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Low-Intensity Focused Ultrasound Safe, Effective in Mild Alzheimer's Disease

A new noninvasive procedure is safe and effective for treating patients with mild Alzheimer's disease, new research suggests.

Pauline Anderson

The approach uses MRI-guided low-intensity focused ultrasound (FUS) and injected microbubbles to temporarily open the blood-brain barrier (BBB).

In a small group of patients, the procedure was significantly associated with reduced amyloid plaque and cognitive decline.

Being able to cross the BBB "on demand" and in a safe way opens up numerous frontiers for treating not only AD but also other neurodegenerative disorders, co-investigator Ali R. Rezai, MD, executive chair, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, West Virginia, told *Medscape Medical News*.

And the possibilities don't end there; the technique may have a role in treating brain tumors and perhaps certain psychiatric conditions, Rezai added. The findings were presented at the American Association of Neurological Surgeons (AANS) 2021 Annual Meeting, which was held online.

Targeted Brain Treatment

An estimated five million Americans live with AD, "and the numbers are rapidly growing," said Rezai. There is no cure or effective treatment for the condition despite more than 1000 clinical trials, he added. However, that could change with a technique that transiently opens the BBB to allow targeted treatments to the brain. The BBB normally limits transport of most substances from the blood to the brain.

The new approach involves low-intensity ultrasound. High-intensity FUS is approved by the US Food and Drug Administration for treating tremors in patients with Parkinson's disease and essential tremor.

Low-intensity ultrasound, combined with an intravenous microbubble contrast agent, has been shown in animal studies to temporarily disrupt the BBB and increase permeability to the brain with substances that normally do not cross this barrier.

As well, this approach was associated with a reduction in plaques and improved behavior in AD preclinical trials. Researchers are now testing this procedure in humans.

For the treatment, patients wear a helmet that has ultrasound probes. Surgeons use MRI to visualize areas of the brain that have amyloid plaques. "The ultrasound waves travel wirelessly through the scalp, the skin, and converge at the location in the brain we target with MRI that has a high degree of plaques," Rezai reported.

The tiny spherical microbubbles that are injected into the bloodstream oscillate or "shake" in areas targeted with ultrasound, resulting in a temporary structural opening of the BBB. The treatment takes about 2 hours. Patients undergo three treatments, each 2 weeks apart.

The study is currently enrolling patients aged 50 to 85 years who have mild AD, have a Mini–Mental State Examination (MMSE) score of 18 to 26, and whose results on positron-emission tomography (PET) are positive for amyloid beta (Aβ) .

Immune System Activation?

Preliminary findings for six participants were published online in October in *Frontiers in Human Neuroscience.* Safety data for three participants were published online in January in *Radiology.*

At the AANS meeting, Rezai presented data on 15 participants who had undergone 45 FUS treatments. Follow-up was 3 to 32 months.

In all 15 patients, the BBB was opened without hemorrhage or other adverse events. The BBB opening was "transient, reversible, and resolved in 24 to 48 hours," said Rezai.

For 10 patients, PET imaging at about 60 days 1 week after their third treatment session showed an average reduction of amyloid plaques in the hippocampus/entorhinal cortex and the parietal and frontal lobes of about 26%.

In eight patients who underwent cognitive assessment at 1 year, there was less decline compared with participants matched for age, sex, and clinical features from the Alzheimer's Disease Neuroimaging (ADNI) cohort. Rezai said ADNI is the best comparator "short of doing a randomized clinical trial."

The relative change for MMSE was 2.2 for the FUS group, vs 3.8 for the ADNI cohort. Change in score on the Alzheimer's Disease Assessment Scale–Cognitive was 4.6 for FUS vs 5.6 for ADNI.

Rezai said that because the sample was small, they can only say that "there was no meaningful cognitive or behavioral worsening with FUS compared to the ADNI comparator group."

Another study limitation was that the amount of Aβ varied among participants; some had low amounts at baseline.

The exact mechanisms involved in this technique are not clear and are "under investigation," Rezai noted. They are likely multifactorial and may involve activation of the immune system and ultrasound breakdown of plaques into smaller pieces, he added.

Encouraging Signs

Overall, the researchers are "cautiously optimistic" about these new "encouraging signs" for the procedure for patients with early AD, said Rezai.

"The benefit, in my opinion, is that it's a noninvasive technique. We're not doing brain surgery; we're not cutting the scalp," he noted.

However, he stressed that "this is early on," and more patients, more long-term follow-up, and a sham controlled trial are needed.

Still, the approach might extend beyond AD, Rezai noted. "This opens a whole new opportunity for being able to reduce brain metabolites or pathological proteins that accumulate in, for example, Parkinson's, in Lewy body dementia, in all brain degenerative conditions," he said.

Some researchers are investigating this approach to deliver chemotherapy for brain tumors. Others are investigating its use in transporting viral vectors or antibodies. In addition, low-intensity ultrasound that targets the brain's reward system may be useful for treating addictions, said Rezai.

