Eva Mishor, a study coauthor and neuroscientist at the Weizmann Institute of Science in Israel tells *New Scientist*, "Our study gives more power to the notion that humans communicate from the chemical volatiles they emit, and that we get lots of information from them."

Hexadecanal, abbreviated HEX, is a chemical that humans emit from their skin, saliva, and feces, and is particularly abundant on babies' heads, reports *Science*. Previous research found that smelling HEX has a relaxing effect on mice. In the new study, Mishor and her colleagues investigated whether HEX might affect human behavior—and, by extension, what role scent might play in human social interactions.

The study exposed 127 participants to a computer game designed to frustrate them by resulting in an unfair division of money. (Participants were told they were playing against another person, but were in fact playing against the computer.) The experimental group had HEX scent strips applied to their upper lips while playing the game, and the control group had an identical strip without HEX applied to their upper lips. A follow up game allowed participants to blast their imaginary opponents with a noise loudness of their choosing, represented by increasingly angrier emojis. Women who smelled HEX responded 19 percent more aggressively in the follow up noise-blast test compared to women who didn't, while men who smelled HEX responded 18.5 percent less aggressively than men who didn't.

The scientists then used fMRI to measure the brain activity of participants while they were exposed to HEX delivered through an olfactometer. As they were scanned, participants were provoked by having money taken away via the computer game and expressed aggression by taking money from others. The scans showed decreased connectivity between brain regions associated with aggression and social cues—a marker of aggressive feelings—in women exposed to HEX compared to controls, and the opposite in men.

Study coauthor and neuroscientist Noam Sobel, also of the Weizmann Institute, tells *Science* that this study does not conclude that HEX is a pheromone because it did not explore whether people emit more of the chemical when feeling aggressive, an important criteria for it to be considered a human signaling pheromone, "But we can say that it's a molecule expressed by the human body that influences human behavior, specifically aggressive behavior, in a predicted manner." New York University neuroscientist Dayu Lin, who was not involved with the research, tells the magazine that the study exhibits "pretty convincing evidence that HEX can modulate aggression in humans in a sex-specific way."

The paper's authors hypothesize in the study that the differing effects of HEX may have to do with survival of babies. "Whereas maternal aggression has a direct positive impact on offspring

survival in the animal world, paternal aggression has a negative impact on offspring survival. This is because maternal aggression (also termed maternal defense behavior) is typically directed at intruders, yet paternal aggression, and more so nonpaternal male aggression, is often directed at the offspring themselves," the authors write.

Radboud University behavioral scientist Jasper de Groot, who was not involved in the work, tells *New Scientist* that a limitation of the study was that it did not measure physiological reactions to the HEX odor. University of Oxford biologist Tristram Wyatt, who specializes in the evolution of pheromones and was not involved with the study, calls the author's explanations for HEX's influence on human behavior speculative in comments to *Science*. He adds that psychological experiments are very difficult to replicate and that the researchers did not provide evidence that humans emit enough HEX to provoke an olfactory response. He calls for a more rigorous approach and cautions that "It's fascinating research, but I'm not sure how much weight to put on it."

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Aspirin Linked With Increased Risk of Heart Failure in New Study

Aspirin use is associated with a 26% raised risk of heart failure in people with at least one predisposing factor for the condition.

That's the finding of a study published today (November 22, 2021) in *ESC Heart Failure*, a journal of the European Society of Cardiology (ESC). Predisposing factors included smoking, obesity, high blood pressure, high cholesterol, diabetes, and cardiovascular disease.

"This is the first study to report that among individuals with a least one risk factor for heart failure, those taking aspirin were more likely to subsequently develop the condition than those not using the medication," said study author Dr. Blerim Mujaj of the University of Freiburg, Germany. "While the findings require confirmation, they do indicate that the potential link between aspirin and heart failure needs to be clarified."

The influence of aspirin on heart failure is controversial. This study aimed to evaluate its relationship with heart failure incidence in people with and without heart disease and assess whether using the drug is related to a new heart failure diagnosis in those at risk.

The analysis included 30,827 individuals at risk for developing heart failure who were enrolled from Western Europe and the US into the HOMAGE study. "At risk" was defined as one or more of the following: smoking, obesity, high blood pressure, high cholesterol, diabetes, and cardiovascular disease. Participants were aged 40 years and above and free of heart failure at baseline. Aspirin use was recorded at enrolment and participants were classified as users or non-users. Participants were followed up for the first incidence of fatal or non-fatal heart failure requiring hospitalization.

The average age of participants was 67 years and 34% were women. At baseline, a total of 7,698 participants (25%) were taking aspirin. During the 5.3-year follow-up, 1,330 participants developed heart failure.

The investigators assessed the association between aspirin use and incident heart failure after adjusting for sex, age, body mass index, smoking, alcohol use, blood pressure, heart rate, blood cholesterol, creatinine, hypertension, diabetes, cardiovascular disease, and treatment with renin-angiotensin-aldosterone-system inhibitors, calcium channel blockers, diuretics, beta-blockers, and lipid-lowering drugs. Taking aspirin was independently associated with a 26% raised risk of a new heart failure diagnosis.

To check the consistency of the results, the researchers repeated the analysis after matching aspirin users and non-users for heart failure risk factors. In this matched analysis, aspirin was associated with a

26% raised risk of a new heart failure diagnosis. To check the results further, the analysis was repeated after excluding patients with a history of cardiovascular disease. In 22,690 participants (74%) free of cardiovascular disease, aspirin use was associated with a 27% increased risk of incident heart failure.

Dr. Mujaj said: “This was the first large study to investigate the relationship between aspirin use and incident heart failure in individuals with and without heart disease and at least one risk factor. Aspirin is commonly used – in our study one in four participants were taking the medication. In this population, aspirin use was associated with incident heart failure, independent of other risk factors.”

He concluded: “Large multinational randomized trials in adults at risk for heart failure are needed to verify these results. Until then, our observations suggest that aspirin should be prescribed with caution in those with heart failure or with risk factors for the condition.”

Reference: “Aspirin use is associated with increased risk for incident heart failure: a patient-level pooled-analysis” by Mujaj B, Zhang ZY, Yang WY, et al., 22 November 2021, ESC Heart Failure. DOI: 10.1002/ehf2.13688

Funding: The European Union (HEALTH-F7-305507 HOMAGE), the European Research Council (Advanced Researcher Grant 2011-294713-EPLORE, the European Research Council Proof-of-Concept Grant 713601-uPROPHET), and the European Research Area Net for Cardiovascular Diseases (JTC2017-046-PROACT) supported the Research Unit Hypertension and Cardiovascular Research. The Non-Profit Association Alliance for the Promotion of Preventive Medicine (APPREMED; URL, http://www.appremed.org), Mechelen, Belgium, received a nonbinding grant from OMRON Healthcare, Co, Ltd, Kyoto, Japan. The sponsors had no role in the preparation of this report.

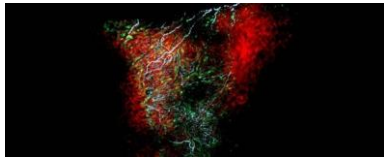
https://bit.ly/3DQeCd3

A New Kind of Cell Discovered in The Heart Seems to Be Critical For Your Heartbeat

Discovery promises to advance our understanding of cardiovascular defects and diseases

David Nield

A new type of cell has been identified in the heart that is linked to regulating heart rate – and the discovery promises to advance our understanding of cardiovascular defects and diseases, once these cells have been more extensively studied.



Astrocyte-like cardiac nexus glia (green) in a zebrafish heart (red). **(Nina L. Kikel-Coury/Smith Lab)**

The new cell is a type of glial cell – cells that support nerve cells – like astrocytes in the central nervous system (the brain and spinal cord). Named nexus glia, they're located in the outflow tract of the heart, the place where many congenital heart defects are found.

The new cell type was first found in zebrafish, before being confirmed in mouse and human hearts too. Experiments on zebrafish found that when the cells were removed, heart rate increased; and when genetic editing blocked glial development, the heartbeat became irregular.

"We don't completely know the function of these cells, but the concept that if you get rid of them, heart rates increase, could link it to certain disease cases," says biologist Cody Smith from the University of Notre Dame in Indiana.

"I think these glial cells could play a pretty important role in regulating the heart. This is another example of how studying basic neurobiology can lead to the understanding of many different disorders."

Finding the nexus glia cells took plenty of detective work. It was previously thought that star-shaped glia (astroglia) such as astrocytes could only be found in the brain and spinal cord, although "glial-like processes" had already been spotted in the heart. Astroglia cells are important to the central nervous system because they help maintain the cellular environment for neurons and provide support and nutrients for them as well. So it seems

plausible that they should be found in the peripheral nervous system (the remaining nerves in the body) too, the researchers reasoned.

Different types of glial cells with astroglia properties have been found in other organs – including the pancreas and the lungs – but their function isn't yet well understood. That led the team to the heart in their search for new types of cells.

"I thought that if we could find a new cellular piece to the cardiovascular puzzle, it could be foundational for future work," says biologist Nina Kikel-Coury from the University of Notre Dame.

Sure enough, a combination of scientific techniques – including time-lapse imaging and single-cell sequencing – revealed the presence of nexus glia in zebrafish, mouse, and human tissue, in cells which appear to support heart function and regulation.

Having only just discovered these cells, it's going to take more time to learn about their roles and functions, but they could potentially be linked to a variety of medical conditions – including something called dysautonomia, caused by breakdowns in the normal workings of the autonomic nervous system, which the brain uses to control involuntary physiological processes like heart rhythm and breathing.

Another possible avenue for future research is analyzing other key organs in the body for cells similar to nexus glia – they could be hidden away, secretly providing crucial support to the way that our biological systems function.

"For me the definition of great science is something that you discover that opens up even more questions, and this, I think, is the definition of that," says Smith.

"It's a discovery that now we have 100 questions we didn't even know existed, so we're following up on them to explore this path that has never been studied before."

