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Virus Mimicking Antibodies May Explain Long Haul COVID-19, Rare Vaccine Side Effects

Researchers are trying to find effective vaccines and therapies and understand long-term effects of the COVID-19

With around 256 million cases and more than 5 million deaths worldwide, the COVID-19 pandemic has challenged scientists and those in the medical field. Researchers are working to find effective vaccines and therapies, as well as understand the long-term effects of the infection.

While the vaccines have been critical in pandemic control, researchers are still learning how and how well they work. This is especially true with the emergence of new viral variants and the rare vaccine side effects like allergic reactions, heart inflammation (myocarditis) and blood-clotting (thrombosis).

Critical questions about the infection itself also remain. Approximately one in four COVID-19 patients have lingering symptoms, even after recovering from the virus. These symptoms, known as "long COVID," and the vaccines' off-target side effects are thought to be due to a patient's immune response.

In an article published on November 24, 2021, in *The New England Journal of Medicine*, the UC Davis Vice Chair of Research and Distinguished Professor of Dermatology and Internal Medicine William Murphy and Professor of Medicine at Harvard Medical School Dan Longo present a possible explanation to the diverse immune responses to the virus and the vaccines.

Antibodies mimicking the virus

Drawing upon classic immunological concepts, Murphy and Longo suggest that the Network Hypothesis by Nobel Laureate Niels Jerne might offer insights. Jerne's hypothesis details a means for the immune system to regulate antibodies. It describes a cascade in which the immune system initially launches protective antibody responses to an antigen (like a virus). These same protective antibodies later can trigger a new antibody response toward themselves, leading to their disappearance over time.

These secondary antibodies, called anti-idiotype antibodies, can bind to and deplete the initial protective antibody responses. They have the potential to mirror or act like the original antigen itself. This may result in adverse effects.

Coronavirus and the immune system

When SARS-CoV-2, the virus causing COVID-19, enters the body, its spike protein binds with the ACE2 receptor, gaining entry to the cell. The immune system responds by producing protective antibodies that bind to the invading virus, blocking or neutralizing its effects.

As a form of down-regulation, these protective antibodies can also cause immune responses with anti-idiotype antibodies. Over time, these anti-idiotype responses can clear the initial protective antibodies and potentially result in limited efficacy of antibody-based therapies.

"A fascinating aspect of the newly formed anti-idiotype antibodies is that some of their structures can be a mirror image of the original antigen and act like it in binding to the same receptors that the viral antigen binds. This binding can potentially lead to unwanted actions and pathology, particularly in the long term," Murphy said.

The authors suggest that the anti-idiotype antibodies can potentially target the same ACE2 receptors. In blocking or triggering these receptors, they could affect various normal ACE2 functions.

"Given the critical functions and wide distribution of ACE2 receptors on numerous cell types, it would be important to determine if these regulatory immune responses could be responsible for some of the off-target or long-lasting effects being reported," Murphy commented. "These responses may also explain why such long-term effects can occur long after the viral infection

has passed."

As for COVID-19 vaccines, the primary antigen used is the SARS-CoV-2 spike protein. According to Murphy and Longo, current research studies on antibody responses to these vaccines mainly focus on the initial protective responses and virus-neutralizing efficacy, rather than other long-term aspects.

"With the incredible impact of the pandemic and our reliance on vaccines as our primary weapon, there is an immense need for more basic science research to understand the complex immunological pathways at play. This need follows to what it takes to keep the protective responses going, as well as to the potential unwanted side effects of both the infection and the different SARS-CoV-2 vaccine types, especially as boosting is now applied," Murphy said. "The good news is that these are testable questions that can be partially addressed in the laboratory, and in fact, have been used with other viral models."

Reference: "A Possible Role for Anti-idiotype Antibodies in SARS-CoV-2 Infection and Vaccination" by William J. Murphy, Ph.D. and Dan L. Longo, M.D., 24 November 2021, New England Journal of Medicine. DOI: 10.1056/NEJMcibr2113694

https://bit.ly/3xNWuym

Humans Have Evolved to Stay Active Even in Old Age, New Hypothesis Claims

We aren't meant to reduce our physical activity as we age at all. Enter the 'active grandparent hypothesis'

Conor Feehly

In the modern western world, people tend to reduce their levels of physical activity as they get older. But with this inactivity comes a raft of adverse health effects, so why didn't evolution engineer us so that people could maintain a decent quality of life as they inevitably slow down? In a newly published paper, researchers argue it is because we aren't meant to reduce our physical activity as we age at all. Enter the 'active grandparent hypothesis'.

Researchers have started to uncover beneficial processes that physical activity helps to promote, such as maintaining a lower blood pressure and reducing systemic inflammation. But it remains unclear why these mechanisms cease to operate to the same degree in the absence of physical activity, especially in older people who would rely on them to maintain their health and quality of life.

In the paper, David E. Liberman, Harvard evolutionary biologist and lead author of the study, adopts an evolutionary approach and draws on previous biomedical findings to explain why physical activity reduces illness and injury and extends longevity.

Evolutionary biologists have tended to argue that since only recent human generations have been able to put their feet up in their twilight years, evolution hasn't had a lot of time to adjust.

This might explain why we should take note of our ancestral habits and stay physically active as we age, but it doesn't tell us why our ancestors stayed active for so many of their 'retirement' years.

In laying out their evolutionary explanations, the authors break down some of the assumptions we have about ancient humans.

"Contrary to the widespread belief that human life-spans until recently were short, hunter-gatherers who survive infancy and childhood tend to live on average seven decades, approximately 20 years past the age at which they cease reproducing, and fossil evidence indicates that extended human lifespans were common by 40,000 years ago," the authors state in the paper.

Older individuals in social groups were not only evolutionarily selected for in humans because they could impart important knowledge and skills, but because they could also physically forage and contribute food supplies for their children and grandchildren.

"While the number of daily steps older Americans take decreases by about half between the ages of 40 and 70, daily walking distances among hunter-gatherers such as the Hadza decline only modestly with age," the authors note.

In debunking the myths that human beings in prehistory lived short lifespans and were relatively sedentary, the authors suggest that it may have been the allocation of resources to physical activity over other biological processes that could in fact have helped to prevent certain health issues from arising in the first place.

Under conditions where energy needs were typically met or exceeded, physical activity meant potentially harmful excess energy wasn't allocated to fat and reproductive tissues, where a large literature exists today demonstrating the negative health impacts of excessive fat storage.

An additional hypothesis put forward by the authors suggests that regular physical activity meant energy resources were allocated towards the repair and maintenance of tissue and cells that degrade with physical activity, and as a result come back stronger.

This includes the repairing of tears in muscle fibers, restoring cartilage damage, healing microfractures, as well as the releasing of exercise-related antioxidants and anti-inflammatories. Without physical activity, these responses are blunted.

Many studies over the years have put forth recommended suitable durations of exercise, with anywhere from around half an hour of moderate exercise a day to an hour of intense effort a week helping combat our sedentary lifestyles. Without it, we run a greater risk of developing a range of diseases, including cardiovascular disease, type 2 diabetes, Alzheimer's, and a number of cancers later in life.

Despite this wisdom, physical activity levels around the world are generally decreasing due to the introduction of technologies that have replaced human labor, such as motor and electric vehicles, agricultural equipment, and autonomous machinery, and have resulted in a growing number of health-related issues among the elderly.

"The key take-home point is that because we evolved to be active throughout our lives, our bodies need physical activity to age well. In the past, daily physical activity was necessary in order to survive, but today we have to choose to exercise, that is, do voluntary physical activity for the sake of health and fitness," says Liberman.

The study was published in *Proceedings of the National Academy of Sciences*.

https://bit.ly/3El3QLX

Earth's earliest water may have come from solar wind and space rocks

Samples from an asteroid collected by a Japanese probe suggest that Earth's water may have come from the sun.

By Tereza Pultarova

Samples from asteroid Itokawa collected by a Japanese space probe suggest that Earth's water may have been created by the sun.

This water may have rained on the fledgling Earth in the form of dust grains produced by the interaction of the solar wind, the stream of charged particles emanating from the sun, with various bodies in the solar system, a new study suggests.

"The solar winds are streams of mostly hydrogen and helium ions which flow constantly from the sun out into space," Luke Daly, a planetary scientist at the University of Glasgow in the U.K., and a lead author of the new paper said in a statement. "When those hydrogen ions hit an airless surface like an asteroid or a spaceborne dust particle, they penetrate a few tens of nanometers [one inch has 24.5 million nanometers] below the surface, where they can affect the chemical composition of the rock."

Over time, this space weathering effect of the hydrogen ions can eject enough oxygen atoms from materials in the rock to create water, which remains locked within the asteroid, Daly added.

This mechanism may be the missing link explaining the abundance and chemical composition of water on Earth that has long baffled scientists. Earth's surface is 70% covered with water. That's much more than any other planet in the solar system. But none of the

existing theories can fully explain all of it. A dominant view suggests that asteroids rich in carbon, which pummeled the young Earth some 4.6 billion years ago, delivered this water to the planet.

But detailed chemical analysis of meteorites known as carbonaceous chondrites, which are chunks of these carbon-rich asteroids, revealed that the water locked inside them doesn't quite match the chemical fingerprint of Earth's water.