During his presentation at the meeting, several attendees used the virtual chat function to praise the research. Some called it "superb," and some said it signifies "exciting possibilities."

Following the presentation, Elizabeth C. Tyler-Kabara, MD, PhD, associate professor, Department of Neurosurgery, University of Texas at Austin Dell Medical School, Austin, Texas, provided a commentary. In it, she congratulated the investigators, saying the study demonstrates a "potential treatment" for early AD.

"This study is significant because it's the first to identify that low-intensity focused ultrasound can be used to open up the BBB up to 33 cc of volume," said Tyler-Kabara, who was not involved with the research.

She added that the study "provides the potential for delivery of biologics and other medications to the brain."

The study was funded by the Rockefeller Neurological Institute and Insightec. Rezai and Tyler-Kabara have reported no relevant financial relationships.

American Association of Neurological Surgeons (AANS) 2021 Annual Meeting: Plenary Session 3, presented August 25, 2021.

https://bit.ly/3qY7uC6

Drug Used To Fight Tumors in Animals May Be Effective in Treating COVID-19

Scientists using the Advanced Photon Source have discovered that a drug used to fight tumors in animals might be effective against many types of coronaviruses, including SARS-CoV-2.

Scientists from the University of Chicago have found that the drug masitinib may be effective in treating COVID-19.

The drug, which has undergone several clinical trials for human conditions but has not yet received approval to treat humans, inhibited the replication of SARS-CoV-2, the virus that causes COVID-19, in human cell cultures and in a mouse model, leading to much lower viral loads.

"(X-ray crystallography) gave us a strong indication of how this drug works, and we became confident that it has a chance to work in humans." — *Nir Drayman, University of Chicago*

The research team, including scientists from the U.S. Department of Energy's (DOE) Argonne National Laboratory, also found that the drug could be effective against many types of coronaviruses and picornaviruses. Because of the way it inhibits replication, it has also been shown to remain effective in the face of COVID-19 variants.

"Inhibitors of the main protease of SARS-CoV-2, like masitinib, could be a new potential way to treat COVID patients, especially in early stages of the disease," said Savas Tay of the University of Chicago's Pritzker School of Molecular Engineering, who led the research. "COVID-19 will likely be with us for many years, and novel coronaviruses will continue to arise. Finding existing drugs that have antiviral properties can be an essential part of treating these diseases."

The research team used the ultrabright X-rays of the Advanced Photon Source (APS), a U.S. Department of Energy Office of Science User Facility at Argonne, to determine structures of the SARS-CoV-2 virus with the drug. The results were published in *Science*.

A race to find COVID-19 treatments

When COVID-19 lockdowns began in March 2020, Tay and Nir Drayman, a postdoctoral fellow with the University of Chicago who specializes in virology, began to think about how they could help.

To search for a better treatment for the disease, they began by screening a library of 1,900 clinically safe drugs against OC43, a coronavirus that causes the common cold and can be studied under regular biosafety conditions. They used cell cultures to determine the drugs' effect on infection.

They then gave the top 30 drug candidates to Glenn Randall, professor of microbiology at the University of Chicago, who tested them in cell cultures against the SARS-CoV-2 virus at the Howard Taylor Ricketts Laboratory. Measurements in the lab revealed nearly 20 drugs that inhibit SARS-CoV-2.

They also sent the drug candidates to other collaborators to test against the 3CL protease, the enzyme within coronaviruses that allows them to replicate inside a cell. They found that of the drug candidates, masitinib completely inhibited the 3CL viral enzyme inside the cell, a fact that was confirmed by X-ray crystallography by Andrzej Joachimiak and his colleagues at the Structural Biology Center (SBC) at the APS. The drug specifically binds to the 3CL protease active site and inhibits further viral replication.

"That gave us a strong indication of how this drug works, and we became confident that it has a chance to work in humans," Drayman said.

Though masitinib is currently only approved to treat mast cell tumors in dogs, it has undergone human clinical trials for several diseases, including melanoma, Alzheimer's disease, multiple sclerosis and asthma. It has been shown to be safe in humans but does cause side effects, including gastrointestinal disorders and edema, and could potentially raise a patient's risk for heart disease.

Drug effective against variants, other viruses

Next, the researchers worked with peers at the University of Louisville to test the drug in a mouse model. They found that it reduced the SARS-CoV-2 viral load by more than 99 percent and reduced inflammatory cytokine levels in mice.

In parallel, the researchers also began to test the drug in cell cultures against other viruses and found that it was also effective

against picornaviruses, which include Hepatitis A, polio, and rhinoviruses that cause the common cold.

They also tested it in cell cultures against three SARS-CoV-2 variants, Alpha, Beta, and Gamma, and found that it worked equally well against them, since it binds to the protease and not to the surface of the virus.

Now, the team is working with the pharmaceutical company that developed masitinib (AB Science) to tweak the drug to make it an even more effective antiviral. Meanwhile, masitinib itself could be taken to human clinical trials in the future to test it as a COVID-19 treatment.