The research has been published in *PLOS Biology*.

https://bit.ly/3laPTsw

We expected people with asthma to fare worse during COVID. Turns out they've had a break

Intuitively, a disease that attacks the lungs should put asthma sufferers at much greater risk

Bruce Thompson*

There were fears at the beginning of the COVID pandemic that people with asthma would fare much worse than those without it. Intuitively, a disease that attacks the lungs should put asthma sufferers at much greater risk. But this hasn't been borne out.

Firstly, it's turned out people with asthma are at slightly lower risk of acquiring COVID, being hospitalised with it or indeed dying from it compared to people without asthma. Though, someone with asthma who is hospitalised with COVID is slightly more likely to require ICU admission. In addition, asthma attack rates have substantially reduced in many parts of the world.

What explains this?

Asthma sufferers aren't getting sicker from COVID

Asthma is an umbrella term for a range of diseases of the airways, which have similar outcomes – constriction of the airways causing difficulty breathing. In some forms of asthma the constriction is a result of inflammation, or rash, within the lung.

Many people with asthma take asthma preventers, which are a type of steroid drug we lung experts call "inhaled corticosteroids". These drugs reduce the amount of inflammation in the lungs.

Interestingly, another steroid, dexamethasone, is being used as a treatment for COVID for this same reason.

Asthmatics might be inadvertently reducing the risk of severe COVID if they contract it by regularly using their preventers, because they are "pre-treated" if you like.

Indeed some preventers are thought to be "anti SARS-CoV-2", that is, they have some ability to kill the virus that causes COVID.

What's more, some good evidence from Australia demonstrates that patients with asthma have decreased "ACE2 gene expression". ACE2 is the point of entry for the SARS-CoV-2 virus to get into our cells. If you have less ACE2 then there are fewer gateways for the virus to enter our cells, and there's less opportunity for the infection to take hold.

Why have asthma attacks declined?

There a number of possible reasons why asthma attacks have declined. Asthma is a chronic condition which can flare up when sufferers are exposed to their "triggers". Common ones are pollens, chemicals, dust mites, pets, mould, smoke, or viruses.

Social distancing and locking down millions of people around the world has been a real time case study in what staying at home would do to asthma rates.

Because people in lockdown go outside a lot less, it could reduce their exposure to pollen and other allergens and irritants outdoors such as smoke, thereby reducing asthma attacks.

What's more, social distancing and lockdowns also significantly reduce the number of interactions between people, thereby reducing the spread of infectious diseases. We've been able to reduce COVID cases this way, and flu cases too. In 2019, there were 302,084 flu cases notified to health departments in Australia. And that was with a significant proportion of the population vaccinated.

In 2021, up to November 7, there have been just 598 flu cases.

Along with this, we can presume there have been far fewer common colds and other types of infectious diseases.

Viruses can cause asthma flare ups, which is known by lung experts as "viral exacerbation of asthma". So fewer people with colds and the flu could also contribute to lower asthma attack rates.

There have also been reports of fewer people seeking medical care for fear of contracting COVID in health-care settings, which may be another reason for fewer people seeking care for asthma.

What will happen to asthma post-COVID?

We're used to tolerating a certain level of many infectious diseases in the community, particularly things like common colds, strep throat, even glandular fever and the flu.

For many of us, this is no big deal and the only effects are feeling not great for a few days or weeks of the year.

But for many others, these sorts of common infectious illnesses can be deadly. Think about someone with cystic fibrosis, which severely damages the lungs and digestive system. If they get a cold or the flu, it can seriously knock them around, or even kill them. Same with someone who takes medications to depress their immune system, for example people with rheumatoid arthritis.

These infections result in many hospitalisations, which puts pressure on the whole hospital system.

From COVID, we know there are simple measures we can take to substantially reduce the transmission of these seemingly "benign" diseases, including wearing masks, not going to work or socialising when you're sick, and washing/sanitising your hands regularly.

We've reached the milestone of having more than 80% of Australians over 16 fully vaccinated against COVID, and international travel is resuming. Returning travellers are likely to bring with them new flu strains that we're totally unprepared for.

Usually flu vaccines for Australia are designed to tackle strains from the Northern Hemisphere winter so we're prepared for when the new strain arrives in our winter.

But there has been such little flu overseas, and with the understandable focus on COVID, our vaccines for flu and other existing conditions may need to be revisited.

Not revisiting existing vaccines for flu and other previously common conditions may lead to a wave of flu and many other diseases, given we'll have limited immunity to them. So we may soon see asthma attacks take off again, exacerbated by viruses.

*Professor and Dean of the School of Health Sciences, Swinburne University of Technology

Disclosure statement *Bruce Thompson receives research funding from the NHMRC, is immediate past president of the Thoracic Society of Australia and New Zealand and has received speaker fees from GSK, Mundipharma, Chiesi and Astra Zeneca.*

Partners *Swinburne University of Technology provides funding as a member of The Conversation AU.*

https://wb.md/30VJ1Zr

'Misleading' Results in Colchicine COVID-19 Trials Meta-Analysis

Inclusion of trials studying differing patient populations and testing different outcomes led to "misleading" results

Jeff Craven

A new meta-analysis appears to show that colchicine has no benefit as a treatment for COVID-19, but its inclusion of trials studying differing patient populations and testing different outcomes led to "misleading" results, says a researcher involved in one of the trials.

The meta-analysis, which includes data from the recent Randomised Evaluation of COVID-19 therapy (RECOVERY) trial, was published in *RMD Open* on November 22.

Kedar Gautambhai Mehta, MBBS, MD, of the GMERS Medical College Gotri in Vadodara, Gujarat, India, and colleagues included outcomes from six studies of 16,148 patients with COVID-19 who received colchicine or supportive care. They evaluated the efficacy outcomes of mortality, need for ventilation, intensive care unit (ICU) admission, and length of stay in hospital, as well as safety outcomes of adverse events, serious adverse events, and diarrhea.

The studies in the meta-analysis included a randomized, controlled trial (RCT) of 105 patients hospitalized with COVID-19 in Greece, the international, open-label RECOVERY RCT of 11,340 patients hospitalized with COVID-19, an RCT of 72 hospitalized patients with moderate or severe COVID-19 in Brazil, an RCT of 100 patients hospitalized with COVID-19 in Iran, the international COLCORONA trial of 4488 patients with COVID-19 who were treated with colchicine or placebo on an outpatient basis, and the randomized COLORIT trial of 43 patients hospitalized with COVID-19 in Russia.

Studies "Asked Very Different Questions" About Colchicine

Commenting on the meta-analysis, Michael H. Pillinger, MD, a rheumatologist and professor of medicine, biochemistry, and molecular pharmacology with NYU Grossman School of Medicine in New York, said the authors combined studies "that are not comparable and that asked very different questions." Two of the studies in the meta-analysis are very large, and four are very small, which skews the results, he explained.

"The larger studies therefore drive the outcome, and while the small studies are potentially insight-providing, the large studies are the only ones worth giving our attention to in the context of the meta-analysis," he said. The two largest studies — RECOVERY and COLCORONA — taken together show no benefit for colchicine as a treatment, even though the former demonstrated no benefit and the latter did show a benefit, explained Pillinger, a co–principal investigator for the COLCORONA trial in the United States.

The studies were designed differently and should not have been included in the same analysis, Pillinger argued. In the case of COLCORONA, early treatment with colchicine was the intervention, whereas RECOVERY focused on hospitalized patients.

"In designing [COLCORONA], the author group (of whom I was a member) expressly rejected the idea that colchicine might be useful for the sicker hospitalized patients, based on the long experience with colchicine of some of us as rheumatologists," Pillinger said.

"In short, COLCORONA proved a benefit of colchicine in outpatient COVID-19 and its authors presumed there would be no inpatient benefit; RECOVERY went ahead and proved a lack of

inpatient benefit, at least when high-dose steroids were also given," he said. "While there is no conflict between these results, the combination of the two studies in this meta-analysis suggests there might be no benefit for colchicine overall, which is misleading and can lead physicians to reject the potential of outpatient colchicine, even for future studies."

Pillinger said he still believes colchicine has potential value as a COVID-19 treatment option for patients with mild disease, "especially for low-vaccine rate, resource-starved countries. "It would be unfortunate if meta-analyses such as this one would put a stop to colchicine's use, or at least its further investigation," he said.

Study Details

The authors of the study assessed heterogeneity of the trials' data across the outcomes using an I^2 test. They evaluated the quality of the evidence for the outcomes using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

The results of their meta-analysis showed that colchicine offered no significant improvement in mortality in six studies (risk difference, -0.0; 95% CI, -0.01 to 0.01; I^2 = 15%). It showed no benefit with respect to requiring ventilatory support in five studies of 15,519 patients (risk ratio, 0.67; 95% CI, 0.38 – 1.21; I^2 = 47%); being admitted to the ICU in three studies with 220 patients (RR, 0.49; 95% CI, 0.19 to 1.25; I^2 = 34%); and length of stay while in the hospital in four studies of 11,560 patients (mean difference, -1.17; 95% CI, -3.02 to 0.67; I^2 = 77%).

There was no difference in serious adverse events in three studies with 4665 patients (RD, -0.01; 95% CI, -0.02 to 0.00; I^2 = 28%) for patients who received colchicine compared with supportive care alone. Patients who received colchicine were more likely to have a higher rate of adverse events (RR, 1.58; 95% CI, 1.07 – 2.33; I^2 = 81%) and to experience diarrhea (RR, 1.93; 95% CI, 1.62 – 2.29; I^2 = 0%) than were patients who received supportive care alone. The researchers note that for most outcomes, the GRADE quality of evidence was moderate.

"Our findings on colchicine should be interpreted cautiously due to the inclusion of open-labeled, randomized clinical trials," Mehta and colleagues write. "The analysis of efficacy and safety outcomes are based on a small number of RCTs in control interventions."