This discrepancy in what scientists call isotopic composition led researchers to believe that there must be at least one additional source of our planet's life-giving liquid. Isotopes are forms of chemical elements that differ just by the number of uncharged neutrons they contain. The carbonaceous chondrites tend to have water that contains more deuterium, a form of hydrogen with one neutron, while Earth's hydrogen is mostly a lighter form called protium that has no neutrons.

In search of the additional source of Earth's water, the team of researchers analyzed the composition of a rocky type of asteroid rich in silicon oxide using a novel technique called the atom probe tomography. Using this technique, the researchers measured the atomic structure of these grains one atom at a time to detect individual water molecules. The samples analyzed in this study came from the asteroid Itokawa, famously visited by the Japanese probe Hayabusa, which delivered tiny pieces of this space rock to Earth in 2010.

"[Our technique] lets us take an incredibly detailed look inside the first 50 nanometers [one inch has 24.5 million nanometers] or so of the surface of dust grains on Itokawa, which orbits the sun in 18-month cycles," Phil Bland, the director of the Space Science and Technology Center at Curtin University in Australia and co-author of the new study, said in the statement. "It allowed us to see that this fragment of space-weathered rim contained enough water that, if we scaled it up, would amount to about 20 liters [4.4 gallons] for every cubic meter [35 cubic feet] of rock."

The particles produced in the interaction of Itokawa's dust and the solar wind had more of the lighter form of hydrogen than the carbon-rich asteroids, Bland added. "That strongly suggests that fine-grained dust, buffeted by the solar wind and drawn into the forming Earth billions of years ago, could be the source of the missing reservoir of the planet's water," Bland said.

But the research isn't just about Earth. The findings also suggest that water might be locked in the surface rocks of many space bodies, including the moon and asteroids, the researchers said in the statement. If so, this could be good news for future human exploration in deep space, as necessary supplies might be easier to find than scientists fear.

"One of the problems of future human space exploration is how astronauts will find enough water to keep them alive and accomplish their tasks without carrying it with them on their journey," Hope Ishii, a geophysicist at the University of Hawai'i at Mānoa and also a co-author of the paper said in the statement.

"We think it's reasonable to assume that the same space weathering process which created the water on Itokawa will have occurred to one degree or another on many airless worlds," she added. "That could mean that space explorers may well be able to process fresh supplies of water straight from the dust on the planet's surface."

The research is described in a paper published Monday (Nov. 29) in the journal Nature Astronomy.

https://bit.ly/3plBbQY

Major Discovery Challenges Decades of Advice to Avoid All Saturated Fats

Instead of paying attention to how much saturated fat is consumed, we should also look at where the saturated fat is coming from.

Marinka Steur* & Nita Forouhi**

Heart disease is a major cause of death worldwide – responsible for some 9 million deaths a year. But it is preventable, and health behavior changes – such as exercising more, quitting smoking, and eating healthier – are often recommended.

One diet change commonly recommended by experts is to eat fewer saturated fats – and instead consume polyunsaturated fats (typically found in nuts, vegetable oils, and fish), which are considered healthier.

But our new research suggests that instead of only paying attention to the amount of saturated fat we consume, we should also look at what food sources the saturated fat is coming from.

Until now, most research on saturated fats has focused solely on looking at saturated fat and its link with heart disease. But foods contain many different types of nutrients.

This is why it's important to investigate which foods containing saturated fats are linked to heart disease, rather than only considering saturated fat alone. This is what our research set out to do.

Our research drew on data from the University of Cambridge's EPIC-CVD study, which looked at the cardiovascular health of middle-aged people in 10 European countries. This included 10,529 participants who developed heart disease during the study, whom we compared against 16,730 participants who did not.

Participants were randomly selected from the 385,747 participants of the EPIC study to ensure our findings were representative of the whole study population. We also looked at data on their dietary habits as part of our analysis.

We made sure to take into account various factors that may be related to heart disease – such as a person's age, sex, physical activity levels, whether they smoked or drank alcohol, and whether they were overweight or obese.

This minimized the chances that our findings about fat consumption and heart disease might actually be explained by these other factors.

We found no overall link between the amount of saturated fats participants consumed and their risk of developing heart disease. But this picture was different when we looked at foods that are typical sources of saturated fats.

We found that people who ate more saturated fats from red meat and butter were more likely to develop heart disease. The opposite was true for those who ate more saturated fats from cheese, yoghurt, and fish – which were actually linked to a lower risk of heart disease.

These findings are in line with what earlier research has shown about the link between these foods and heart disease. These findings show us that the link between heart disease and saturated fats depends on what food sources it comes from.

One caveat with our research is that it's based on observing the associations between diet and health. As such, this cannot prove cause and effect.

However, conducting a randomized controlled trial, where participants would be randomly assigned a certain diet to follow for many years, would likely be impractical – and many participants may not wish to stick to a specific diet for the length of the study.

More than one nutrient

Foods are more than just the sum of their parts. They contain many different nutrients, vitamins, minerals and properties that may act together to prevent or cause certain diseases.

For example, although cheese and yoghurt contain saturated fats, they also contain nutrients such as vitamin K2 and probiotics. Each of these nutrients may affect heart disease risk through different interrelated pathways – such as by their effects on blood sugar, cholesterol levels, or inflammation.

Previous studies have also shown that different saturated fats carry different levels of risk when it comes to heart disease.

For instance, palmitic acid (a sub-type of saturated fat) is more abundant in red meat compared to cheese and yoghurt. Research shows that it may have a detrimental effect on the levels of cholesterol circulating in our blood – a well known risk factor for heart disease.

In contrast, pentadecanoic acid (another sub-type of saturated fat, commonly found in dairy) is generally linked with lower risk of heart disease.

This shows us that ultimately, our health is affected by the combination of all the nutrients and bioactive components (including vitamins, minerals, and phytochemicals) in the foods we eat. This is why it's important to consider the foods we eat alongside the nutrients they contain.

Preventing heart disease depends on numerous factors, such as being physically active, not smoking and adopting a healthier diet.

But as our research shows, reducing saturated fat intake may not be enough for reducing risk. Rather, it's about focusing more on reducing foods such as red meat and butter which are linked to a significantly higher risk than other foods that contain saturated fats.

*Marinka Steur, Career Development Fellow, MRC Epidemiology Unit, University of Cambridge and **Nita Forouhi, Programme Leader, MRC Epidemiology Unit, University of Cambridge.

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Does COVID-19 During Pregnancy Harm the Baby's Brain?

Mild to moderate COVID-19 in pregnant women appears to have no effect on the brain of the developing fetus

COVID-19 of mild to moderate severity in pregnant women appears to have no effect on the brain of the developing fetus, according to a study being presented today (November 30, 2021) at the annual meeting of the Radiological Society of North America (RSNA).

Two years into the pandemic, there is evidence that pregnant women are more vulnerable to the SARS-CoV-2 virus that causes COVID-19. However, little is known about the possible consequences for an unborn child if the mother is infected during pregnancy. The likelihood and impact of a vertical transmission, meaning the passage of the virus from mother to the fetus, remains unclear.

"Women infected with SARS-CoV-2 during pregnancy are concerned that the virus may affect the development of their unborn child, as is the case with some other viral infections," said study senior author Sophia Stöcklein, M.D., from the Department of Radiology at Ludwig Maximilian University of Munich, in Germany. "So far, although there are a few reports of vertical transmission to the fetus, the exact risk and impact remain largely unclear. The aim of our study was to fill this gap in knowledge regarding the impact of a maternal SARS-CoV-2 infection on fetal brain development."

Dr. Stöcklein and colleagues used fetal MRI to study 33 patients with COVID-19 infection during pregnancy. The patients were roughly 28 weeks into their pregnancies, on average, with symptom onset occurring at a mean of just over 18 weeks into the pregnancy. The most common maternal symptoms were loss or a reduced sense of smell and taste, dry cough, fever, and shortness of breath.

Two board-certified radiologists with several years of experience in fetal MRI evaluated the scans. They found that the brain development in the assessed areas was age-appropriate in all fetuses. There were no findings indicative of infection of the fetal brain.

"In our study, there was no evidence that a maternal SARS-CoV-2 infection has any effect on the brain development of the unborn child," Dr. Stöcklein said. "This fact should help to reassure affected parents."

Dr. Stöcklein cautioned that only mothers with mild to moderate

symptoms and without hospitalization were included in the study.

"Since the impact of severe infection on brain development in the fetus has not been conclusively determined, active protection against SARS-CoV-2 infection during pregnancy remains important," she said.

As part of that protection, the Centers for Disease Control and Prevention (CDC) recommends vaccination for all people ages 12 and older, including women who are pregnant or thinking about getting pregnant. The CDC notes that the vaccine can protect against severe illness.

"So far, vaccination is the most promising protection against COVID-19," Dr. Stöcklein said. "Any potential side effects are manageable, even in pregnant women. Therefore, despite the encouraging results of our study, pregnant women should strongly consider vaccination."

The researchers will be following the patients over the next five years, including detailed neonatal assessment, as well as assessment of neurological development.