"Masitinib has the potential to be an effective antiviral now, especially when someone is first infected and the antiviral properties of the drug will have the biggest effect," Drayman said. "This isn't the first novel coronavirus outbreak, and it's not going to be the last. In addition to vaccines, we need to have new treatments available to help those who have been infected."

Reference: "Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2" by Nir Drayman, Jennifer K. DeMarco, Krysten A. Jones, Saara-Anne Azizi, Heather M. Froggatt, Kemin Tan, Natalia Ivanovna Maltseva, Siquan Chen, Vlad Nicolaescu, Steve Dvorkin, Kevin Furlong, Rahul S. Kathayat, Mason R. Firpo, Vincent Mastrodomenico, Emily A. Bruce, Madaline M. Schmidt, Robert Jedrzejczak, Miguel Á. Muñoz-Alía, Brooke Schuster, Vishnu Nair, Kyu-yeon Han, Amornrat O'Brien, Anastasia Tomatsidou, Bjoern Meyer, Marco Vignuzzi, Dominique Missiakas, Jason W. Botten, Christopher B. Brooke, Hyun Lee, Susan C. Baker, Bryan C. Mounce, Nicholas S. Heaton, William E. Severson, Kenneth E. Palmer, Bryan C. Dickinson, Andrzej Joachimiak, Glenn Randall and Savas Tay, 20 August 2021, Science.

DOI: 10.1126/science.abg5827

The Advanced Photon Source is a U.S. Department of Energy (DOE) Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory. Additional funding for beamlines used for COVID-19 research at the APS is provided by the National Institutes of Health (NIH) and by DOE Office of Science Biological and Environmental Research. Supplemental support for COVID-19 research was provided by the DOE Office of Science through the National Virtual Biotechnology Laboratory, a consortium of DOE national laboratories focused on response to COVID-19 with funding provided by the Coronavirus CARES Act.

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Huge Find of 400,000-Year-Old Bone Tools Challenges Our Understanding of Early Humans

98 elephant-bone tools at a site dating back some 400,000 years

David Nield

As far as Lower Paleolithic archaeology goes, this is quite the haul: Experts have uncovered a record 98 elephant-bone tools at a site dating back some 400,000 years. This discovery could change our thinking on how some of the early humans – such as Neanderthals – fashioned implements like these.

(Villa et al, PLOS One, 2021)

The bones were collected from a place called Castel di Guido, close to modern-day Rome. In the dim and distant past, it was a popular watering hole for the now-extinct straight-tusked elephant (*Palaeoloxodon antiquus*), and it looks as though a substantial number of the animals died there too.

This newly identified collection of tools shows the ancient hominids of Castel di Guido didn't waste the bones that were left, but instead set up a primitive production line with methods that we haven't previously seen this far back in time, at least not to this extent.

"We see other sites with bone tools at this time," says archaeologist Paola Villa, from the University of Colorado Boulder. "But there isn't this variety of well-defined shapes."

"At Castel di Guido, humans were breaking the long bones of the elephants in a standardized manner and producing standardized blanks to make bone tools. This kind of aptitude didn't become common until much later."

Based on the evidence gathered from other sites, early humans would usually just make use of whatever bone fragments were

available, without refining or adapting them – but at Castel di Guido, it was different.

The technique they used is known as percussion flaking, or chipping off bits of bone with a separate implement to make specific tools. Stone tools would have been shaped in a similar way, and they were much more common at this time, which makes the discovery of 98 bone tools such a surprise.

That's not to say the ancient humans living here were particularly 'smart', the researchers note. The explanation might simply be that they had a lot more elephant bones to work with than other groups, and less access to naturally occurring, large pieces of flint for making stone tools instead.

The tools they produced included ones that may have been used to slice through meat, as well as wedges that could have been deployed to create leverage for breaking up large bones like elephant femurs. "First you make a groove where you can insert these heavy pieces that have a cutting edge," says Villa. "Then you hammer it, and at some point, the bone will break."

One of the most interesting tools discovered at the site is what's known as a lissoir: a bone that's long and smooth at one end, and would have been used to treat leather. These kinds of tools didn't become common until about 300,000 years ago.

A lissoir found at the site. **(Villa et al., 2021, PLOS One)**

Given the diversity of tool types here, and the techniques used to create them, archaeologists may have to recalibrate the timelines for when these instruments and their production methods were originally developed.

For now though, this seems like an isolated spurt of bone production technology. Based on the available evidence, the researchers think that Neanderthals occupied the site and produced the record-breaking number tools that have now been cataloged.

"About 400,000 years ago, you start to see the habitual use of fire, and it's the beginning of the Neanderthal lineage," says Villa. "This is a very important period for Castel di Guido."

The research has been published in *PLOS One*.

https://bit.ly/3kMcFpB

Teacher with COVID symptoms went maskless, making her class an experiment

Study shows how small slip ups can fuel an outbreak.