The authors reported no relevant financial relationships. Pillinger is co–principal investigator of the US component of the COLCORONA trial; he reported no other relevant conflicts of interest.

RMD Open. Published online November 23, 2021. Full text

https://wb.md/3oZo3Rj

New Blood Test May Detect Preclinical Alzheimer's Years in Advance

A new blood test that identifies a variant of the protein P53 appears to predict Alzheimer's disease (AD) progression up to 6 years in advance of a clinical diagnosis, early research suggests.

Pauline Anderson

Analysis of two studies showed the test (AlzoSure Predict), which uses less than 1 ml of blood, had numerous benefits compared with other blood tests that track AD pathology.

"We believe this has the potential to radically improve early stratification and identification of patients for trials 6 years in advance of a diagnosis, which can potentially enable more rapid and efficient approvals of therapies," Paul Kinnon, CEO of Diadem, the test's manufacturer, told *Medscape Medical News.*

The findings were presented at the 14th Clinical Trials on Alzheimer's Disease (CTAD) conference.

Positive "Discovery" Results

P53, which is present in both the brain and elsewhere in the body, "is one of the most targeted proteins" for drug development in cancer and other conditions, said Kinnon.

The current blood test measures a derivative of P53 (U-$p53^{AZ}$).

Previous research suggests this derivative, which affects amyloid and oxidative stress, is also implicated in AD pathogenesis.

Researchers used blood samples from patients aged 60 years and older from the Australia Imaging, Biomarkers, and Lifestyles (AIBL) study who had various levels of cognitive function.

They analyzed samples at multiple timepoints over a 10-year period, "so we know when the marker is most accurate at predicting decline," Kinnon said.

The first of two studies was considered a "discovery" study and included blood samples from 224 patients.

Results showed the test predicted decline from mild cognitive impairment (MCI) to AD at the end of 6 years, with an area under the curve (AUC) greater than 90%.

These results are "massive," said Kinnon. "It's the most accurate test I've seen anywhere for predicting decline of a patient."

The test can also accurately classify a patient's stage of cognition, he added. "Not only does it allow us to predict 6 years in advance, it also tells us if the patient has SMC [subjective memory complaints], MCI, or AD with a 95% certainty," Kinnon said.

He noted that test sensitivity was higher than results found from traditional methods that are currently being used. The positive predictive value (PPV) and negative predictive value (NPV), which were at 90% or more, were "absolutely fantastic," said Kinnon.

"Better than Expected" Results

In the second "validation" study, investigators examined samples from a completely different group of 482 patients. The "very compelling" results showed AUCs over 90%, PPVs over 90%, and "very high" NPVs, Kinnon said.

"These are great data, better than we expected," he added.

However, he noted the test is "very specific" for decline to AD and not to other dementias.

In addition, Kinnon noted the test does not monitor levels of amyloid beta or tau, which accumulate at a later stage of AD. "Amyloid and tau tell you you've got it. We're there way before those concentrations become detectable," he said.

Identifying patients who will progress to AD years before they have symptoms gives them time to make medical decisions. These patients may also try treatments at an earlier stage of the disease, when these therapies are most likely to be helpful, said Kinnon.

In addition, using the test could speed up the approval of prospective drug treatments for AD. Currently, pharmaceutical companies enroll thousands of patients into a clinical study "and they don't know which ones will have AD," Kinnon noted.

"This test tells you these are the ones who are going to progress and should go into the study, and these are the ones that aren't. So it makes the studies statistically relevant and accurate," he said.

Investigators can also use the test to monitor patients during a study instead of relying on expensive PET scans and painful and costly spinal fluid taps, he added.

Previous surveys and market research have shown that neurologists and general practitioners "want a blood test to screen patients early, to help educate and inform patients," said Kinnon.

Further results that will include biobank data on more than 1000 patients in the United States and Europe are due for completion toward the end of this year.

The company is currently in negotiations to bring the product to North America, Europe, and elsewhere. "Our goal is to have it on the market by the middle of next year in multiple regions," Kinnon said.

Encouraging, Preliminary

Commenting on the findings for *Medscape Medical News*, Percy Griffin, PhD, MSc, director of scientific engagement at the Alzheimer's Association, said "it's exciting" to see development of novel ways for detecting or predicting AD.

"There is an urgent need for simple, inexpensive, noninvasive, and accessible early detection tools for Alzheimer's, such as a blood test," he said.

However, Griffin cautioned the test is still in the early stages of development and has not been tested extensively in large, diverse clinical trials.

In addition, although the test predicts whether a person will progress, it does not predict when the person will progress, he added.

"These preliminary results are encouraging, but further validation is needed before this test can be implemented widely," he said.

Technologies that facilitate the early detection and intervention before significant loss of brain cells from AD "would be game-changing" for individuals, families, and the healthcare system, Griffin concluded.

14th Clinical Trials on Alzheimer's Disease (CTAD) conference: Late-breaking (LB) presentation #3. Presented November 11, 2021.

https://wb.md/317iKHi

Premenopausal Bilateral Oophorectomy Linked to Later Cognitive Impairment

Women undergoing bilateral oophorectomy before the age of 46 had a higher risk of mild cognitive impairment around 30 years later

Kate Johnson

Women whose ovaries were surgically removed before the age of 46 had a higher risk of mild cognitive impairment (MCI) around 30 years later, compared with those who did not undergo bilateral oophorectomy, according to a population-based linkage study published in JAMA Network Open.

The findings suggest that "physicians treating women with premenopausal bilateral oophorectomy need to be aware of their patients' risk of cognitive impairment or MCI and should consider implementing treatment-monitoring plans," noted lead author Walter A. Rocca, MD, MPH, from the division of epidemiology, department of quantitative health sciences, at the Mayo Clinic, Rochester, Minn. and colleagues.

The results may particularly "help women at mean risk levels of ovarian cancer to better evaluate the risk-to-benefit ratio of undergoing bilateral oophorectomy prior to spontaneous menopause for the prevention of ovarian cancer," they emphasized.

While the link between premenopausal bilateral oophorectomy and higher risk of cognitive impairment has been previously suggested, this new study "contributes valuable new data to a major public health importance issue and addresses a number of important shortcomings of existing literature," Marios K. Georgakis, MD, PhD, and Eleni T. Petridou, MD, PhD, noted in an accompanying commentary.

"As bilateral oophorectomy is still a common procedure at least in well-resourced countries, the results of these studies should alert clinicians about its potential public health consequences. Given that the abrupt cessation of ovarian hormones might be accompanied by previously underestimated long-term adverse effects, treating physicians proposing the operation should weigh its benefits against potential long-term harmful effects, especially among women without an absolute indication," noted Georgakis and Petridou, respectively from the Center for Genomic Medicine at Massachusetts General Hospital in Boston and the National and Kapodistrian University of Athens.

The case-control cross-sectional study used data from the Mayo Clinic Study of Aging (MCSA), a prospective, population-based study examining risk factors for, as well as prevalence and incidence of cognitive decline and MCI among a representative sample of women in Olmsted County, Minn. It included 2,732 women aged 50-89 years who participated in the MCSA study from

2004 to 2019 and underwent a clinical evaluation and comprehensive cognitive testing including nine tests covering four cognitive domains. Almost all of the subjects (98.4%) were White. The mean age of cognitive evaluation was 74 years – at which time 283 women (10.4%) were diagnosed with MCI (197 with amnestic and 86 with nonamnestic MCI). Data from the Rochester Epidemiology Project medical record–linkage system showed a total of 625 women (22.9%) had a history of bilateral oophorectomy. Among this group, 161 women underwent the procedure both before age 46, and before menopause, with 46 (28.6%) receiving oral conjugated equine estrogen (unopposed) and the remaining 95 (59.0%) receiving no estrogen therapy.

The study found that, compared with women who did not undergo bilateral oophorectomy, those who did so before age 46, but not after this age, had statistically significantly increased odds of MCI (adjusted odds ratio, 2.21; $P < .001$). When type of MCI was examined, the risk was statistically significant for nonamnestic MCI (aOR, 2.96; $P < .001$), and amnestic (aOR, 1.87; $P = .03$). The study also found no evidence that estrogen therapy was associated with decreased risk of MCI among women aged less than 46 years, with an aOR of 2.56 in those who received estrogen therapy and 2.05 in those who did not ($P = .01$ for both).

Finally, in women who had bilateral oophorectomy before menopause and before age 50, surgical indication for the procedure affected the association with MCI. Indications of either cancer or "no ovarian condition" (i.e., performed at the time of hysterectomy) were associated with no increased risk, whereas there was a statistically significantly increased risk associated with benign indications such as an adnexal mass, cyst or endometriosis (aOR, 2.43; $P = .003$). "This is important," noted the commentators, "because in many of those cases removal of both ovaries could be avoided."

The study also found that, compared with women who had not undergone bilateral oophorectomy, those who had also had increased frequency of cardiovascular risk factors, heart disease, and stroke at the time of their cognitive evaluation. "Additional research is needed to clarify the biological explanation of the association," the investigators said.

The prevailing hypothesis for why premenopausal bilateral oophorectomy is associated with cognitive decline "is that the abrupt endocrine cessation of exposure to ovarian hormones accelerates the aging process," the commentators noted. "Most important from a clinical perspective is whether these women would benefit from specific hormone replacement therapy schemes. Observational studies cannot reliably answer this question, and possibly it is time to rethink designing trials in specific groups of women who underwent bilateral oophorectomy before 46 years of age starting treatment immediately thereafter."

In an interview Georgakis elaborated on this point, saying that, while the Women's Health Study clearly showed no benefit of hormone replacement therapy for preventing dementia, it recruited women who were aged 65 years or older and had therefore undergone menopause more than 10-15 years earlier. "A hypothesis suggests that a critical vulnerability window exists shortly after menopause during which hormone replacement therapy might be needed to ameliorate any elevated risk," he said. "Thus, it might make sense to reconsider a trial focused on this group of premenopausal women, who need to undergo oophorectomy at a young age (<46 years). Early initiation would be important. Unfortunately, such a trial would be difficult to conduct, because these women would need to be followed up for very long periods, as cognitive decline usually does not occur before the age of 65."