Co-authors are Olaf Dietrich, Ph.D., Andreas Flemmer, M.D., Julien Dinkel, M.D., Nicola Fink, Vanessa Koliogiannis, M.D., Christoph Hubener, M.D., Tobias Prester, Maria Delius, M.D., M.P.H., Thomas Kolben, and Sven Mahner, M.D.

Meeting: 107th Scientific Assembly and Annual Meeting of the Radiological Society of North America

https://bit.ly/3oju4Jc

COVID-19 Infection Increases Complications in Pregnancy and Birth

Pregnant women with COVID-19 more likely to have complications with pregnancy and birth compared to those without

Pregnant women with COVID-19 are more likely to have complications with pregnancy and birth compared to those without, according to research publishing today (November 30th, 2021) in the open-access journal *PLOS Medicine*. The study looks at hospitalization for births in France during the first six months of the pandemic and suggests that vaccination may be useful to protect women and their babies, particularly for women at a higher risk of developing severe COVID-19 infections.

Few studies have looked at associations between COVID-19 and pregnancy outcomes, particularly during the first wave in early 2020. Sylvie Epelboin and colleagues from the Universite de Paris analyzed data for hospitalizations for birth after 22 weeks gestation in France between January and June 2020. Until 15 March, all confirmed cases of COVID were hospitalized but after this hospital admission was based on the medical condition of the patient. Of 244,465 births in hospital, 874 or 0.36% of mothers had been diagnosed with COVID-19.

Women in the COVID-19 group were more likely to be older, have obesity, be carrying more than one baby, or have a history of high blood pressure compared to those without. The women with COVID-19 had a higher frequency of admission to ICU; death; preeclampsia and eclampsia; gestational hypertension; hemorrhage either before or after birth; very premature spontaneous or induced birth; and cesarean section. Rates of pregnancy terminations, stillbirths, gestational diabetes, placenta previa, placental abruption, and blood clots were not increased.

Being aware of these complications is important for health care providers to support pregnant women and provide the best care. The authors believe that although causality cannot be established in this study, vaccination to protect pregnant women from COVID-19 may be useful, particularly for those in higher risk groups.

The authors add, "We conducted a retrospective analysis of prospectively collected data in a national cohort of all hospitalizations for births ≥22 weeks of gestation occurring in France from January to June 2020 using the French National hospitalization database, including a total of 244645 births, of

which 874 (0.36%) with COVID-19 diagnosis. When compared to the non-COVID-19 group, women in the COVID-19 group were associated to an increased frequency of admission to ICU, mortality, preeclampsia/eclampsia, gestational hypertension, postpartum hemorrhage, spontaneous and induced preterm and very preterm birth, fetal distress and Cesarean section."

Reference: "Obstetrical outcomes and maternal morbidities associated with COVID-19 in pregnant women in France: A national retrospective cohort study" by Epelboin S, Labrosse J, De Mouzon J, Fauque P, Gervoise-Boyer M-J, Levy R, et al., 30 November 2021, PLOS Medicine. DOI: 10.1371/journal.pmed.1003857

https://wb.md/3osA1E5

Single-Dose HPV Vaccination Highly Effective

Single dose of HPV vaccine highly effective at preventing oncogenic infection, rivals protection of multidose regimens

Sharon Worcester

A single dose of human papillomavirus (HPV) vaccine was highly effective at preventing oncogenic infection, rivaling the protection offered by multidose regimens, according to results from the KEN SHE trial, based in Kenya.

The findings, published on the preprint server Research Square and presented November 17 at the 34th International Papillomavirus Conference in Toronto, Canada, bring "renewed energy to the push to make cervical cancer the first cancer to be wiped out globally," according to co–principal investigator Ruanne V. Barnabas, PhD, a professor of global health at the University of Washington School of Medicine, Seattle.

Decision-makers will consider these findings, which have not yet been peer-reviewed, along with other evidence to determine if dosing-schedule changes are warranted, she told *Medscape Medical News.*

In a press release, Samuel Kariuki, PhD, acting director general, Kenya Medical Research Institute, who was not involved in the research, called the findings a "game changer" that could "substantially reduce the incidence of HPV-attributable cervical cancer."

Between 2018 and 2019, Barnabas and her colleagues enrolled 2275 sexually active, HPV-vaccine-naive women in Kenya in their study. The women, 15 to 20 years of age, were randomly assigned to receive a bivalent vaccine (HPV 16/18), a nonavalent vaccine (HPV 16/18/31/33/45/52/58/6/11), or a vaccine against meningococcal meningitis.

Most participants (57%) were between 15 and 17 years of age, and 61% reported one lifetime sexual partner. The women underwent genital and cervical swabs at enrollment to test for HPV DNA and had blood drawn to test for antibodies. During 18 months of follow-up, they had cervical swabs every 6 months and a vaginal swab at 3 months to test for HPV DNA.

The researchers detected 38 persistent HPV 16/18 infections in women who had tested negative for HPV 16/18 antibodies at enrollment and for HPV 16/18 DNA at enrollment and month 3 — one in each of the HPV-vaccine groups and 36 in the meningococcal group. This infection rate corresponded to a vaccine efficacy of 97.5% ($P < .001$) against HPV 16/18 for both the bivalent and nonavalent vaccines, which is "comparable to that seen in multidose vaccine trials," the researchers write.

Among women negative for HPV 16/18/31/33/45/52/58 at the beginning of the trial, 33 had persistent infections: four in the nonavalent vaccine group and 29 in the meningococcal group, demonstrating an efficacy of 89% ($P < .001$) against all seven oncogenic strains contained in the vaccine.

Even if women tested positive for one strain of HPV, the vaccine protected them from other strains of the virus, the investigators noted. Serious adverse events occurred in 4.5% to 5.2% of participants across the study arms.

The KEN SHE trial comes 15 years after the US Food and Drug

Administration approved the first HPV vaccine — Merck's Gardasil. Two others, Cervarix and Gardasil-9, have since been approved, but cost and supply issues have inhibited coverage, particularly in areas where the cervical cancer burden is high, the researchers noted.

Recent data indicate that just 15% of girls globally are vaccinated against HPV, but a single-dose vaccine would "simplify logistics and decrease costs," thereby improving the chances of reaching the World Health Organization goal of vaccinating 90% of 15-year-old girls against HPV by 2030, Barnabas said in a press release about the trial.

Co–principal investigator Nelly Mugo, MBChB, MPH, senior principal clinical research scientist with the Center for Clinical Research at the Kenya Medical Research Institute in Nairobi, further emphasized the importance of the findings, noting in the press release that the "trial brings new energy to the elimination of cervical cancer. It brings great hope to the women living in countries like Kenya, who have a high burden of the disease."

Mugo is also an associate research professor of global health at the University of Washington, Seattle.

Barnabas said women have been given multiple doses of the HPV vaccine because of "gaps in evidence for the effectiveness of a single-dose vaccine and concerns about clinically meaningful differences in efficacy.

"Observational data suggested that the single-dose HPV vaccine could have good efficacy, but because the data were not from randomized trials, that could have been from chance," she explained, noting, however, that "sufficient evidence supported the decrease in doses from three to two doses for girls 15 years of age and younger."

Going forward, the researchers will conduct immunobridging studies to other populations and will continue follow-up to assess the durability of single-dose efficacy, Barnabas said.

"The results from the KEN SHE trial support the use of single-dose HPV vaccination to increase access and coverage," she concluded.

The KEN SHE trial was funded by the Bill & Melinda Gates Foundation (BMGF). Barnabas reports grants from BMGF and grants from King K. Holmes Professorship in STDs and AIDS during the conduct of the study and grants from BMGF, National Institutes of Health, and manuscript and abstract writing support from Regeneron Pharmaceuticals outside the submitted work.

This research is from a preprint study. The full text can be found at researchsquare.com.

34th International Papillomavirus Conference: Presented November 17, 2021.

https://bit.ly/3DoCUd9

Breakthrough Infection Study Compares Decline in COVID Vaccine Effectiveness: Pfizer vs Moderna vs J&J

Study in *Science* of more than 780,000 Veterans is the first to compare waning protection rates across all three vaccine types available to most Americans and to directly report death rates after breakthrough infection.

A new study in the leading journal Science reviewed COVID-19 breakthrough infections among 780,225 Veterans, finding that vaccine protection declined from 87.9% to 48.1% during the 2021 Delta surge in the U.S. The researchers from PHI, the Veterans Affairs Medical Center and the University of Texas Health Science Center found a dramatic decline in effectiveness for the Janssen (Johnson and Johnson) vaccine, from 86.4% in March to 13%.1 in September. They also found that vaccination of any type was protective against death among infected individuals.

As COVID-19 breakthrough infections continue to emerge in some vaccine recipients and health authorities are developing policies around booster vaccinations, national data on COVID-19 vaccine breakthrough infections is inadequate but urgently needed. Now a study from the Public Health Institute, the Veterans Affairs Medical Center and the University of Texas Health Science Center published today in the journal *Science* analyzed COVID infection

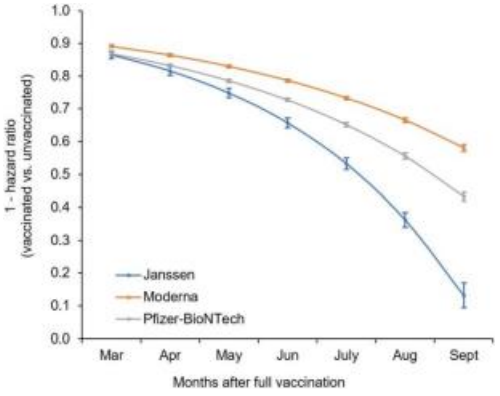
by vaccination status among 780,225 Veterans.