John Timmer

On Friday, the CDC released a report that traced the spread of the delta variant through a California elementary school. It's tempting to make this into a story of gross irresponsibility—a teacher was unvaccinated and read to the class while unmasked. But beyond that, it provides a number of warnings about how our public health system remains under stress as we close in on two years since the start of the pandemic. It also reemphasizes how the delta variant ensures that small errors can easily explode into big problems.

One bad apple

The school in question was a small one, with only a bit over 200 students and 24 staff. It is an elementary school, meaning that its student population is also younger than the cutoff for approved vaccine use. The school did a number of things right, though. Class sizes were kept small, and individual classes were kept in separate rooms, with doors and windows kept open and air filtration equipment installed. There was also a standing policy requiring mask use in place.

But not everything was ideal. The CDC notes that two of the 24 staff members were unvaccinated. While the vaccinated can clearly transmit the delta variant, they are likely to be less infectious, and in a worst case they'd be infectious for a shorter period of time.

One of the unvaccinated staff members, a teacher, began

experiencing congestion and fatigue on May 19, problems that they ascribed to allergies. (The "allergies or COVID?" internal conversation is one I suspect most of us have had within the past year.) The individual went for a test but ran into a systemic problem: It took two days for the results of the test to come back. This problem was then compounded by a couple of poor choices. The teacher put too much stock in their self-diagnosis of allergies and continued going to school. And during that time, while reading to class, the teacher removed their mask. On May 23, the test results came back and confirmed that the teacher was infected.

At this point, the school district again responded well, shutting classrooms and starting widespread testing. But by this point, at least 12 of the 22 students in the class were infected (the parents of two students declined testing). In the two rows of seats that were closest to the teacher, eight of the nine students who were tested had infections. For the rest of the class, 28 percent of the students were infected.

Beyond the classroom

For reasons that are unclear, the infection had spread to a second classroom—the CDC suggests it was likely through some informal interactions among students outside the classroom at the school. Six cases occurred in that classroom, although at least two of the infected picked it up from a third person at a sleepover some student's parents had hosted. Four other individual cases were identified in other classrooms. It's impossible to tell whether these came from contact at school or through community spread.

The students managed to spread the virus to eight parents and siblings in total. There were also a number of cases in the community diagnosed at the same time. All of these viruses were closely related to the version of the delta strain that the teacher had, so their relationship to the school outbreak is uncertain. Still, the CDC notes that the community has a vaccination rate of over 72 percent, which probably limited the scope of the outbreak. Fortunately, none of the people infected by this outbreak required hospitalization.

All of this shows how hard it is to get things right given the infectivity of delta and its persistence in most communities in the US. The school had instituted reasonable policies, although they came up short on mandating all staff be vaccinated. And those policies were undercut by a series of problems that, on the surface, aren't entirely unreasonable. Prior to the pandemic, it had become common practice for people to go to work when feeling ill, and confusing COVID-19 and allergies has likely been a widespread experience. We've all probably made an exception to best public health practices on things like mask wearing at one point or another during the last year and a half. And we as a society have decided to accept a two-day turnaround on test results.

All of these easy-to-make errors get magnified when the background of community spread is higher, which is true in large areas of the US right now. In many of those areas, political leaders are even actively interfering with schools' attempts to implement the sort of policies that were in use in Marin County.

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New Study Finds Likely Driver of COVID-19 Deaths – Dispels Previous Theories

A buildup of coronavirus in the lungs is likely behind the steep mortality rates seen in the pandemic, a new study finds.

The results contrast with previous suspicions that simultaneous infections, such as bacterial pneumonia or overreaction of the body’s immune defense system, played major roles in heightened risk of death, the investigators say.

Led by researchers at NYU Grossman School of Medicine, the new study showed that people who died of COVID-19 had on average 10 times the amount of virus, or viral load, in their lower airways as

did severely ill patients who survived their illness. Meanwhile, the investigators found no evidence implicating a secondary bacterial infection as the cause of the deaths, although they cautioned that this may be due to the frequent course of antibiotics given to critically ill patients.

"Our findings suggest that the body's failure to cope with the large numbers of virus infecting the lungs is largely responsible for COVID-19 deaths in the pandemic," says study lead author Imran Sulaiman, MD, PhD, an adjunct professor in the Department of Medicine at NYU Langone Health.

Current guidelines from the Centers for Disease Control and Prevention, he notes, do not encourage use of antivirals such as remdesivir for severely ill patients on mechanical ventilation. But Sulaiman says the NYU Langone study results suggest that these medications may still remain a valuable tool in treating these patients.

Despite previous concerns that the virus may prompt the immune system to attack the body's own lung tissue and lead to dangerous levels of inflammation, the investigators found no evidence that this was a major contributor to COVID-19 deaths in the group studied. In fact, Sulaiman notes that the strength of the immune response appeared proportionate to the amount of virus in the lungs.