Asked to comment on the study, Meadow Good, DO, an ob.gyn., female pelvic medicine and reconstructive surgeon, and physician

adviser for Winnie Palmer Hospital for Women & Babies in Orlando, said this study adds credibility to previous studies showing the cognitive risk associated with premenopausal bilateral oophorectomy. "The literature is now pointing to a need to refrain from elective bilateral oophorectomy in women less than 60," she said in an interview. "It should not be common that a women receives a bilateral oophorectomy before 60 for benign reasons."

She added that cognition is not the only think at stake. "Bilateral oophorectomy before the age of 60 has a higher risk of incident heart disease, stroke, lung cancer and total cancers," she said, citing a prospective cohort study within the Nurses' Health Study.

Rocca reported financial support from the Mayo Clinic Research Committee during the conduct of the study. One coauthor reported unrestricted grants from Biogen and consulting fees from Brain Protection outside the submitted work. No other disclosures were reported from the authors. Georgakis, Petridou, and Good reported no conflicts of interest. The study was funded by the National Institute on Aging. It also used resources of the Rochester Epidemiology Project medical record–linkage system, which is supported by the NIA, the Mayo Clinic Research Committee, and user fees. Rocca was partly funded by the Ralph S. and Beverley E. Caulkins Professorship of Neurodegenerative Diseases Research of the Mayo Clinic.

This article originally appeared on MDedge.com, part of the Medscape Professional Network.

https://bit.ly/3lqqoWZ

"Vulture bees" evolved a taste for flesh—and their microbiomes reflect that

"The only bees... that have evolved to use food sources not produced by plants."

Jennifer Ouellette

Ask a random person to picture a bee, and they'll likely conjure up the familiar black-and-yellow striped creature buzzing from flower to flower collecting pollen to bring back to the hive. But a more unusual group of bees can be found "slicing chunks of meat from carcasses in tropical rainforests," according to the authors of a new paper published in the journal mBio.

As a result, these bees have gut microbiomes that are markedly different from their fellow buzzers, with populations more common to carrion-loving hyenas and vultures. So they are commonly known as "vulture bees" (or "carrion bees").

Enlarge / University of California, Riverside scientists suspended fresh pieces of raw chicken from branches to attract carrion-feeding "vulture bees" in Costa Rica. **Quinn McFrederick/UCR**

According to the authors—entomologists who hail from the University of California, Riverside (UCR), the University of Massachusetts, Amherst, Columbia University, and the American Museum of Natural History—most bees are essentially "wasps that switched to a vegetarian lifestyle." But there are two recorded examples of bumblebees feeding on carrion dating back to 1758 and 1837, and some species are known to occasionally feed on carrion in addition to foraging for nectar and pollen. (They are considered "facultatively necrophages," as opposed to vulture bees, which are deemed "obligate necrophages" because they only eat meat.)

An entomologist named Filippo Silvestri identified the first "vulture bee" in 1902 while analyzing a group of pinned specimens, although nobody called it that since they didn't know at the time that this species fed on carrion. Silvestri dubbed it *Trigona hypogea*, and he also described their nests as being used for honey and pollen, although later researchers noted a surprising absence of pollen.

Rather, biochemical analysis revealed the presence of secretions similar to those fed to queen bees in the nests of honeybees.

Then, in 1982, entomologist David Roubik of the Smithsonian Tropical Research Institute in Panama reported some surprising findings from his observations of *Trigona hypogea* colonies. Rather than gathering pollen from flowers, this species ingested the flesh of dead animals: lizards, monkeys, snakes, fish, and birds. Bees that stumbled on a tasty bit of rotting flesh deposited a trail of pheromones to call its nest mates, who typically converged *en masse* on the corpse within eight hours.

The vulture bees often entered a carcass via the eyes, similar to maggots, and Roubik made particular note of just how efficiently they could consume a carcass. A large lizard was reduced to a skeleton over two days, while the bees took just eight hours to remove all feathers and flesh from the head of a dead passerine. They reduced two frogs to skeletons in six hours. Because they fed on carrion rather than collecting pollen, this species had a distinctive hind leg, with a drastically reduced pollen basket compared to "vegetarian" bees.

The bees consumed the flesh on-site, storing a kind of "meat slurry" in their crops to bring back to the hive. Roubik hypothesized that, once at the hive, the bees converted that slurry into some kind of glandular substance, which they then stored in wax pots. "Considering animal flesh rots and would be unsuitable as stored food, its metabolic conversion is essential to allow storage," he wrote. Another hypothesis, proposed in 1996, suggests that the actual flesh is what's stored in the wax pots.

We now know of three distinct groups of vulture bees that exclusively get their protein from carcasses: the aforementioned *Trigona hypogea*, *Trigona crassipes*, and *Trigona necrophages*. These are stingless bees, but they have five large, pointed teeth, and they have been known to bite. Some excrete substances with their bites that can cause painful blisters and sores.

"These are the only bees in the world that have evolved to use food sources not produced by plants, which is a pretty remarkable change in dietary habits," said Doug Yanega, a UCR entomologist who co-authored the new study. He and his colleagues wondered whether these vulture bees, given their radical shift in diet, had also evolved distinct microbiomes, and they conducted a series of experiments to find out.

The adult bees used in the experiments were collected at field stations in La Selva and Las Cruces, Costa Rica, in April 2019. Each site featured 16 "bait stations" with large chunks of fresh chicken suspended from branches with string. The string was coated with petroleum jelly to ward off ants, although a few particularly intrepid bullet ants managed to overcome that barrier. For comparison, the team also collected bees that fed on both meat and flowers as well as bees who fed exclusively on pollen.

Each bee was stored in a sterile tube filled with 95 percent ethanol. Because the specimens were so tiny, the entire abdomens were used for the microbiome analysis, except in the case of larger *Melipona* bees, whose guts were carefully dissected. That analysis revealed that the most extreme microbiome changes were found in the vulture bees that fed exclusively on meat. Those microbiomes had a lot of *Lactobacillus* bacteria, commonly found in fermented foods like sourdough, as well as *Carnobacterium*, known to help digest flesh.

"The vulture bee microbiome is enriched in acid-loving bacteria, which are novel bacteria that their relatives don't have," said UCR entomologist and co-author Quinn McFrederick. "These bacteria are similar to ones found in actual vultures, as well as hyenas and other carrion-feeders, presumably to help protect them from pathogens that show up on carrion." The next step will be to learn

more about the bacterial genomes, as well was those of the various fungi and viruses found in the vulture bees.

Even though the vulture bees had much smaller baskets on their hind legs, the authors noted, they were nonetheless able to use them to collect pieces of masticated chicken, much like their vegetarian cousins collect pollen. "They had little chicken baskets," said McFrederick.

McFrederick, Yanega, and their colleagues suggest two hypothetical scenarios to explain their findings, noting that the two are not mutually exclusive. "The diet shift may have led to symbiont extinction and replacement of microbes that can break down carrion, or the core stingless bee microbiome may persist, suggesting that these microbes evolved along with the bee over its diet shift and are adapted to a new protein source," they wrote.

DOI: mBio, 2021. https://doi.org/10.1128/mBio.02317-21

https://bit.ly/317pqFi

Fossil of 115-Million-Year-Old Bird Found in Brazil

Paleontologists working in Brazil have uncovered the fossil of an ornithuromorph bird that lived during the Early Cretaceous epoch.

by Sergio Prostak

"*Kaririavis mater* lived during the Cretaceous period, when the supercontinent Gondwana — which included the South America, Africa, Australia, Antarctica and India — was splitting," said Dr. Ismar de Souza Carvalho, a paleontologist at the Universidade Federal do Rio de Janeiro and the Universidade de Coimbra, and colleagues.

The new species is a member of Ornithuromorpha, a large group of birds that contains all extinct and living species but not Mesozoic enantiornithes. "It had both primitive and modern morphological characteristics, making its behavior and ecological niche still mysterious," the paleontologists said.

Life reconstruction of Kaririavis mater. Image credit: Divulgação. Kaririavis mater lived in what is now Brazil some 115 million years ago (Early Cretaceous epoch).

"It had coarse feet, very stout toe phalanges, and a claw on the second toe, very curved and proportionately large for its size, unlike those found in most ornithuromorphs, which had slender feet and slender toes."

The fossilized remains of *Kaririavis mater* — an isolated right foot with some feathers — were recovered from the Crato Formation at Pedra Branca Mine, in Brazil's Ceará state.

Its unique foot conformation indicates that it may belong to an unknown ornithuromorph clade with some cursory similarities to living flightless ratites, such as the rhea or the ostrich.

According to the scientists, *Kaririavis mater* is the earliest known member of Ornithuromorpha from Gondwana and the oldest fossil bird from South America. "The presence of Early Cretaceous ornithuromorphs in Brazil indicates that the clade was widespread in Gondwana during the Mesozoic," they said.

"The discovery brings light to the discussion on the origin of birds on Earth," said Professor José Xavier Neto, a researcher at the Universidade Federal do Ceará.

"China is the world's most important source of primitive bird fossils. But, with this unprecedented discovery, the place of origin of the birds is now not clear and definitive: did the birds appear in China and then fly to Brazil or did they appear in Brazil and then fly to China?" The discovery of *Kaririavis mater* is described in a paper published online in the *Journal of Vertebrate Paleontology*.

Ismar de Souza Carvalho et al. A new ornithuromorph bird from the Lower Cretaceous of South America. Journal of Vertebrate Paleontology, published online November 11, 2021; doi: 10.1080/02724634.2021.1988623

https://bit.ly/3cT9bOL

Australopithecus sediba Comfortably Walked on Two Legs, But Could Climb Like Ape

Paleoanthropologists have discovered and examined the fossil lumbar vertebrae of Australopithecus sediba, a small hominin that lived about 2 million years ago.