Researchers found that protection against any COVID-19 infection declined for all vaccine types, with overall vaccine protection declining from 87.9% in February to 48.1% by October 2021.

- The decline was greatest for the Janssen (Johnson & Johnson) vaccine, with protection against infection declining from 86.4% in March to 13%.1 in September
- Declines for PfizerBioNTech were from 86.9% to 43.3%
- Declines for Moderna were 89.2% to 58%.

While most previous studies have focused on the PfizerBioNTech or Moderna vaccines, the *Science* study is the first to compare protection declines across the three main vaccine types, and the first to show the comparably dramatic decline in effectiveness for the Janssen vaccine. Declines were assessed over the period February 1, 2021 to October 1, 2021, reflecting the emergence and dominance of the Delta variant in the U.S. Patterns of breakthrough infection over time were consistent by age, despite rolling vaccine eligibility, implicating the Delta variant as the primary determinant of infection.

Importantly, vaccination of any type was protective against death among individuals who did become infected. The relative benefit of vaccination for protection against death was greater for persons under 65 but was also very strong for persons over 65.



Credit: Public Health Institute

The study showed that the risk of death from COVID infection was highest in unvaccinated Veterans, regardless of age and comorbidities. While some breakthrough infections resulted in death, vaccination remained protective against death in those who became infected during the Delta surge.

For those under 65 years old, vaccines overall were 81.7% effective against death.

- Protection against death was greatest for the Pfizer vaccine, at 84.3%.
- Moderna was the next most effective, at 81.5%.
- Jansen was 73% effective.

For those 65 and over, overall vaccine effectiveness against death was 71.6%.

- Moderna was 75.5% effective.
- Pfizer was 70.1% effective.
- Jansen was 52.2% effective.

"Our study gives researchers, policymakers, and others a strong basis for comparing the long-term effectiveness of COVID vaccines, and a lens for making informed decisions around primary vaccination, booster shots, and other multiple layers of protection, including masking mandates, social distancing, testing and other public health interventions to reduce chance of spread," said Dr. Barbara Cohn of PHI, the lead author of the study. "For example, the CDC recommendation for boosters for all Janssen recipients over 18 is supported by our results. And, given the declines in vaccine protection and the dominance of the more infective Delta variant, we urge swift action to promote primary vaccination, boosters and to also encourage masking, social distancing and other layers of protection against infection. This is supported by our finding that breakthrough infections are not benign, but also by the strong evidence that vaccination still protects against death even for persons with breakthrough infections, compared to persons who become infected and are not vaccinated."

The FDA authorized Pfizer boosters for some groups in September

and Moderna and Janssen boosters in October, and the CDC has made similar recommendations, including supporting a "mix and match" approach that allows people to choose any of the three vaccine boosters regardless of which they were given initially.

Reference: "SARS-CoV-2 vaccine protection and deaths among US veterans during 2021" by Barbara A. Cohn, Piera M. Cirillo, Caitlin C. Murphy, Nickilou Y. Krigbaum and Arthur W. Wallace, 4 November 2021, Science. DOI: 10.1126/science.abm0620

https://bit.ly/31zamAf

Decades-Old 'Water Pill' Opens New Avenues for Alzheimer's Treatment

In genetically engineered mice prone to Alzheimer's, bumetanide shrank the size of the plaques and improved brain function.

By Shelly Fan

The cause of Alzheimer's was supposedly simple. Mangled proteins aggregate into tangles and clumps. These clumps overwhelm neurons. Neurons lose their function and eventually die, leading to cognitive troubles that are the hallmark of Alzheimer's disease.

But this central dogma is only a fraction of the story.

This month, two studies broadened the scope, taking a slightly different approach to understanding the mind-wasting disorder. One study, led by Dr. Melanie Meyer-Luehmann at the University of Freiburg in Germany, surprisingly found that a long-thought ally in the battle against amyloid protein clumps—microglia cells—may instead promote the toxic protein's spread across unaffected brain regions. In mice, microglia "seeded" amyloid plaques into healthy donor cells, spreading the clumps like wildfire into previously unaffected regions.

Another study ditched the amyloid hypothesis altogether. Scouring a database of FDA-approved treatments, Dr. Yadong Huang's team at Gladstone Institutes stumbled onto a decades-old drug that reverses Alzheimer's symptoms in mice and human cells in petri dishes. By mining health data from people over 65 who regularly take the medication, the team found that this population was up to 75 percent less likely to be diagnosed with Alzheimer's.

The twist? The drug, bumetanide, is a strong "water pill" that dehydrates the body—something that seemingly has nothing to do with amyloid plaques. Yet in genetically engineered mice prone to Alzheimer's, the drug shrank the size of the plaques and improved brain function.

"There are many cellular and molecular changes in Alzheimer's disease patients besides plaques, but we usually don't talk about them," said Huang to *STAT News*.

For now, the studies are only in mice or human cells. Neither dispute the central dogma that amyloid proteins are a culprit. But they also join the recent renaissance of taking a broader view of Alzheimer's.

It's about time. Since the early 90s, drug development for Alzheimer's has often been dubbed the "graveyard of dreams," in which initially promising drugs in animal models crash and burn when tested in patients.

By expanding our view, "I would see this much more as pointing us towards a repertoire of pathways that have not been adequately investigated," said Dr. Jeffrey Cumming at the University of Nevada Las Vegas, who was not involved in either study.

The Amyloid Enigma

Alzheimer's doesn't have a cure. But we do have a hint of what it does to the brain.

By studying mice genetically engineered to have Alzheimer's, scientists have found amyloid protein clumps that increasingly accumulate outside cells. A similar process happens inside neurons with a different protein, tau. Together, they overwhelm a neuron's waste disposal system. Like overfilled garbage cans that start reeking in the height of summer, these protein clumps create a toxic

environment that eventually leads to malfunctioning neurons.

But that simple story gets weird. For one, amyloid protein clumps tend to spread like viruses. In many cases, they follow a rough, but similar, trajectory as they infect different brain regions, as if navigating with a cellular Google Maps direction. For another, treatments aimed simply at reducing the amount of amyloid clumps have mostly failed. One exception? Biogen's Aduhelm, which was approved by the FDA this summer and cleared the clumps, but with marginal impact on patients' cognition.

Clearly, something is missing.

Enter Microglia

Like other parts of our body, the brain has a prominent immune system. Top of the line are microglia cells, which usually lie dormant but activate when they sense an invader—may it be bacteria, viruses, or tangled protein clumps.

Once activated, these cells—with a hefty body and shrunken branches all across the body like a morning star—link up into a barrier. Like a wired fence, the barrier limits amyloid plaques from spreading across the brain as microglia gulp them up.

"These cellular defense processes have crowned microglia as perhaps the most important cell type" in controlling amyloid proteins, said Yun Chen and Dr. Marco Colonna at Washington University School of Medicine in St Louis, who were not involved in the study.

Yet as the new study from Meyer-Luehmann shows, they have a dark side. Here, the team transplanted healthy embryonic neural cells into the brains of young mice that were genetically engineered to be more susceptible to Alzheimer's. Just a month after transplant, the newly grafted healthy tissue began showing signs of amyloid plaques. These deposits increased over time.

But why? Digging deeper, the team found that the culprit was microglia. These cells are hungry; they'll happily chew up and burp up whatever's toxic in the environment to protect the brain. That is, until—like after a massive thanksgiving dinner—they're overwhelmed. Without fully "digesting" the amyloid food, the cells can travel to other brain regions to "seed" the toxic proteins.

For now, the authors don't yet understand what triggers microglia to spread amyloid across the brain like a viral carrier. Part of it could be due to trauma caused by the transplantation, which provides a mysterious secondary signal that activates the cell's dark side.

What's clear is that contrary to popular belief, microglia aren't solely protectors. Instead, they act as double agents. IRF8 seems to be key: genetically deleting the protein dampened the spread of amyloid seeds, while keeping microglia's ability to engulf existing clumps.

"[The authors] have exposed an enigmatic side of microglia," said Chen and Colonna.

For now, it's still anyone's guess how much the brain's defense system double crosses us in Alzheimer's as the disease progresses. But, said the authors, if we can understand *why* they're two-faced—one that battles against amyloid plaques, versus one that helps them along—we could bolster their plaque-eating powers while keeping their dark side at bay.

A Paradigm Shift?

In another study, Huang and colleagues took a big data approach, side-stepping the amyloid story—although not overturning it—while searching for other potential genetic disruptions in Alzheimer's. One of the largest risk factors for Alzheimer's is a gene called APOE4. Carriers of two copies of the gene have 10 times the risk of getting the disorder than the average Joe, and one gene therapy trial is looking for a genetic fix.

Huang's team decided to neutralize APOE4 with medication. Their special sauce is drug repurposing: searching through existing FDA-

approved drugs to see if they can help Alzheimer's in any way, even when those drugs weren't originally created for the disease.