The coronavirus has so far killed over 4 million people worldwide, researchers say. Those placed on mechanical ventilators in order to breathe fare particularly poorly, with 70 percent nationwide succumbing to the illness. Notably, experts attribute the high mortality seen in other viral pandemics such as the Spanish flu in 1918 and swine flu in 2009 to a secondary bacterial infection. However, it remained unclear whether a similar issue afflicted people with COVID-19.

The new study, publishing online today (August 31, 2021) in the journal *Nature Microbiology*, was designed to clarify the role of secondary infections, viral load, and immune cell populations in COVID-19 mortality, according to Sulaiman. He says the investigation provides the most detailed survey of the lower airway environment in coronavirus patients.

For the investigation, the researchers collected bacterial and fungal samples from the lungs of 589 men and women who were hospitalized in NYU Langone facilities in Manhattan and on Long Island. All required mechanical ventilation. For a subset of 142 patients who also received a bronchoscopy procedure to clear their air passages, the investigators analyzed the amount of virus within their lower airways and identified the microbes present by studying small pieces of the germs' genetic code. The study authors also surveyed the type of immune cells and compounds located in the lower airways.

Among the findings, the study revealed that those who died had on average 50 percent lower production of a type of immune chemical that targets the coronavirus compared with the COVID-19 patients who survived the illness. These customized proteins are part of the body's adaptive immune system, a subset of cells and chemicals that "remember" invading newly encountered microbes, leaving the body better prepared for future exposure.

"These results suggest that a problem with the adaptive immune system is preventing it from effectively combating the coronavirus," says study senior author Leopoldo Segal, MD. "If we can identify the source of this issue, we may be able to find an effective treatment that works by bolstering the body's own defenses," says Segal, an associate professor in the Department of Medicine at NYU Langone.

He cautions that the investigators only studied coronavirus patients who survived their first two weeks of hospitalization. It is possible, he says, that bacterial infections or autoimmune reactions may play a greater role in COVID-19 mortality that occurs earlier.

Segal says the research team next plans to observe how the microbe community and immune response in the lungs of coronavirus patients change over time.

Reference: "Microbial signatures in the lower airways of mechanically ventilated COVID-19 patients associated with poor clinical outcome" by Imran Sulaiman, Matthew Chung, Luis Angel, Jun-Chieh J. Tsay, Benjamin G. Wu, Stephen T. Yeung, Kelsey Krolikowski, Yonghua Li, Ralf Duerr, Rosemary Schluger, Sara A. Thannickal, Akiko Koide, Samaan Rafeq, Clea Barnett, Radu Postelnicu, Chang Wang, Stephanie Banakis, Lizzette Pérez-Pérez, Guomiao Shen, George Jour, Peter Meyn, Joseph Carpenito, Xiuxiu Liu, Kun Ji, Destiny Collazo, Anthony Labarbiera, Nancy Amoroso, Shari Brosnahan, Vikramjit Mukherjee, David Kaufman, Jan Bakker, Anthony Lubinsky, Deepak Pradhan, Daniel H. Sterman, Michael Weiden, Adriana Heguy, Laura Evans, Timothy M. Uyeki, Jose C. Clemente, Emmie de Wit, Ann Marie Schmidt, Bo Shopsin, Ludovic Desvignes, Chan Wang, Huilin Li, Bin Zhang, Christian V. Forst, Shohei Koide, Kenneth A. Stapleford, Kamal M. Khanna, Elodie Ghedin and Leopoldo N. Segal, 31 August 2021, Nature Microbiology. DOI: 10.1038/s41564-021-00961-5

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In addition to Sulaiman and Segal, other NYU Langone researchers included Luis Angel, MD; Jun-Chieh Tsay, MD; Benjamin Wu, MD; Kelsey Krolikowski, BA; Yonghua Li, MD, PhD; Rosemary Schluger, RN; Stephen Yeung, PhD; Ralf Duerr, MD, PhD; Sara Thannickal; Chang Wang, MS; George Jour, MD; Guomiao Shen, PhD; Joseph Carpenito, BS; Xiuxiu Liu, MD; Kun Ji, MD; Destiny Collazo, BA; Anthony Labarbiera, BA; Nancy Amoroso, MD; Shari Brosnahan, MD; Vikramjit Mukherjee, MD; David Kaufman, MD; Jan Bakker, MD, PhD; Anthony Lubinsky, MD; Deepak Pradhan, MD; Daniel Sterman, MD; Michael Weiden, MD; Adriana Heguy; PhD; Ludovic Desvignes, PhD; Shohei Koide, PhD; Kenneth Stapleford, PhD; Kamal Khanna, PhD; Ann Marie Schmidt, MD; Bo Shopsin, MD, PhD; Peter Meyn; Chan Wang, PhD; and Huilin Li, PhD. Other study coinvestigators were Matthew Chung, PhD; Stephanie Banakis, MS; and Elodie Ghedin, PhD, at the National Institute of Allergy and Infectious Diseases in Bethesda, Md.; Lizzette Perez-Perez, MSc; and Emmie De Wit, PhD, at the National Institute of Allergy and Infectious Diseases in Hamilton, Mont.; Laura Evans, MD, MSc, at the University of Washington in Seattle; Timothy Uyeki, MD, at the Centers for Disease Control and Prevention in Atlanta, Ga.; and Jose Clememte, PhD; Bin Zhang, PhD; and Christian Forst, PhD, at Icahn School of Medicine at Mount Sinai in New York City.

https://bit.ly/3kMDRVi

Intense exercise could trigger ALS in those with genetic risk

More research needs to be done to confirm the link.