Life reconstruction of Australopithecus sediba commissioned by the University of Michigan Museum of Natural History. **Image credit: Elisabeth Daynes / S. Entressangle.**

Their results suggest that *Australopithecus sediba* would have had an upright posture and comfortably walked on two legs, and the curvature of their lower back was similar to modern humans; however, other aspects of the bones' shape suggest that as well as walking, this hominin probably spent a significant amount of time climbing in trees.

Australopithecus sediba is a close-relative of modern humans that lived 2 million years ago in what is now South Africa.

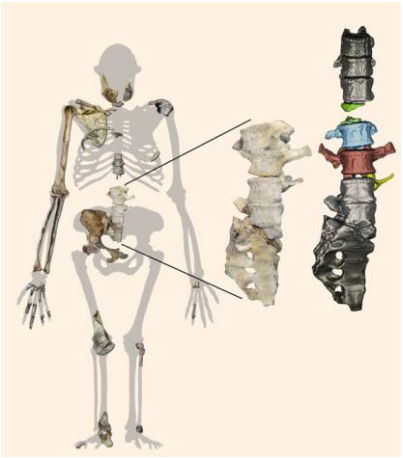
In 2008, fossils from an adult female *Australopithecus sediba* were discovered at a cave site called Malapa. However, the fossils of the lower back region were incomplete, so it was unclear whether the female — referred to as Malapa Hominin 2 (MH2) — had a forward-curving spine and other adaptations needed to walk on two legs.

In 2015, Professor Scott Williams, a paleoanthropologist at New York University and the University of the Witwatersrand, and his colleagues uncovered new fossils — mainly bones from the lower back — at the Malapa site. They fit together with the previously discovered MH2 fossils, providing a nearly complete lower spine. The discovery also shows that like humans, *Australopithecus sediba* had only five lumbar vertebrae.

"The lumbar region is critical to understanding the nature of bipedalism in our earliest ancestors and to understanding how well adapted they were to walking on two legs," Professor Williams said. "Associated series of lumbar vertebrae are extraordinarily rare in the hominin fossil record, with really only three comparable lower spines being known from the whole of the early African record."

The discovery of the new specimens means that MH2 (also known as 'Issa,' meaning protector in Swahili) now becomes one of only two early hominin skeletons to preserve both a relatively complete lower spine and dentition from the same individual, allowing certainty as to what species the spine belongs to.

"While Issa was already one of the most complete skeletons of an ancient hominin ever discovered, these vertebrae practically complete the lower back and make Issa's lumbar region a contender for not only the best-preserved hominin lower back ever discovered, but also probably the best preserved," Professor Berger said.



Australopithecus sediba silhouette showing the newfound vertebrae along with other skeletal remains from the species; the enlarged detail (a photograph of the fossils in articulation on the left; micro-computed tomography models on the right) shows the fossils, in color on the right between previously known elements in gray. **Image credit: Williams et al., doi: 10.7554/eLife.70447.**

Previous studies of the incomplete lower spine hypothesized that MH2 would have had a relatively straight spine, without the curvature, or lordosis, typically seen in modern humans.

They further hypothesized MH2's spine was more like that of the extinct species Neanderthals and other more primitive species of ancient hominins older than 2 million years.

Lordosis is the inward curve of the lumbar spine and is typically used to demonstrate strong adaptations to bipedalism.

However, with the more complete spine, and excellent preservation of the fossils, Professor Berger and colleagues found the lordosis of MH2 was in fact more extreme than any other australopithecines yet discovered, and the amount of curvature of the spine observed was only exceeded by that seen in the spine of the 1.6-million-year-old Turkana boy (*Homo erectus*) from Kenya and some modern humans.

"While the presence of lordosis and other features of the spine represent clear adaptations to walking on two legs, there are other features, such as the large and upward oriented transverse processes, that suggest powerful trunk musculature, perhaps for arboreal behaviors," said Professor Gabrielle Russo, a researcher at Stony Brook University.

Strong upward oriented transverse spines are typically indicative of powerful trunk muscles, as observed in apes. "When combined with other parts of torso anatomy, this indicates that *Australopithecus sediba* retained clear adaptations to climbing," said Professor Shahed Nalla, a researcher at the University of Johannesburg and the University of the Witwatersrand.

The authors concluded that *Australopithecus sediba* is a transitional form of ancient human relative and its spine is clearly intermediate in shape between those of modern humans (and Neanderthals) and great apes. "Issa walked somewhat like a human, but could climb like an ape," Professor Berger said.

The findings were published in the journal *eLife*.

Scott A. Williams et al. 2021. New fossils of Australopithecus sediba reveal a nearly complete lower back. eLife 10: e70447; doi: 10.7554/eLife.70447 11111

https://bit.ly/317YzsK

Higher Coffee Consumption Associated with Slower *Cognitive Decline*

A new long-term study led by Edith Cowan University scientists further supports the hypothesis that coffee intake may be a protective factor against Alzheimer's disease, with increased coffee consumption potentially reducing cognitive decline.

Worldwide, a high proportion of adults drink coffee daily, making it one of the most popular beverages globally," said lead author Dr. Samantha Gardener from Edith Cowan University and Australian Alzheimer's Research Foundation and her colleagues from Australia and the United States.

"Coffee contains a range of bioactive compounds, including caffeine, chlorogenic acid, polyphenols and small amounts of vitamins and minerals. Epidemiological studies suggest coffee has beneficial effects on various conditions including stroke, heart failure, cancers, diabetes, and Parkinson's disease."

"Alzheimer's disease is a neurodegenerative disease characterized by progressive impairment of learning, memory and other cognitive deficits, with extracellular deposition of Aβ-amyloid (Aβ) protein within the brain leading to neuroinflammation, synaptic loss and neuronal death," they added.

"Several studies suggest a protective role of coffee, with reduced risk of mild cognitive impairment and Alzheimer's disease. However, there are limited longitudinal data from cohorts of cognitively normal older adults describing associations of coffee consumption with distinct domains of cognition, and concurrently investigating potential neuropathological mechanisms underpinning any such associations."

In the new research, the authors investigated whether self-reported habitual coffee intake affected the rate of cognitive decline in 227 older adults over 126 months. The study was conducted using data

from the well-characterized Australian Imaging, Biomarkers and Lifestyle study of ageing (AIBL).

"The results showed an association between coffee and several important markers related to Alzheimer's disease," Dr. Gardener said. "We found participants with no memory impairments and with higher coffee consumption at the start of the study had lower risk of transitioning to mild cognitive impairment — which often precedes Alzheimer's disease — or developing Alzheimer's disease over the course of the study."

"Drinking more coffee gave positive results in relation to certain domains of cognitive function, specifically executive function which includes planning, self-control, and attention."

"Higher coffee intake also seemed to be linked to slowing the accumulation of the amyloid protein in the brain, a key factor in the development of Alzheimer's disease." The researchers were unable to differentiate between caffeinated and de-caffeinated coffee, nor the benefits or consequences of how it was prepared (brewing method, the presence of milk and/or sugar etc).

"It's a simple thing that people can change," Dr. Gardener said. "It could be particularly useful for people who are at risk of cognitive decline but haven't developed any symptoms. We might be able to develop some clear guidelines people can follow in middle age and hopefully it could then have a lasting effect."

"If you only allow yourself one cup of coffee a day, the study indicates you might be better off treating yourself to an extra cup, although a maximum number of cups per day that provided a beneficial effect was not able to be established from the study."

"If the average cup of coffee made at home is 240 g, increasing to two cups a day could potentially lower cognitive decline by 8% after 18 months. It could also see a 5% decrease in amyloid accumulation in the brain over the same time period." The study was published in the journal *Frontiers of Ageing Neuroscience*.

Samantha L. Gardener et al. Higher Coffee Consumption is Associated with Slower Cognitive Decline and Less Cerebral Aβ-Amyloid Accumulation over 126 Months: Data from the Australian Imaging, Biomarkers, and Lifestyle Study. Front. Aging Neurosci, published online November 19, 2021; doi: 10.3389/fnagi.2021.744872

https://bit.ly/32BrExf

Over the Counter Antihistamines Could Help Against Cancer

The binding of histamine with one of its receptors within the tumor environment makes cancer cells more resistant to immunotherapy, according to a new study. Blocking that binding could improve responses to treatment.

Alejandra Manjarrez

Immunotherapy aims to turn the body's immune system into an ally in the fight against cancer. One way that can happen is by stimulating T cells to identify and kill unwanted tumor cells. Unfortunately, it's not successful in every patient, as tumors can become resistant to the T cells' attacks. The mechanisms behind this resistance are varied, and new ones continue to be uncovered. But the secret to overcoming some of them might already be in medicine cabinets everywhere: antihistamines.

A paper published today (November 24) in *Cancer Cell* reports that high levels of histamine—best known for being released in response to allergens—and one of its receptors are associated with tumor resistance to immunotherapy drugs called immune checkpoint inhibitors in patients with a range of cancer types. In tumor cells, immune checkpoints are proteins expressed to evade surveillance; by inhibiting them, checkpoint therapy boosts antitumor defenses. The study also shows that patients who happened to be taking antihistamine treatment responded better to immune checkpoint inhibitor therapy than those not on antihistamines. Using tumor cells and mouse models, the authors further uncovered details on the mechanism behind this effect.

"It sounds really exciting that antihistamines may be beneficial in a

subset of patients undergoing immunotherapy," says University of South Australia immunologist Damon Tumes, who did not participate in the study. "It's just a matter of proving that with controlled trials."

Becca Martin, an immunologist at the Virginia Commonwealth University who also was not involved in the research, agrees that if this intervention can be combined with immunotherapy to improve the patients' outcome, it could be a really important addition. "Antihistamines are cheap drugs that have been around for a long time."