They first examined how APOE4 changes a cell's gene expression patterns, and then compared those to people who don't carry the mutation. Tapping into a data bank of over 1,300 drugs, they next identified candidates to restore genetic patterns back to their normal, healthy state.

The result? Bumetanide, a powerful water pill approved by the FDA back in the 1980s. When given to aging mice—about 60 years old in human age—genetically engineered to have two copies of APOE4, the drug increased performance on memory and cognitive tests. In another experiment, the drug also improved Alzheimer's symptoms, including fewer amyloid clumps, in mice with two genetic predispositions to the disorder.

While bumetanide has been used off-label for epilepsy and other brain disorders, it's a new (and slightly bizarre) option for Alzheimer's. It clears amyloid plaques in mouse models, suggesting however it works to do so—scientists don't yet know—taps into the amyloid hypothesis, just in a completely unexpected way.

Together, the two studies showcase different yet converging approaches. One starts with biological theories to parse the brain's reaction to Alzheimer's, looking to cells other than neurons that could lead to new treatments. The other works with drugs we already have—using computational screens—to find candidates previously ignored, while generating new hypotheses to test in the lab.

For now, these results are in mice, not men, and many drugs have failed to bridge the gap. But what's increasingly clear is that Alzheimer's is a multi-headed beast.

"These results suggest that in order to treat Alzheimer's we should probably not target only one or two but multiple genes and multiple pathways involved in the disease," said Huang.

https://nyti.ms/3rFG9KW

This Extinct Eagle May Have Gulped Guts Like a Vulture

Scientists suggest the largest eagle that ever existed hunted down its 500-pound prey and then stuck its head inside to gorge on organs.

By Sabrina Imbler

At Craigmore Station in Canterbury, New Zealand, an ancient Maori painting decorates the limestone overhang of a cave. Thought to depict an extinct eagle, the painted raptor gives the cave its name: Te Ana Pouakai, or the Cave of the Eagle. But this wasn't just any bird — it may have been a Haast's eagle, which had wingspans between six and 10 feet, making the species the largest known eagle.

The Maori artist painted the bird with a dark body and an outline of a head and neck that is more reminiscent of the bald head of a vulture than the feathery dome of an eagle.

While this Haast's eagle depicted preying on a flightless moa has a feathery head, new research speculates it may have been bald. **Credit...Jaime Chirinos/Science Source**

Now, a group of scientists suggest the extinct eagle may have looked just like its painted form. By creating 3-D models of the extinct bird's skull, beak and talons, the group tested how well the eagle performed against living raptors in a series of feeding simulations. Their results, published Wednesday in the journal Proceedings of the Royal Society B, argue the Haast's eagle hunted like a predatory eagle but feasted like a scavenging vulture.

"It's a unique, chimera-like combination for a bird," said Stephen Wroe, a researcher from the University of New England in Armidale, Australia, and an author on the paper.

The Haast's eagle went extinct around 1400 when its prey, the flightless moa, was hunted into extinction by Maori settlers. The eagles were gigantic, weighing up to 30 pounds. In Maori lore, Haast's eagle may have been represented by Pouakai, a giant bird of prey that could kill and eat humans.

A painting in the Te Ana Pouakai, or the Cave of the Eagle, in Canterbury, New Zealand, showing a possible Haast's eagle, which went extinct around 600 years ago.Credit...Gerard Hindmarsh

Though the eagles were first described in the late 19th century, the question of whether the creature was a hunter or carrion feeder went unresolved for decades. Recent analyses of the eagle's nervous system and sensitive, powerful talons have made a strong case that the large bird killed prey like modern eagles.

"Modern eagles eat things that are smaller than themselves, so they can eat it in two or three bites," said Anneke van Heteren, a researcher at the Bavarian State Collection of Zoology in Munich and an author on the paper.

But many scientists have pointed to the Haast's eagle's more vulture-like characteristics, such as bony structures around the nostrils, which help scavengers feed inside a much larger animal without accidentally suffocating themselves.

"When they get their head into the goo, they don't want to get that in their nose," Dr. van Heteren said. Dr. Wroe had received CT scans of a Haast's eagle skull around a decade ago. But study of the animal's potentially vulture-like features remained on the back burner for years until Dr. van Heteren took it on.

The researchers used a technique called geometric morphometrics, identifying landmarks on the bone, to capture the shape of the Haast's eagle's skull, beak and talons in three dimensions.

Just as eagles can specialize in hunting specific prey, vultures do not all scavenge in the same way. Some, known as "rippers," feed on the tough skin of a carcass. "Gulpers" slurp up the soft, nutrient-rich innards. And "scrappers" eat small scraps.

The authors compared their model of the Haast's eagle to models of living vultures and eagles, which exhibited a range of feeding styles from hunting to scavenging. They examined the cinereous vulture, a "ripper," and the Andean condor, a "gulper," as well as several eagles that hunted prey of various sizes. The researchers ran the models through simulations of feeding behavior.

"Vultures feed on animals that are a lot bigger than themselves," Dr. Wroe said. "They have to thrust their head deep into the abdominal cavity of a rotting zebra carcass and pull out the high nutrient value, soft internal organs: heart, lungs, liver."

The Haast's eagle model performed like a vulture in certain tests and like an eagle in others. It had the talons of an eagle and was excellent at biting down on prey. But it was not as good at ripping off chunks of meat. It fed like a vulture, closely matching the gulping Andean condor in its ability to nose inside a carcass.

The researchers say these results suggest the Haast's eagle killed moa and then ate their guts. "It's no mean feat, because it was a heck of a big bird," Dr. Wroe said of moa, which could weigh up to 550 pounds.

Guillermo Navalón, a postdoctoral researcher at the University of Cambridge who was not involved with the study, said he found the authors presented strong evidence for Haast's eagle's hunting prowess.

But he said that the similarity in skull shape between the Haast's eagle and vultures could be a result of their similarly large sizes rather than an indication of feeding behavior, and pointed to a 2016 study that found larger raptors have different cranial shapes than smaller raptors. Dr. Navalón suggested a more comprehensive

analysis of the skull shapes could have clarified whether the similarities were related to scavenging, instead of just the birds' large size.

When the paper was nearly finished, one of the authors wondered if the Haast's eagle was bald like many modern vultures. Dr. van Heteren thought of the scientific accuracy of European cave art, and the researchers scoured the internet for drawings of Haast's eagle in New Zealand caves.

In their searching, they stumbled upon a photo of the painted overhang of the Cave of the Eagle, depicting the dark-colored bird with the uncolored head — evidence, perhaps, of baldness.

"When you look at it, I don't know what else it could be," Dr. van Heteren said. "These people were eyewitnesses, why not take their word for it?"

https://bit.ly/3EFgQfX

Presidential Pox, 1863

Researchers continue to debate whether US president Abraham Lincoln was coming down with smallpox as he delivered his famous Gettysburg Address, and if he had been immunized.

Annie Melchor

Seven score and 18 years ago, Abraham Lincoln delivered a brief but consequential speech in Gettysburg, Pennsylvania, the site of the bloodiest battlefield of the American Civil War, where thousands of soldiers had died.

Lincoln was known for his general air of melancholy and bouts of severe depression, but the night after his November 19, 1863 address, he was plagued by something more. According to contemporary accounts, the president's weakness and dizziness from the day before had worsened into a high fever and a severe headache. A few days later, he developed a rash all over his body, followed by blisters. Although the diagnosis was a mild case of smallpox—suggesting he had preexisting immunity—Lincoln was ordered to quarantine and didn't resume official duties for almost a month. A more recent analysis suggests Lincoln's case may have been more severe, and some researchers speculate that his doctor may have intentionally softened the diagnosis to avoid stirring panic in the war-torn nation.

Lincoln survived, of course, and seemed to make a full recovery before his assassination less than two years later. His valet, however, died of smallpox shortly after the president's recovery. William Johnson, a free Black man who had accompanied the president to Gettysburg, was most likely the one caring for Lincoln, and experts think Johnson probably caught the virus from the president. Lincoln paid off Johnson's debts and had him buried at Arlington National Cemetery.

No one alive today knows if Lincoln had been immunized against smallpox. In 1796, Edward Jenner showed that vaccination with cowpox also protected against smallpox, but a standardized smallpox vaccine didn't exist in Lincoln's time, says University of Rhode Island medical historian Andrea Rusnock. Rather, immunity was often passed along "through [the] arm-to-arm vaccination of children," she says.

Healthcare workers would make a small incision in a child's arm to introduce scabs or fluid drained from smallpox pustules from an immunized child. Repeating that process—which caused pustules in the newly immunized child but not full-blown smallpox—kept the vaccine strain alive in a community. But without organized infrastructure to track immunizations and to continuously harvest the virus from newly inoculated children, the vaccine strain could peter out—and often did, says Rusnock, leaving the community vulnerable unless they got samples elsewhere, often through the mail.

Additionally, routine smallpox vaccination was uncommon outside of large cities, she says. Growing up in the rural town of Springfield,

Illinois, Lincoln probably wouldn't have been vaccinated as a child unless there had been a major outbreak.