By Jonathan D. Gelber

Exercise may trigger the onset of the deadly nerve disease amyotrophic lateral sclerosis (ALS), a new study finds.

The research showed that people who exercised vigorously, and who also carried genes tied to ALS, developed the disease at younger ages than those who were sedentary. The findings suggest that exercise could exacerbate a genetic predisposition to the devastating disease.

"We are used to thinking of exercise being good. In this unusual case, intense exercise is bad for you," said study co-author Michael Snyder, chair of the Department of Genetics at Stanford University.

Lou Gehrig is shown before the mic delivering his farewell speech on Lou Gehrig Day on July 4, 1939 at Yankee Stadium in the Bronx, New York. He would die less than two years later, at age 36. **(Image credit: The Stanley Weston Archive / Getty)**

ALS is a progressive and fatal neurodegenerative disease that results from the death of motor neurons, or nerve cells. No one knows exactly why this happens. It is also known as Lou Gehrig's disease after the legendary baseball player who was diagnosed on his 36th birthday, after setting the record for playing the most consecutive professional baseball games. (Famous physicist Stephen Hawking was struck by the disease in his early 20s.)

The role of exercise in the development of ALS was controversial. The disease affects anaerobic fast-twitch muscle fibers, but systematic reviews of past research failed to show a connection between exercise and ALS. Because the disease typically presents later in life, it is often referred to as a "two-hit" disease, meaning that a person may have the genes for the disease (the "first hit"), but a second switch must be flipped for that person to get sick. The new study suggests that for ALS, frequent and prolonged exercise may be a "second hit" that turns such genes on or off, thereby leading to neuronal death.

For the new study, researchers relied on data from the U.K.

Biobank, a biomedical database containing in-depth genetic and health information for half a million people. The researchers first identified individuals who exercised at least two to three days per week. They then used a statistical technique to analyze the relationship between exercise and ALS and found that the risk of ALS was directly proportional to the dose of frequent strenuous, and likely anaerobic, exercise.

In the second part of their study, the researchers asked 36 healthy people to do aerobic exercise, then drew blood to see how that exercise changed the expression of genes known to be associated with ALS, including the most common ALS risk gene: C9orf72. This gene codes for a protein of the same name, which is found in brain cells and other nerve cells, including those that direct movement, according to MedlinePlus, a service of the National Library of Medicine. A mutation in the gene for this protein is found in up to 40% of people with familial ALS, according to the ALS association.

Exercise reduced the expression of C9orf72, which mirrors the decreased expression found in ALS patients with a mutation in this gene.

Overall, of 43 known ALS-related genes, 52% were turned on or off following acute exercise. In the final part of the study, the researchers compared exercise history in ALS patients with a C9orf72 mutation to both ALS patients without a C9orf72 mutation and people without ALS. In ALS patients with the C9orf72 mutation, the more people exercised, the younger they tended to be at diagnosis. For those without the mutation, exercise showed a trend towards increasing likelihood of developing ALS, but that result was not statistically significant..

While strenuous exercise increased the risk of ALS, being sedentary did not decrease the risk of developing ALS, nor did having more body fat.

Snyder was surprised by the results. "I find this whole thing quite remarkable," Snyder told Live Science, "that exercise exacerbates a genetic condition for a disease."

For study co-author Johnathan Cooper-Knock, a researcher and lecturer on genetic neuromuscular diseases at the University of Sheffield in the U.K., the most surprising aspect was the significant number of known ALS risk genes that were affected by acute exercise. "This suggests that exercise could play a role in all forms of ALS, including ALS that we may have previously supposed was purely genetic," he told Live Science.

In Cooper-Knock's view, his research group has likely ended the controversy of exercise's role in ALS and showed that physical exercise is a risk factor for the disease. "Our hope is that the community will build on this and take it to the next step, which is to quantify the risk of exercise-induced ALS for individuals based on their personal genetics and environment," he said.

He hopes this will lead to potential prevention measures or at least appropriate counseling. "This will allow us to identify at-risk individuals and offer individualized counseling to allow them to make informed decisions regarding their exercise habits," Cooper-Knock said.

At the moment, the researchers are not recommending that any ALS patient or family members, including individuals with C9orf72 mutations, change their exercise habits. More work needs to be done in a larger cohort, because the way the gene is expressed could vary a lot, the researchers said.

They are, however, advocating for genetic screening of ALS patients to deepen understanding of the roles genetics and environment play in the disease.