The goal is to make more patients benefit from immunotherapy, says Dihua Yu, a cancer researcher at MD Anderson in Texas and corresponding author of the new study. Her team first approached this quest by looking at whether common drugs consumed in combination with immune checkpoint inhibitors may influence the patients' response to this cancer treatment. By retrospectively scanning data of patients receiving immunotherapy together with any of 40 common drugs—antibiotics, aspirin, and hydrocortisone, among them—they found that melanoma and lung cancer patients taking antihistamines that target the histamine receptor H1 (HRH1), such as fexofenadine, loratadine, and cetirizine, had significantly higher survival rates.

This initial result, showing "you have an increased survival in checkpoint therapy if you are [taking] antihistamines" is one of "the most impressive" within the paper, according to Martin.

Based on this first promising hint at the beneficial role of antihistamines, Yu and her team explored the role that histamine and its receptor might play in the immune response to cancer. In existing patient samples, they found that high levels of HRH1 in tumors were correlated with markers of T cell dysfunction and poor survival in patients suffering from certain cancer types. These histamine receptors were mainly expressed in tumor-associated macrophages, a class of immune cells often involved in suppressing the anti-tumor response.

In follow-up experiments in mice, the binding of histamine to HRH1 receptors on the surface of tumor-associated macrophages contributes to the suppression of T cell function, resulting in tumor resistance to immunotherapy. Specifically, blocking the histamine receptors on macrophages—either through gene knockouts or treatment with the antihistamine fexofenadine—restored T cell antitumor activity, ultimately inhibiting tumor growth in the animals.

"This is a sophisticated, detailed, exhaustive, and original study that provides new insights into combinatorial therapeutic approaches targeting H1 receptors to improve cancer immunotherapy," Vanina Medina, a biomedical researcher at the Pontifical Catholic University of Argentina who was not involved in the study, writes in an email to *The Scientist*.

Tumes says the evidence presented for the role of histamine in tumor response to immunotherapy is strong. "The question for me is where the histamine is coming from," he says.

Yu and her colleagues found that both histamine and HRH1 are upregulated in the tumor microenvironment, suggesting that cancer cells are one of the major sources of increased histamine levels in cancer patients. But the authors of the study also explored histamine released from allergic reactions. Based on an allergic disease mouse model and on clinical data from patients reporting allergic reactions before undergoing immunotherapy, they conclude that histamine released from an allergy response also affects response to checkpoint inhibitors.

Tumes says that, in his opinion, the evidence for this link between allergy and response to immunotherapy is not as robust. Moreover, previous controversial data on the link between allergies and cancer begs for further research on this question, he says. In summary,

these new findings just indicate that "in some contexts, histamine from allergy might be important for immune evasion by the tumor, and more work needs to be done to . . . confirm or refute that hypothesis."

MD Anderson cancer researcher and study coauthor Yi Xiao says these new findings provide "strong evidence" of the benefits of combining antihistamine treatment with immunotherapy, but still a "prospective clinical trial to prove it" is needed. While the team does not yet have "a solid plan" to perform such a study, Yu says, there is excitement among the physicians collaborating with them to start one.

https://bit.ly/3rmDkye

AI Reveals Previously Unknown Biology – We Might Not Know Half of What's in Our Cells

Artificial intelligence-based technique reveals previously unknown cell components that may provide new clues to human development and disease.

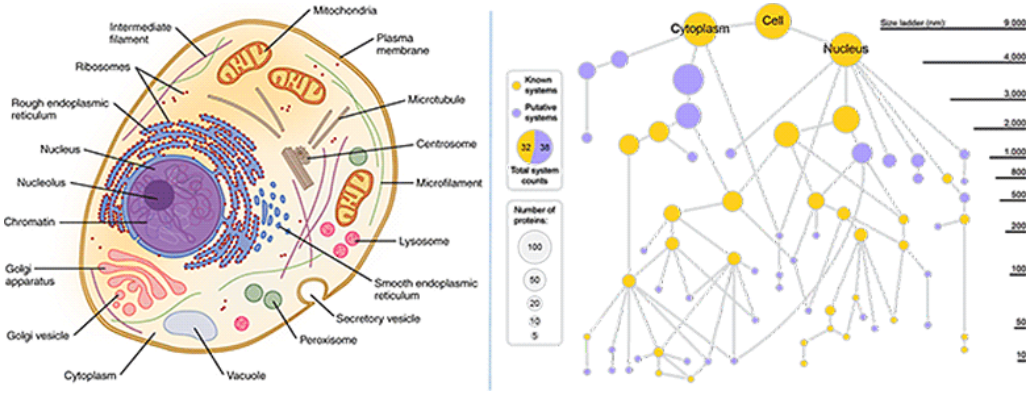
Most human diseases can be traced to malfunctioning parts of a cell — a tumor is able to grow because a gene wasn't accurately translated into a particular protein or a metabolic disease arises because mitochondria aren't firing properly, for example. But to understand what parts of a cell can go wrong in a disease, scientists first need to have a complete list of parts.

By combining microscopy, biochemistry techniques and artificial intelligence, researchers at University of California San Diego School of Medicine and collaborators have taken what they think may turn out to be a significant leap forward in the understanding of human cells. The technique, known as Multi-Scale Integrated Cell (MuSIC), is described on November 24, 2021, in *Nature*.

"If you imagine a cell, you probably picture the colorful diagram in your cell biology textbook, with mitochondria, endoplasmic reticulum and nucleus. But is that the whole story? Definitely not," said Trey Ideker, PhD, professor at UC San Diego School of Medicine and Moores Cancer Center. "Scientists have long realized there's more that we don't know than we know, but now we finally have a way to look deeper."

Ideker led the study with Emma Lundberg, PhD, of KTH Royal Institute of Technology in Stockholm, Sweden and Stanford University.

Left: Classic textbook cell diagrams imply all parts are clearly visible and



defined. (Credit: OpenStax/Wikimedia). Right: A new cell map generated by MuSIC technic reveals many novel components. Gold nodes represent known cell components, purple nodes represent new components. The size of node reflects number of distinct proteins in that component. **Credit: UC San Diego Health Sciences**

In the pilot study, MuSIC revealed approximately 70 components contained within a human kidney cell line, half of which had never been seen before. In one example, the researchers spotted a group of proteins forming an unfamiliar structure. Working with UC San Diego colleague Gene Yeo, PhD, they eventually determined the structure to be a new complex of proteins that binds RNA. The complex is likely involved in splicing, an important cellular event that enables the translation of genes to proteins, and helps determine which genes are activated at which times.

The insides of cells — and the many proteins found there — are

typically studied using one of two techniques: microscope imaging or biophysical association. With imaging, researchers add florescent tags of various colors to proteins of interest and track their movements and associations across the microscope's field of view. To look at biophysical associations, researchers might use an antibody specific to a protein to pull it out of the cell and see what else is attached to it.

The team has been interested in mapping the inner workings of cells for many years. What's different about MuSIC is the use of deep learning to map the cell directly from cellular microscopy images. "The combination of these technologies is unique and powerful because it's the first time measurements at vastly different scales have been brought together," said study first author Yue Qin, a Bioinformatics and Systems Biology graduate student in Ideker's lab.

Microscopes allow scientists to see down to the level of a single micron, about the size of some organelles, such as mitochondria. Smaller elements, such as individual proteins and protein complexes, can't be seen through a microscope. Biochemistry techniques, which start with a single protein, allow scientists to get down to the nanometer scale. (A nanometer is one-billionth of a meter, or 1,000 microns.)

"But how do you bridge that gap from nanometer to micron scale? That has long been a big hurdle in the biological sciences," said Ideker, who is also founder of the UC Cancer Cell Map Initiative and the UC San Diego Center for Computational Biology and Bioinformatics. "Turns out you can do it with artificial intelligence — looking at data from multiple sources and asking the system to assemble it into a model of a cell."

The team trained the MuSIC artificial intelligence platform to look at all the data and construct a model of the cell. The system doesn't yet map the cell contents to specific locations, like a textbook diagram, in part because their locations aren't necessarily fixed. Instead, component locations are fluid and change depending on cell type and situation.

Ideker noted this was a pilot study to test MuSIC. They've only looked at 661 proteins and one cell type. "The clear next step is to blow through the entire human cell," Ideker said, "and then move to different cell types, people and species. Eventually, we might be able to better understand the molecular basis of many diseases by comparing what's different between healthy and diseased cells."

Reference: "A multi-scale map of cell structure fusing protein images and interactions" by Yue Qin, Edward L. Huttlin, Casper F. Winsnes, Maya L. Gosztyla, Ludivine Wacheul, Marcus R. Kelly, Steven M. Blue, Fan Zheng, Michael Chen, Leah V. Schaffer, Katherine Licon, Anna Bäckström, Laura Pontano Vaites, John J. Lee, Wei Ouyang, Sophie N. Liu, Tian Zhang, Erica Silva, Jisoo Park, Adriana Pitea, Jason F. Kreisberg, Steven P. Gygi, Jianzhu Ma, J. Wade Harper, Gene W. Yeo, Denis L. J. Lafontaine, Emma Lundberg and Trey Ideker, 24 November 2021, Nature.

DOI: 10.1038/s41586-021-04115-9

Co-authors include: Maya L. Gosztyla, Marcus R. Kelly, Steven M. Blue, Fan Zheng, Michael Chen, Leah V. Schaffer, Katherine Licon, John J. Lee, Sophie N. Liu, Erica Silva, Jisoo Park, Adriana Pitea, Jason F. Kreisberg, UC San Diego; Edward L. Huttlin, Laura Pontano Vaites, Tian Zhang, Steven P. Gygi, J. Wade Harper, Harvard Medical School; Casper F. Winsnes, Anna Bäckström, Wei Ouyang, KTH Royal Institute of Technology; Ludivine Wacheul, Denis L. J. Lafontaine, Université Libre de Bruxelles; and Jianzhu Ma, Peking University.