While quarantining and encouraging patients to get fresh air reduced deaths and spread, the mortality rate for the unvaccinated was still roughly 30 percent. According to Rusnock, smallpox was "an equal opportunity disease," killing prince and pauper alike, and she adds that crowded wartime conditions and disrupted supply chains likely contributed to additional outbreaks.

"It's important to remember that smallpox was incredibly frightening, because one out of three people [wasn't] going to survive," says Rusnock. "For Lincoln to have smallpox and then recover—it's such a precarious moment in our nation's history."

https://bit.ly/3El6MIF

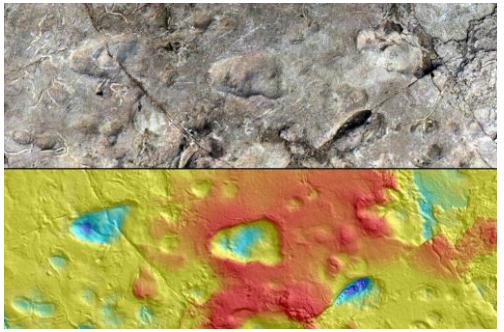
Ancient footprints suggest famed human ancestor 'Lucy' had company

Reanalysis of 3.6-million-year-old footprints suggest a second kind of hominin walked in Lucy's neighborhood

By Michael Price

Some 3.6 million years ago, an upright walking creature trudged through layers of freshly fallen volcanic ash in what today is northern Tanzania. When anthropologists uncovered five of its fossilized footprints nearly 50 years ago, they couldn't say whether this ancient biped was a hominin, a bear, or some other ape. Now, a new team claims to have solved this paleontological cold case, identifying the mystery walker as an unknown species of hominin. If true, this creature lived in the same place at the same time as the famed human ancestor, "Lucy." It would also offer a window into the early day of our distant ancestors' evolutionary forays into bipedalism.

Back in 1976, paleoanthropologists were combing a site called Laetoli in northern Tanzania's hill country for fossils. Two members of the team began playfully flinging dried elephant dung at each other. In the fracas, one jumped into a gully and spotted what appeared to be an animal footprint preserved in hardened volcanic ash. The team, led by famed paleoanthropologist Mary Leakey, eventually found tracks left by ancient elephants, hippopotamuses, and more, all later dated to 3.6 million years ago.



Five fossilized wide-footed, broad-heeled footprints are stamped into the ground in Laetoli, Tanzania. Researchers scanned and color-coded them to highlight details and depths. **Austin C. Hill and Catherine Miller**

Five consecutive footprints stood out. They were semitriangular in shape, with a wide sole that narrowed toward the heel. Whatever left them walked on two legs, "somewhat shambling, with one foot crossing in front of the other," Leakey wrote.

At the time, nobody knew what to make of the impressions at what came to be called Site A, says Jeremy DeSilva, a paleoanthropologist at Dartmouth College and senior author of the new study. "They looked strange," DeSilva says. Leakey suggested they might have been made by a hominin, but other experts suggested they were bear prints. Bears do sometimes walk on two legs, and their feet strike the ground heel first, similar to humans.

Then in 1978, Leakey's team discovered dozens of fossil prints left by multiple individuals, about 1 kilometer away but in the same layer of volcanic ash. They bore little resemblance to the previously discovered tracks. In fact, these Site G tracks were "very similar to the kinds of footprints that you or I would make on a beach," DeSilva says. Many speculated they were left by close kin of the famous fossil hominin known as Lucy, a member of *Australopithecus afarensis*, a human ancestor that lived between 3.9

and 3 million years ago. As for Site A tracks? “The field kind of forgot about them,” DeSilva says.

One of DeSilva’s former graduate students, Ellison McNutt, picked up the thread while working on her doctoral dissertation in the late 2010s. McNutt, now a medical anatomist at Ohio University’s Heritage College of Osteopathic Medicine, had read about the bizarre Laetoli footprints and their proposed bear origin. A few miles up the road from Dartmouth lies the Kilham Bear Center, which rehabilitates orphaned black bear cubs. Why not compare the Laetoli Site A tracks to some actual bear tracks?

Working with the center’s staff, McNutt built a mud-covered trackway and enticed four juvenile black bears—whose paws were approximately the same size as the Laetoli tracks—to walk upright across it to get either applesauce or a maple syrup treat.

Then she measured the muddy bear prints, including stride length, gait pattern, and feet dimensions. Next, McNutt and colleagues compared those characteristics with a digital reconstruction of the Laetoli prints—the original casts made in 1976 were lost—and to previously collected data on human and chimpanzee feet and gait.

The footprints found at Laetoli Site A in Tanzania have wide soles, broad heels, and a prominent big toe. **Jeremy DeSilva**

When the analysis was done, McNutt was confident a bear didn’t leave the Laetoli Site A tracks. Bears have narrow heels and nearly equally sized toes, with exterior toes just slightly bigger than the others. The Laetoli tracks had broad heels and a prominent big toe. Bears also lack the hip or knee flexibility to cross their feet in front of one another, McNutt says. Chimps, too, lack that cross-stepping ability. The closest match, she says, is humans. Whatever left the Laetoli prints had feet “a little bit wider, with a little bit more extended big toe, than what we see in humans now.”

DeSilva was convinced, but he knew others in the field would want more evidence. So, he and colleagues, including a researcher from Tanzania’s Department of Cultural Heritage, returned to Laetoli and consulted Leakey’s old maps to find and re-excavate Site A, which had been covered over the years by sediment washing down a hill. After digging through a few inches of debris, they found the footprints “beautifully preserved,” DeSilva says.

New casts of the footprints reveal a prominent big toe adjacent to a smaller second toe. That’s another strong indication it belonged to a bipedal hominin, DeSilva says. Because the Site A and Site G footprints sit within the same layer of volcanic ash—and because the two sets of prints are so different from each other—the find suggests that 3.6 million years ago, two different species of bipedal hominins at Laetoli were walking within 1 kilometer of each other within the span of a few days, the researchers report today in *Nature*. “It’s showing there were these different experiments in bipedalism occurring at this time,” DeSilva says.

Although DeSilva agrees with many in the field that the Site G tracks were made by *A. afarensis*, the identity of Site A’s footprint maker remains a mystery. Candidates living in the region include *Kenyanthropus platyops* and *A. deyiremeda*. Researchers haven’t uncovered foot fossils for the former, but they have for the latter, and they share some suggestive similarities with the Site A tracks, DeSilva notes. “That one, to me, is really intriguing as a possible candidate for the hominin that would have made these footprints, but we're not going to know for certain until we do some more work at that site.”

The idea that bears may have made the Site A tracks “was always a little bit of an odd explanation,” says William Harcourt-Smith, a paleoanthropologist at Lehman College and the American Museum of Natural History, and the researchers here have convincingly

debunked it.

But he’s not completely convinced they’re homininmade, either. “I think it’s entirely possible—not likely, but possible—that one of the options for who made these prints could be a nonhominin ape,” Harcourt-Smith says. “Without more prints, it’s quite hard to know.”

That’s exactly what DeSilva and McNutt hope to find as soon as it’s safe to travel again given COVID-19 concerns. “We’d like to go back and continue excavating and try to extend this trackway,” McNutt says.

https://bit.ly/3ooNLQ7

This 'Very Weird' Newly Discovered Dinosaur Was Armed With a Slashing Weapon

Paleontologists in subantarctic Chile have discovered the remains of a "very weird" ankylosaur that had a deadly armored tail like no other known dinosaur, the researchers said.

Laura Geggel, Live Science

"The tail would have looked like a sword; it's so flat," study co-lead researcher Alexander Vargas, a vertebrate paleontologist in the Department of Biology at the University of Chile, told Live Science. It would have looked "a bit like an Aztec sword, or the Aztec club called the macuahuitl."

(Lucas Jaymez/@dinoesculturas)

In addition to revealing its weaponized tail, the dinosaur's remains tell a previously unknown tale about ankylosaur evolution: The breaking apart of the supercontinent Pangaea during the Jurassic period (201.3 million to 145 million years ago) led to extreme differences between ankylosaurs on the northern supercontinent Laurasia and those on the southern supercontinent Gondwana, like this newfound species, named *Stegouros elengassen*.

The newfound species was described in a study published online Wednesday (December 1) in the journal *Nature*.

Paleontologists found *S. elengassen* in Cretaceous period rocks dating to between 71.7 million and 74.9 million years ago in February 2018. The well-preserved skeleton was about 80 percent complete, and "it's weird, because it's articulated [the bones are in order] from the waist down, and everything from the waist up was kind of scattered," Vargas said. The beast died by a river, perhaps in quicksand, which would explain why its bottom half is so well preserved, although this is just speculation, he said.

The team had only five days left in the field season to excavate the dinosaur remains, and that short timeline led to a painstaking effort involving a sprained ankle, a broken rib and near-hypothermia among the crew, Vargas said.

But their hard work paid off: Now, the largely Chilean team has an exquisite specimen of a roughly 6.5-foot-long (2 meters) ankylosaur sporting a tail that looks like a fern frond.

The dinosaur's genus name, *Stegouros*, comes from the Greek words for "roof" (stego) and "tail" (uros) – a nod to its covered tail – and its species name, *elengassen*, refers to an armored beast in the mythology of the local Aónik'enk people.