As to whether Lou Gehrig's iron streak may have led to his development of ALS, Snyder commented, "It seems very likely."

The findings were published May 26 in the journal The Lancet.

https://bit.ly/38Ddxaz

A breathing tube through the butt could be an alternative to mechanical ventilators

Inspired by animals that breathe through their butts, scientists show that mammals can also harness the incredible breathing ability of our butts

Simon Spichak

To survive in extreme low-oxygen conditions deep in the ocean, fish and other creatures have developed remarkable adaptations. For example, sea spiders, loaches, and catfish evolved the ability to breathe through their butts. And they might not be the only butt breathers out there. A recent study in the journal *Med* now suggests that mammals, humans included, may be able to breathe through their rear ends as well. Mice, rats, and pigs could all stave off the devastating effects of oxygen deprivation if given an oxygen enema. But could this new method provide temporary oxygen while a patient awaits a ventilator?

Can Mammals Breathe Through Their Butt?

While we often consider the butt as the exit for waste in our body, it is also an entryway with lifesaving potential. After all, humans and plenty of other mammals can absorb medications rectally. That's because there's a lot of blood vessels in the area, allowing medicine easy entry.

But medicine is specially designed to maximize absorption in the body. Oxygen doesn't have nearly as easy a path towards entry into the bloodstream through the rectum because of the mucus membrane mammals have on the intestines. There are also important anatomical differences between our intestines and those of fish that already harness this ability. Animals that can breathe through their butts, like loaches, had a much thinner epithelium in their guts and a lot less mucus. During the course of early development, a butt-breathing genetic pathway is turned on that helps dictate the structure of the intestine. When it's all said and done, the posterior end of the intestine is equipped with all the structures necessary for respiration (and gas exchange).

Would this mucus prevent oxygenation in mice? In the first experiment, researchers used a model of oxygen deprivation in mice, preventing them from breathing through their lungs. The control group didn't receive any intestinal ventilation, one group received oxygen through an anal catheter, and the final group had the mucus layer on their intestines "scrubbed" before receiving anal ventilation.

Remarkably, the mice supplied oxygen through their anus had elevated oxygen levels in their blood. The final group that also had their intestinal mucus scrubbed fared even better, surviving the longest in the low-oxygen conditions — five times as long as the control group. This experiment proved that there is potential for mammals to breathe through their butt, however, the mucus layer covering the intestinal epithelial cells makes it more difficult.

In a clinical setting, scrubbing the mucus off of a person's intestines isn't really feasible, and doesn't sound like a pleasant experience. But using a method akin to an enema may work, by infusing safe, oxygenated liquid through the butt. This liquid, called perfluorodecalin, could safely store and deliver oxygen via an enema. Due to the properties of this liquid, it doesn't need to scrub the mucus off of the intestines, meaning less discomfort and abrasion. Oxygen diffuses into the bloodstream while carbon dioxide diffuses out. Since it holds a lot of oxygen and carbon dioxide very easily, it is also delivered safely to the lungs, and is already in clinical use.

In their next experiment, mice were placed in chambers with only 10 percent oxygen. While this isn't lethal, it is enough to induce the physiological effects of a lack of oxygen, hypoxia. The mice that received oxygen-loaded PFD rectally normalized their

oxygenation back to normal levels.

In rats and pigs, the researchers repeated these experiments finding that two days of the protocol didn't lead to any significant adverse effects. Importantly, the diffusion and distribution of many different drugs are tested in pigs due to similarities in physiology. While the authors couldn't figure out how exactly the oxygen passes into the intestine, they showed enough efficacy to permit more studies trials in animals and in humans. According to the press release, the research team is working with Japan Agency for Medical Research and Development to conduct more experiments and potentially head to a human trial. This could increase the ventilation capacity of hospitals during future outbreaks of respiratory diseases.

Can Rectal Ventilation Mitigate a Ventilator Shortage?

During COVID-19, many hospitals find themselves short on ventilators. During the pandemic, many will require the use of a ventilator for an average of 15 days, while a few people will need significantly more time. Ventilators aren't something that a person can use for one day and then get discharged. The first wave of people requiring ventilators will receive them immediately. However, someone whose lungs fail the next day may need to survive for two weeks without one.

In an interview with *The Scientist*, corresponding author Takanori Takebe, Assistant Professor, UC Department of Pediatrics and a Professor at the Institute of Research, Tokyo Medical and Dental University, Japan, explained how his father was hospitalized with acute respiratory distress syndrome due to a chronic lung condition. He saw first-hand how difficult and damaging mechanical ventilation can be on the body.

While these ventilators are the gold standard for treating acute respiratory distress syndrome, occurring through COVID-19 infection, it isn't always available. In the intervening period, there is a need for more techniques and strategies to deliver oxygen and stave off hypoxia and death. If rectal ventilation can work in humans, it will provide a way for doctors to keep some of these people in a stable condition while they await a ventilator. Additionally, since there are no patents or complex mechanical components to rectal ventilation set up, it could be cost-effective to implement.