Funding for this research came, in part, from the National Institutes of Health (grants U54CA209891, U01MH115747, F99CA264422, P41GM103504, R01HG009979, U24HG006673, U41HG009889, R01HL137223, R01HG004659, R50CA243885), Google Ventures, Erling-Persson Family Foundation, Knut and Alice Wallenberg Foundation (grant 2016.0204), Swedish Research Council (grant 2017-05327), Belgian Fonds de la Recherche Scientifique, Université Libre de Bruxelles, European Joint Programme on Rare Diseases, Région Wallonne, Internationale Brachet Stiftung, and Epitran COST action (grant CA16120).

Disclosures: Trey Ideker is co-founder of, on the Scientific Advisory Board and has an equity interest in Data4Cure, Inc. Ideker is also on the Scientific Advisory Board, has an equity interest in and receives sponsored research funding from Ideaya BioSciences, Inc. Gene Yeo is a co-founder, member of the Board of Directors, on the Scientific Advisory Board, an equity holder and a paid consultant for Locanabio and Eclipse BioInnovations. Yeo is also a visiting professor at the National University of Singapore. The terms of these arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict-of-interest policies. Emma Lundberg is on the

Scientific Advisory Boards of and has equity interests in Cartography Biosciences, Nautilus Biotechnology and Interline Therapeutics. J. Wade Harper is a co-founder of, on the Scientific Advisory Board and has an equity interest in Caraway Therapeutics. Harper is also Founding Scientific Advisor for Interline Therapeutics.

https://bit.ly/3lhhI2w

Collapse of Ancient Liangzhu Culture – "China's Venice of the Stone Age" – Caused by Climate Change

Referred to as "China's Venice of the Stone Age," the Liangzhu excavation site in eastern China is considered one of the most significant testimonies of early Chinese advanced civilization.

More than 5000 years ago, the city already had an elaborate water management system. Until now, it has been controversial what led to the sudden collapse. Massive flooding triggered by anomalously intense monsoon rains caused the collapse, as an international team with Innsbruck geologist and climate researcher Christoph Spötl has now shown in the journal Science Advances.

In the Yangtze Delta, about 160 kilometers southwest of Shanghai, the archeological ruins of Liangzhu City are located. There, a highly advanced culture blossomed about 5300 years ago, which is considered to be one of the earliest proofs of monumental water culture.

The oldest evidence of large hydraulic engineering structures in China originates from this late Neolithic cultural site. The walled city had a complex system of navigable canals, dams, and water reservoirs. This system made it possible to cultivate very large agricultural areas throughout the year.

In the history of human civilization, this is one of the first examples of highly developed communities based on a water infrastructure. Metals, however, were still unknown in this culture. Thousands of elaborately crafted jade burial objects were found during excavations.

Long undiscovered and underestimated in its historical significance, the archaeological site is now considered a well-preserved record of Chinese civilization dating back more than 5000 years. Liangzhu was declared a UNESCO World Heritage Site in 2019. However, the advanced civilization of this city, which was inhabited for almost 1000 years, came to an abrupt end. Until today, it remains controversial what caused it.

"A thin layer of clay was found on the preserved ruins, which points to a possible connection between the demise of the advanced civilization and floods of the Yangtze River or floods from the East China Sea. No evidence could be found for human causes such as warlike conflicts," explains Christoph Spötl, head of the Quaternary Research Group at the Department of Geology. "However, no clear conclusions on the cause were possible from the mud layer itself."

Dripstones store the answer

Caves and their deposits, such as dripstones, are among the most important climate archives that exist. They allow the reconstruction of climatic conditions above the caves up to several 100,000 years into the past. Since it is still not clear what caused the sudden collapse of the Liangzhu culture, the research team searched for suitable archives in order to investigate a possible climatic cause of this collapse.

Geologist Haiwei Zhang from Xi'an Jiaotong University in Xi'an, who spent a year at the University of Innsbruck as a visiting researcher in 2017, took samples of stalagmites from the two caves Shennong and Jiulong, which are located southwest of the excavation site.

"These caves have been well explored for years. They are located in the same area affected by the Southeast Asian monsoon as the Yangtze delta and their stalagmites provide a precise insight into the time of the collapse of the Liangzhu culture, which, according to archaeological findings, happened about 4300 years ago," Spötl explains.

Data from the stalagmites show that between 4345 and 4324 years

ago there was a period of extremely high precipitation. Evidence for this was provided by the isotope records of carbon, which were measured at the University of Innsbruck. The precise dating was done by uranium-thorium analyses at Xi'an Jiaotong University, whose measurement accuracy is ± 30 years.

"This is amazingly precise in light of the temporal dimension," says the geologist. "The massive monsoon rains probably led to such severe flooding of the Yangtze and its branches that even the sophisticated dams and canals could no longer withstand these masses of water, destroying Liangzhu City and forcing people to flee." The very humid climatic conditions continued intermittently for another 300 years, as the geologists show from the cave data.

Reference: "Collapse of the Liangzhu and other Neolithic cultures in the lower Yangtze region in response to climate change" 24 November 2021, Science Advances.
DOI: 10.1126/sciadv.abi9275

https://bit.ly/3pbbZfS

A butterfly's wings are the perfect mold to grow neurons on

Butterfly wings provide the right topography for nerve cells to grow, with an aim towards ameliorating hearing loss

Reinack Hansen

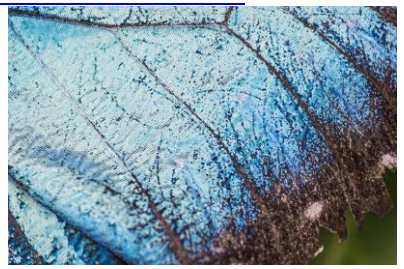
Around 15% of American adults report some trouble hearing. That is about 37.5 million people who may need hearing aids for the majority of their lives. A common cause of hearing loss stems from special cells called spinal ganglion neurons (SGN) that transmit signals from hair cells in the ear to the brain. In these cases, regenerating SGN in the inner ear is our best bet to restore hearing. However, controlling how and where nerve cells grow is notoriously difficult. Fortunately, our dependence on hearing aids may soon wind down thanks to the beautiful blue morpho butterfly.

When nerve cells grow on a surface, they respond to physical features such as bumps and grooves. They also communicate with neighboring nerve cells through electrical signals. So, a good growth surface for nerve cells must provide topological cues and be electrically conductive.

The blue morpho butterfly wing has an intricate structure consisting of parallel ridges. Turns out these ridges are perfect templates for cell growth. Engineering an equivalent surface with ridges that is flexible yet light is impossible with today's technology. Rendering a butterfly wing biocompatible on the other hand, is possible. This is what inspired scientists to consider growing cells directly on butterfly wings. In 2019, cardiac tissue assembled on blue morpho – carbon nanotube composites was shown to recover its beating ability. In that case, the elastic composite wing mimicked the cyclic contractions of cardiac cells and shifted colors. By simply observing color changes, they could assess if the cells were behaving as expected.

For nerve cells, which are long, could the parallel ridges on the wing also align neurons end-to-end and make them grow in one direction? This is what Renjie Chai and team at Nanjing University sought to find out, as directionally controlled regeneration of auditory nerve cells is critical to restore hearing. Through a collaborative effort involving university researchers and surgeons, they transferred a thin layer of super aligned carbon nanotubes onto the wing of a blue morpho butterfly to make it conductive.

Not only was the conducting composite wing excellent at orienting nerve cells as they grew, it facilitated maturation of neuronal junctions, which is the site where nerve cells transmit electrical signals.



A close-up view of the veins and details of a blue morpho butterfly's wings
Tambako the Jaguar via Flickr

Interestingly, nerve cells grow on both plain butterfly wing and

aligned carbon nanotubes. However, only when the two are combined do the cells grow in a specific direction and the neuronal junctions mature. Super aligned carbon nanotubes are special in that they are simply individual nanotubes connected end-to-end. This makes a sheet of this material extremely conductive along one direction – the direction in which the nanotubes are aligned. When these aligned nanotubes are transferred onto butterfly wings, the composite retains the parallel ridges of the wing below while acquiring high conductivity along the ridges thanks to the nanotubes. Further, being extremely thin and lightweight, they hardly add any heft to the wing structure.

Nerve cells have what's called a "growth cone," which is a protein supported structure that explores the environment, determines the direction of growth, and guides the nerve fiber to extend in that direction. Turns out that in the case of nerve cells grown on the composite wing, growth cones aligned along the grooves. Considering the fact that nerve cells grew on butterfly wings as is, this goes to show that these grooves are features that nerve cells readily sense and respond to as they grow. Even with aligned carbon nanotubes, the composite surface retained the ridged butterfly wing structure. Nerve cells could sense the grooves on the composite wing surface and orient within them, just like they would on the unmodified butterfly wing.

More importantly, the growth cone filopodia, which are antennas for nerve cells to probe the environment, was much longer for nerve cells that grew on the composite wing. This is important as longer filopodia is a sign of improved communication between nerve cells. Moreover, the density of neuronal junctions, also called synapses, was much higher. The orientation within ridges, long filopodia, and high density of synapses clearly show that nerve cells can be controllably cultured on conductive butterfly wings. As promising as these results are, the SGN used in this study was sourced from mice. So any hearing restorative treatment for humans based on this approach is still years away.

From a materials perspective, the structure of the blue morpho butterfly wing is decades ahead of any microfabrication process available today. As such, this study is a classic example of how borrowing ideas from seemingly unlikely sources in nature can yield incredible results. So the next time you see a butterfly, remember those pretty wings could be our gateway to perfect hearing.

https://bit.ly/3xwpBWO

Molecule Derived From Poisonous Plant Blocks All SARS-CoV-2 Variants in Cell Cultures

Appears to be effective against all variants of SARS-CoV-2 in the lab

David Nield

The plant-based antiviral agent thapsigargin (TG), derived from a group of poisonous plants known as 'deadly carrots', appears to be effective against all variants of SARS-CoV-2 in the lab – and that includes the quick-spreading Delta variant.