S. elengassen is strikingly different from Laurasian ankylosaurs; it's lightly armored with a few rows of osteoderms, or bony plates, and has a "rather large head with a narrow, curved beak, which is not common for ankylosaurs," Vargas said. "It has slender limbs. … It doesn't have pointed claws; it has rounded, hoof-like claws on both hands and feet."

What's more, the ankylosaur's pelvis is wide and stegosaur-like. "If you had only the pelvis, you would think you had the first Stegosaurus of the Cretaceous," he said. (Stegosaurus lived earlier, during the Jurassic period.)

S. elengassen's most distinctive feature, its tail, is the shortest tail of any known armored dinosaur. It's made of seven paired large and flattened osteoderms. The first two pairs are near the body, and the next five pairs are fused together as a flat, powerful weapon, Vargas said. In contrast, other ankylosaurs have paired spikes or clubs on their tails.

Until now, it wasn't clear whether Laurasian ankylosaurs had somehow journeyed south to populate Gondwana, Vargas said.

But now, *S. elengassen*, "the first completely studied ankylosaur from the Southern Hemisphere", shows that it and two other known Southern Hemisphere ankylosaurs – *Antarctopelta*, from Antarctica, and *Kunbarrasaurus*, from Australia – are lacking many of the specialized traits that the ankylosaurs of the North had and that they already had in the mid-Jurassic," Vargas said. "So these must have split off before the mid-Jurassic, which speaks of very ancient roots."

It's exciting to find an armored dinosaur with a never-before-seen tail, Vargas said. "We all know tail clubs, we all know the tail spine, but this is a new lineage … a Southern Hemisphere lineage that evolved a third kind of tail weapon," Vargas said.

According to Matt Lamanna, a vertebrate paleontologist at the Carnegie Museum of Natural History in Pittsburgh, who wasn't involved with the study, "It's just exceptional material and just a really unexpected dinosaur."

https://wb.md/3dmRhUM

The Hidden Cost of Prostatectomy: Patient Regret

More likely to regret their decision than those who opt for radiotherapy or active surveillance

M. Alexander Otto, MMS, PA

Men with localized prostate cancer who opt for radical prostatectomy are more likely to regret their decision than those who opt for radiotherapy or active surveillance, according to a survey study of 2072 patients.

At 5 years, 13% of men surveyed experienced treatment-related regret, which varied by treatment type — 16% (183) of surgery patients regretted their decision vs 11% (76) of men who opted for radiotherapy and 7% (20) who chose active surveillance.

The main driver of regret was a sense of not being fully informed of the risks and benefits of the three options and the risks of surgery, in particular.

"A disconnect between patient expectations and treatment outcomes, in relation to both treatment efficacy and toxicity, contributes more substantially to treatment-related regret than patient-reported functional outcomes," which includes erectile dysfunction, urinary incontinence, and bowel dysfunction, according to the authors, led by Christopher Wallis, MD, PhD, a urologic oncologist at Mount Sinai Hospital in Toronto, Canada.

The study appeared online on November 18 in *JAMA Oncology*.

In an accompanying editorial, Randy Jones, PhD, RN, a nursing professor at the University of Virginia, Charlottesville, said the study makes a strong case for the role of in-depth counselling and shared decision-making.

Considering "the potential to enhance quality of life and decrease decisional regret, it is well worth the time for clinicians to assess and address patients' treatment concerns," he wrote.

Although not used often in routine practice, Jones noted that interactive decision aids can help. These tools "provide the space for patients, caregivers, and clinicians to discuss the major concerns of the patient, assess and work through any challenges patients and caregivers may have regarding treatment options, provide clear information about the treatment options, and help the patient make the best decision for himself," Jones wrote.

Study Details

Men surveyed in the analysis were diagnosed with low-risk prostate

cancer between January 2011 and December 2012 at several centers in the US. The study participants were members of the Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) cohort, launched a decade ago primarily to compare the effectiveness of surgery and radiation.

Median age at diagnosis was 64 years. Radiotherapy patients (32%) were older with more comorbidities and slightly higher-risk disease than surgery patients (55%). Men opting for active surveillance (13%) were typically older than those undergoing surgery but younger than the radiotherapy group, and more likely to have low-risk disease.

The authors gauged patient regret using a validated questionnaire, with statements including "I would [have been] better off with a different treatment," "I feel the treatment was the wrong one," "I would choose another treatment if I could," and "I wish I could change my mind about the treatment I chose."

The men were surveyed 6 months after diagnosis and then again at 1, 3, and 5 years. At 5 years, the response rate was 71%.

Adjusting for baseline differences, men who had surgery were more than twice as likely to regret their decision at 5 years than men who opted for active surveillance. Men who chose radiotherapy were about 50% more likely to experience regret, although this finding was not statistically significant.

Not surprisingly, regret was far more common among men who judged their treatment to be much less effective than anticipated and their adverse events to be much more severe.

Interestingly, participatory decision-making and social support appeared to protect against regret, as did older age.

The authors noted that many low-risk men in the study who underwent surgery or radiation would likely be counseled toward surveillance today, given National Comprehensive Cancer Network recommendations.

Even so, the findings can inform practice now. "Improved counseling at the time of diagnosis and before treatment, including identification of patient values and priorities, may decrease regret among these patients," the authors concluded.

The study was funded by the Agency for Healthcare Research and Quality. Several investigators reported industry ties, including Wallis, who disclosed receiving personal fees from Janssen Canada. Jones did not report any disclosures.

JAMA Oncol. Published online November 18, 2021. Abstract, Editorial

https://bit.ly/3Er9Piy

Regenerative Nanotransfection: Innovative Nanochip Can Reprogram Biological Tissue in Living Body

Silicon device can change skin tissue into blood vessels and nerve cells

A silicon device that can change skin tissue into blood vessels and nerve cells has advanced from prototype to standardized fabrication, meaning it can now be made in a consistent, reproducible way. As reported in *Nature Protocols*, this work, developed by researchers at the Indiana University School of Medicine, takes the device one step closer to potential use as a treatment for people with a variety of health concerns.

The technology, called tissue nanotransfection, is a non-invasive nanochip device that can reprogram tissue function by applying a harmless electric spark to deliver specific genes in a fraction of a second. In laboratory studies, the device successfully converted skin tissue into blood vessels to repair a badly injured leg. The technology is currently being used to reprogram tissue for different kinds of therapies, such as repairing brain damage caused by stroke or preventing and reversing nerve damage caused by diabetes.

“This report on how to exactly produce these tissue nanotransfection chips will enable other researchers to participate in this new development in regenerative medicine,” said Chandan Sen, director of the Indiana Center for Regenerative Medicine and Engineering, associate vice president for research and

Distinguished Professor at the IU School of Medicine.

Sen also leads the regenerative medicine and engineering scientific pillar of the IU Precision Health Initiative and is lead author on the new publication.

“This small silicon chip enables nanotechnology that can change the function of living body parts,” he said. “For example, if someone’s blood vessels were damaged because of a traffic accident and they need blood supply, we can’t rely on the pre-existing blood vessel anymore because that is crushed, but we can convert the skin tissue into blood vessels and rescue the limb at risk.”

In the Nature Protocols report, researchers published engineering details about how the chip is manufactured.

Sen said this manufacturing information will lead to further development of the chip in hopes that it will someday be used clinically in many settings around the world.

“This is about the engineering and manufacturing of the chip,” he said. “The chip’s nanofabrication process typically takes five to six days and, with the help of this report, can be achieved by anyone skilled in the art.”

Sen said he hopes to seek FDA approval for the chip within a year. Once it receives FDA approval, the device could be used for clinical research in people, including patients in hospitals, health centers and emergency rooms, as well as in other emergency situations by first responders or the military.

Reference: “Fabrication and use of silicon hollow-needle arrays to achieve tissue nanotransfection in mouse tissue in vivo” by Yi Xuan, Subhadip Ghatak, Andrew Clark, Zhigang Li, Savita Khanna, Dongmin Pak, Mangilal Agarwal, Sashwati Roy, Peter Duda and Chandan K. Sen, 26 November 2021, Nature Protocols.

DOI: 10.1038/s41596-021-00631-0

Other study authors include Yi Xuan, Subhadip Ghatak, Andrew Clark, Zhigang Li, Savita Khanna, Dongmin Pak, Mangilal Agarwal and Sashwati Roy, all of IU, and Peter Duda of the University of Chicago.

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https://bit.ly/32QpIB4

Omicron variant may have evolved in rats, one theory says

There are several theories as to how the omicron variant evolved.

By Nicoletta Lanese

The newly identified omicron coronavirus variant may have evolved in a nonhuman animal species, potentially a rodent, some scientists suggest.

According to this theory, an animal may have picked up SARS-CoV-2, the virus that causes COVID-19, around mid-2020, STAT reported. After accumulating many mutations in the animal, the altered coronavirus then would have made the jump back to humans. This chain of events can be described as reverse zoonosis, in which a pathogen jumps from humans to animals, followed by zoonosis, in which a germ passes from animals to humans.

One key piece of evidence in support of this theory is that omicron diverged from other SARS-CoV-2 variants very far back in time, Kristian Andersen, an immunologist at the Scripps Research Institute, told STAT.

Compared with other theories about omicron's origin, such as it evolving in an immunocompromised person or in a human population with poor viral surveillance, "this reverse zoonosis followed by new zoonosis seems more likely to me, given just the available evidence of the really deep branch," meaning the early split from other coronavirus variants, "and then the mutations themselves, because some of them are quite unusual," Andersen said.

Omicron carries seven mutations that would allow the variant to infect rodents, such as mice and rats; other variants of concern, like alpha, carry only some of these seven mutations, Robert Garry, a professor of microbiology and immunology at Tulane Medical School, told STAT. (Garry also said it's still unclear whether

omicron emerged in an animal or human host.)

In addition to these "rodent adaptation" gene variants, omicron carries a slew of mutations not seen in any other versions of SARS-CoV-2, and some scientists take this as potential evidence that the variant emerged in an animal host, Science reported.

"It is interesting, just how crazily different it is," Mike Worobey, an evolutionary biologist at the University of Arizona, told Science in reference to omicron's genome. "It does make me wonder if other species out there can become chronically infected," which could drive the emergence of new variants with many mutations. But at this point, Worobey suspects that omicron evolved in an immunocompromised human, not in an animal.

This is one of the leading theories other experts have suggested, Science reported. In this scenario, an immunocompromised person would have contracted COVID-19 but developed a chronic infection, in which they couldn't rid their body of the virus; as it continued to multiply, it picked up many mutations. Evidence suggests that the alpha variant may have acquired mutations in this way, but this has yet to be confirmed for omicron, Science reported.

If it didn't emerge in either an animal or immunocompromised person, Omicron may have first appeared in a population with poor viral surveillance, meaning it may have spread and evolved, unnoticed, for upwards of a year. "I assume this evolved not in South Africa, where a lot of sequencing is going on, but somewhere else in southern Africa during the winter wave," Christian Drosten, a virologist at Charité University Hospital Berlin, told Science.

But for this to be true, the affected population would have had to be extremely isolated, such that omicron didn't spread much beyond its ranks, said evolutionary biologist Andrew Rambaut of the University of Edinburgh. "I'm not sure there's really anywhere in the world that is isolated enough for this sort of virus to transmit for that length of time without it emerging in various places."

Read more about the potential origin of the omicron variant in STAT and Science.

https://bit.ly/3rGbk8W

Brain Drain: Scientists Solve Puzzling Mystery of Why Neurons Consume So Much Energy Even When at Rest

The brain remains a fuel-guzzler even when its neurons are not firing neurotransmitters to each other

Pound for pound, the brain consumes vastly more energy than other organs, and, puzzlingly, it remains a fuel-guzzler even when its neurons are not firing signals called neurotransmitters to each other. Now researchers at Weill Cornell Medicine have found that the process of packaging neurotransmitters may be responsible for this energy drain.

In their study, reported today (December 3, 2021) in *Science Advances*, they identified tiny capsules called synaptic vesicles as a major source of energy consumption in inactive neurons. Neurons use these vesicles as containers for their neurotransmitter molecules, which they fire from communications ports called synaptic terminals to signal to other neurons. Packing neurotransmitters into vesicles is a process that consumes chemical energy, and the researchers found that this process, energy-wise, is inherently leaky—so leaky that it continues to consume significant energy even when the vesicles are filled and synaptic terminals are inactive.

“These findings help us understand better why the human brain is so vulnerable to the interruption or weakening of its fuel supply,” said senior author Dr. Timothy Ryan, a professor of biochemistry and of biochemistry in anesthesiology at Weill Cornell Medicine.

The observation that the brain consumes a high amount of energy, even when relatively at rest, dates back several decades to studies of the brain’s fuel use in comatose and vegetative states. Those studies found that even in these profoundly inactive states, the

brain's consumption of glucose typically drops from normal by only about half—which still leaves the brain as a high energy consumer relative to other organs. The sources of that resting energy drain have never been fully understood.

Dr. Ryan and his laboratory have shown in recent years that neurons' synaptic terminals, bud-like growths from which they fire neurotransmitters, are major consumers of energy when active, and are very sensitive to any disruption of their fuel supply. In the new study they examined fuel use in synaptic terminals when *in*active, and found that it is still high.

This high resting fuel consumption, they discovered, is accounted for largely by the pool of vesicles at synaptic terminals. During synaptic inactivity, vesicles are fully loaded with thousands of neurotransmitters each, and are ready to launch these signal-carrying payloads across synapses to partner neurons.

Why would a synaptic vesicle consume energy even when fully loaded? The researchers discovered that there is essentially a leakage of energy from the vesicle membrane, a "proton efflux," such that a special "proton pump" enzyme in the vesicle has to keep working, and consuming fuel as it does so, even when the vesicle is already full of neurotransmitter molecules.

The experiments pointed to proteins called transporters as the likely sources of this proton leakage. Transporters normally bring neurotransmitters into vesicles, changing shape to carry the neurotransmitter in, but allowing at the same time for a proton to escape—as they do so. Dr. Ryan speculates that the energy threshold for this transporter shape-shift was set low by evolution to enable faster neurotransmitter reloading during synaptic activity, and thus faster thinking and action.

"The downside of a faster loading capability would be that even random thermal fluctuations could trigger the transporter shape-shift, causing this continual energy drain even when no neurotransmitter is being loaded," he said.

Although the leakage per vesicle would be tiny, there are at least hundreds of trillions of synaptic vesicles in the human brain, so the energy drain would really add up, Dr. Ryan said.

The finding is a significant advance in understanding the basic biology of the brain. In addition, the vulnerability of the brain to the disruption of its fuel supply is a major problem in neurology, and metabolic deficiencies have been noted in a host of common brain diseases including Alzheimer's and Parkinson's disease. This line of investigation ultimately could help solve important medical puzzles and suggest new treatments.

"If we had a way to safely lower this energy drain and thus slow brain metabolism, it could be very impactful clinically," Dr. Ryan said.

Reference: "Synaptic vesicle pools are a major hidden resting metabolic burden of nerve terminals" 3 December 2021, Science Advances. DOI: 10.1126/sciadv.abi9027

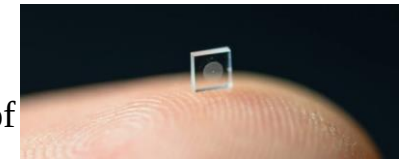
https://bit.ly/3psWzUf

This New Ultra-Compact Camera Is The Size of a Grain of Salt And Takes Stunning Photos

It's able to produce images of much better quality than a lot of other ultra-compact cameras

David Nield

Scientific ingenuity means cameras keep on getting smaller and smaller, and the latest to appear is not only incredibly tiny – the same size as a grain of salt – it's also able to produce images of much better quality than a lot of other ultra-compact cameras.



The salt-grain-sized camera. **(Princeton University)**

Using a technology known as a metasurface, which is covered with 1.6 million cylindrical posts, the camera is able to capture full-color photos that are as good as images snapped by conventional lenses

some half a million times bigger than this particular camera.

And the super-small contraption has the potential to be helpful in a whole range of scenarios, from helping miniature soft robots explore the world, to giving experts a better idea of what's going on deep inside the human body.

Existing micro-sized camera (left) versus the new model (right). **(Princeton University)**

"It's been a challenge to design and configure these little microstructures to do what you want," says computer scientist Ethan Tseng from Princeton University in New Jersey.

"For this specific task of capturing large field of view RGB images, it was previously unclear how to co-design the millions of nano-structures together with post-processing algorithms."

One of the camera's special tricks is the way it combines hardware with computational processing to improve the captured image: Signal processing algorithms use machine learning techniques to reduce blur and other distortions that otherwise occur with cameras this size. The camera effectively uses software to improve its vision. Further down the line, those algorithms could be used for more than just image enhancement. They could be deployed to automatically detect particular objects that the camera is looking for, like signs of disease inside the human body.

That processing is added to the metasurface construction that replaces the usual curved glass or plastic lenses with a material a mere half a millimeter wide. Each of the 1.6 million cylindrical posts was individually designed to best capture what's in front of the camera, with computational modeling used to work out the optimal configuration.

"The significance of the published work is completing the Herculean task to jointly design the size, shape, and location of the metasurface's million features and the parameters of the post-detection processing to achieve the desired imaging performance," says computer imaging consultant Joseph Mait from Mait-Optik, who wasn't involved in the research.

The glass-like silicon nitride that the metasurface is made from is a material that fits in with conventional electronics manufacturing processes, which means that it shouldn't be too difficult to scale up production of these super-tiny cameras using procedures and equipment that's already in place.

So while there's still plenty of work to do to get this from the lab to a commercial production line, the signs are good that it's possible. Once that's done, we'll have access to super-small cameras that can actually take a decent picture, too.

There is another potential use for miniature cameras such as this: Using them as a covering layer to turn entire surfaces into cameras, removing the need for a conventional camera above a laptop screen or on the back of a smartphone.

"We could turn individual surfaces into cameras that have ultra-high resolution, so you wouldn't need three cameras on the back of your phone anymore, but the whole back of your phone would become one giant camera," says computer scientist Felix Heide from Princeton University. "We can think of completely different ways to build devices in the future."

The research has been published in *Nature Communications*.