A previous study published in February demonstrated that TG can be effective against a host of viruses. Now, this latest work by the same research team confirms that the antiviral also isn't being outflanked as SARS-CoV-2 evolves. With the emergence of new variants an ongoing possibility, it's intriguing to observe the continuous efficacy of TG.

In tests on cell cultures in the lab, doses of TG delivered either before infection or during active infection were shown to block and inhibit SARS-CoV-2 variants, triggering a broad and powerful protective response.

"A single pre-infection priming dose of TG effectively blocked all single-variant infections and every combination (AB, AD, BD variants) of co-infection at greater than 95 percent relative to

controls," write the researchers in their published paper.

As a host-centric antiviral, TG seems to break some of the mechanisms that viruses like SARS-CoV-2 hijack in host cells to replicate themselves and spread throughout the body.

Fruit of Thapsia villosa – deadly carrot plant. **(Daniel Hernanz Ramos/Getty Images)**

"All available data (generated by us and others) as exemplified in influenza virus, respiratory syncytial virus, and coronaviruses, including SARS-CoV-2, indicate that TG does not prevent viral entry but rather triggers intracellular pathways to inhibit virus replication," the team writes.

The cell culture study also confirmed the higher replication rate and cell-to-cell transmission rate of the Delta variant: it was found to spread at four times the rate of the Alpha variant of coronavirus and at nine times the rate of the Beta variant.

What's more, Delta can accelerate the multiplication of other variants when co-infections occur. If someone succumbs to two variants of SARS-CoV-2 at the same time, then Delta acts as an extra boost for whatever other variant it's partnering up with.

"Our new study has given us better insights into the dominance of the Delta variant," says Kin-Chow Chang, a professor of Veterinary Molecular Medicine at the University of Nottingham in the UK.

"Even though we have shown that this variant is clearly the most infectious and promotes production of other variants in co-infections, we are pleased to have shown that TG is just as effective against all of them."

While vaccinations massively reduce the risk of getting infected with SARS-CoV-2, they don't reduce the risk entirely – and of course, there are substantial numbers of people who can't or won't agree to get a jab to protect themselves against the virus.

With that in mind, finding new treatments to manage COVID-19 will remain a high priority for controlling the ongoing global pandemic. It's not certain that TG would be as effective against future variants, but the signs are good.

After demonstrating its efficacy in the lab, the next step is actually developing treatments from TG, which would of course take time – as you might expect from an agent developed from a poisonous plant, it's going to take a significant amount of further research to turn it into something safe for humans.

Testing it against cell cultures and getting promising results is by no means even a guarantee that this antiviral would eventually pass a clinical trial, but it's a hugely exciting first step for sure.

"Together, these results point to the antiviral potential of TG as a post-exposure prophylactic and an active therapeutic agent," says Kin-Chow Chang. The research has been published in *Virulence*.

https://bit.ly/3cYdhoD

'Patience is crucial': Why we won't know for weeks how dangerous Omicron is

Lab tests and patterns of spread will show whether the new SARS-CoV-2 variant's many mutations are a serious threat

By Kai Kupferschmidt

At 7.30 a.m. on Wednesday, Kristian Andersen, an infectious disease researcher at Scripps Research in San Diego, received a message on Slack: “This variant is completely insane.” Andrew Rambaut of the University of Edinburgh was reacting to a new SARS-CoV-2 genome sequence found in three samples collected in Botswana on 11 November and one picked up a week later in a traveler from South Africa to Hong Kong.

Andersen looked at the data and then replied: “Holy shit—that is quite something. The length of that branch...” A few minutes later he added: “Just had a look at the list of mutations—so nuts.”

They were talking about what is now called Omicron, a new variant

of concern, and the long branch Andersen noticed refers to its distance to every other known virus on SARS-CoV-2's evolutionary tree. The variant seemed to have picked up dozens of mutations, many of them known to be important in evading immunity or increasing transmissibility, with no intermediate sequences in the database of millions of viral genomes. On Tuesday, after spotting the odd sequences in a global database, Tom Peacock, a virologist at Imperial College London, had already posted his own verdict on GitHub: "This could be of real concern."

Now, once again, the world is watching as researchers work nights and weekends to learn what a new variant has in store for humanity. Is Omicron more infectious? More deadly? Is it better at re-infecting recovered people? How well does it evade vaccine-induced immunity? And where did it come from? Finding out will take time, warns Jeremy Farrar, the head of the Wellcome Trust: "I'm afraid patience is crucial."

Researchers in South Africa were already on the trail of this new variant. Several teams were independently trying to figure out why cases were spiking in Gauteng, a northern province that includes Johannesburg and Pretoria. And a private lab called Lancet had noticed that routine PCR tests for SARS-CoV-2 were failing to detect a key target, the S gene, in many samples, a phenomenon previously seen with Alpha, another variant of concern. When Lancet sequenced eight of these viruses, they found out why: The genome was so heavily mutated that the test missed the gene.

Lancet shared the genomes with the Network for Genomics Surveillance in South Africa (NGS-SA), which called an urgent meeting on Tuesday. "We were shocked by the number of mutations," says Tulio de Oliveira, a virologist at the University of KwaZulu-Natal and NGS-SA 's principal investigator. After the meeting, de Oliveira says, he called South Africa's Director General of Health and "asked him to inform the minister and president that a potential new variant was emerging." The team sequenced another 100 randomly selected sequences from Gauteng in the next 24 hours. All showed the same pattern. After informing the government, de Oliveira and his colleagues presented their evidence at a press conference on Thursday morning. On Friday, the World Health Organization (WHO) designated the virus a "variant of concern" and christened it Omicron. (Variant names follow the Greek alphabet but WHO skipped the letters Nu and Xi, it said, "because Nu is too easily confounded with 'new' and Xi was not used because it is a common surname.")

One reason for concern about Omicron is that sequenced samples indicate it has rapidly replaced other variants in South Africa. But that picture might be skewed. For one, sequencing might have been focused on possible cases of the new variant in recent days, which could make it appear more frequent than it is. PCR data provide broader coverage and a less biased view, but there too, samples with the S gene failure indicate a rapid rise of Omicron.

But the rising frequency could still be due in part to chance. In San Diego, a series of superspreading events at a university resulted in an explosion of one particular strain of SARS-CoV-2 earlier this year, Andersen says: "It was thousands of cases and they were all the same virus." But the virus wasn't notably more infectious. South Africa has seen relatively few cases recently, so a series of superspreading events could have led to the rapid increase of Omicron. "I suspect that a lot of that signal is explained by that and I desperately hope so," Andersen says. Based on a comparison of different Omicron genomes, Andersen estimates that the virus emerged sometime around late September or early October, which suggests it might be spreading more slowly than it appears to have.

The other reason to be concerned is Omicron's confusing genome. Its spike protein, which latches on to cells on human receptors, has 30 amino acid differences from that of the original Wuhan virus. In

addition, amino acids have disappeared in three places and new ones appeared in one place. (Other proteins too, have undergone changes.) Many of the changes in spike are around the receptor binding domain, the part of the protein that makes contact with the human cell. “That is very troubling,” Farrar says. Structural biology mapping last year showed that some of these changes made the virus bind to the receptor much better.

It’s hard to tell how infectious a virus is based on mutations alone, says Aris Katzourakis, an evolutionary biologist at the University of Oxford. “But if we were looking out for mutations that do affect transmissibility, it's got all of them,” he says.

The sequence also suggests the virus could excel at evading human antibodies, says Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center. The human immune system produces a host of different antibodies that can neutralize SARS-CoV-2, but many of the most important ones fall into three categories that each target a slightly different site on the spike protein of the virus, simply called 1, 2 and 3. A mutation called E484K has long been worrying because it changes the shape of the site that class 2 antibodies recognize, making them less potent. Omicron carries a mutation called E484A in this site and similar changes in the sites for the other two classes of antibodies.

Bloom thinks people who recovered from COVID or were vaccinated are unlikely to completely lose their ability to neutralize the virus. “But I would expect, based on this particular combination of mutations, that the drop in neutralization is larger than for all the other major variants.”

Experiments in the laboratory will have to show whether he is right. Alex Sigal, an infectious disease researcher at the Africa Health Research Institute, says he received swabs with Omicron on Wednesday and has started to grow the virus. Producing enough of it to test against sera from vaccinated and recovered individuals will take a week or two, he says. Other researchers will test viruses genetically engineered to carry just the spike protein of Omicron, a process that is faster than growing the variant itself but a bit further removed from what happens in real life.

As such studies take place, it's crucial to closely monitor any shifts in the pandemic, Farrar says. “Do you see cases increasing not just in South Africa but the broader South African region?” The virus has already been picked up in Belgium, the United Kingdom, and Israel, Farrar points out, and will probably be found elsewhere as well. “Do you see transmission increasing in other parts of the world around presumed index cases?” Epidemiologists will also watch for changes in disease severity—how many people are hospitalized and die. All that will take time.

In the meantime, the European Union, the United States, and many other countries have restricted travel to and from southern Africa in a bid to protect themselves. Travel restrictions are unlikely to stop the variant, Farrar says, but they can buy some time. “The question is what you then do with the time.”

Travel restrictions come with an economic and social cost, which could be a disincentive to report new variants. “I've heard through the grapevine that countries didn't push sequences out very quickly [in the past] because they were worried about travel bans,” says Emma Hodcroft, a virologist at the University of Bern. “This is the opposite of what we want.”

Such considerations did not stop South African researchers, de Oliveira says. “We do risk a massive backlash in case [Omicron] does not cause a massive wave of infection and can be controlled,“ he wrote in a message. "But this is a risk that I am comfortable to live with as the pandemic has caused so many deaths and suffering. [Our] hope is that our early identification will help the world.“