But humans aren't pigs, or rats, or mice. Lots of incredible research and findings do not translate to humans. One problem remains unaddressed however how will patients or even animals receiving rectal ventilation poop? Can the enema be adjusted to facilitate bowel movements or could this tank the technology? Takebe will be working hard to test this method in more animal models and potentially a human clinical trial soon.

However, a company called Respirogen Inc. may beat him and his colleagues to it. Respirogen Inc. has registered a clinical trial to assess the safety of this method in healthy humans. Six healthy volunteers will experience induced hypoxia, by breathing in a mixture of gases with low oxygen content. In this study, these volunteers will then receive oxygen rectally to monitor whether this method can successfully increase oxygen levels and stave off symptoms of hypoxia. However, Respirogen Inc. will be using standard enemas and colonoscopy-cleansing procedures to reduce the chances someone will need to poop during the trial.

"In human use for treatment of hypoxia, cleansing of the colon will take place by standard enema or colonoscopy prep procedures, which are well understood and accepted," Respirogen CEO Bob Scribner explained over email. "The use of an oxygen bolus delivery allows the procedure to be suspended and restarted as needed to accommodate a patient's need to void." Their technology uses an oxygen bolus, essentially a gas bubble, that is delivered into the butt, and could be stopped temporarily in case of a fecal

emergency.

With at least two different groups working toward this goal, we may finally be able to say with some certainty, whether humans can effectively breathe through their butt. What sounds like a ridiculous question may end up saving people that aren't immediately able to access a ventilator.

https://bit.ly/3qZtnks

Can Birds Help Us Avoid Natural Disasters?

Researchers think birds can hear hurricanes and tsunamis—a sense they're hoping to tap into to develop a bird-based early warning system.

by Jason Gregg

Five years ago, French navy officer Jérôme Chardon was listening to a radio program about the extraordinary journey of the bar-tailed godwit, a bird that migrates 14,000 kilometers between New Zealand and Alaska. In his job as the coordinator of rescue operations across Southeast Asia and French Polynesia, Chardon understood better than most how treacherous the journey would be, as ferocious storms frequently disrupt Pacific island communities. Yet, somehow, bar-tailed godwits routinely pass through the area unscathed. Chardon wondered whether learning how godwits navigate could help coastal communities avoid disaster. Could tracking birds help save lives?

This past January, a team from France's National Museum of Natural History (NMNH), funded primarily by the French Ministry for the Armed Forces, began experiments designed to test Chardon's idea. Researchers with the new Kivi Kuaka project, led by Frédéric Jiguet, an ornithologist at NMNH, equipped 56 birds of five species with cutting-edge animal tracking technology. The French navy ferried the team to remote atolls and islands in French Polynesia, where the scientists attached tags using ICARUS tracking technology. These tags transmit the birds' locations to the International Space Station, which bounces the data back to scientists on Earth who can then follow the birds as they forage, migrate, and rest—all the while waiting to see how the birds respond to natural disasters.

The Kivi Kuaka project is focusing on birds' ability to hear infrasound, the low-frequency sound inaudible to humans that the researchers believe is the most likely signal birds would use to sense storms and tsunamis. Infrasound has myriad sources, from lightning strikes and jet engines to the songlike vocalizations of rhinoceroses. Even the Earth itself generates a continuous infrasonic hum. Though rarely measured, it is known that tsunamis generate infrasound, too, and that these sound waves travel faster than the tsunami wave, offering a potential window to detect a tsunami before it hits.

There is some evidence that birds dodge storms by listening to infrasound. In a 2014 study, scientists tracking golden-winged warblers in the central and southeastern United States recorded what's known as an evacuation migration when the birds flew up to 1,500 kilometers to evade an outbreak of tornadoes that killed 35 people and caused more than US $1-billion in damage. The birds fled at least 24 hours before any foul weather hit, leaving the scientists to deduce they had heard the storm system from more than 400 kilometers away.

The idea that birds avoid tsunamis, on the other hand, is based primarily on anecdotal evidence from the 2004 Indian Ocean tsunami, when survivors reported birds traveling inland in advance of the deadly wave. Jiguet says the idea makes sense from an evolutionary perspective, because birds that survive tsunamis would be more successful at reproducing.

If Kivi Kuaka's birds are able to perceive infrasound generated by Pacific storms or tsunamis, the scientists suspect the birds will move to avoid them. Tracking that behavior, and learning to

identify tsunami-specific bird movements if they exist, may help the team develop an early warning system, Jiguet says.

For the Kivi Kuaka team, tsunamis are the main interest; satellites and computer models already forecast hurricanes and typhoons accurately. But infrasound-producing storms are a useful test because they're more common than tsunamis. If their tagged birds evade them from afar, Jiguet says, it provides further evidence that they could serve as tsunami sentinels.

The team plans on tagging hundreds more birds across the Pacific to prepare for a potential tsunami. "I think if there is one wave that spreads across islands, yes, we should get data from different species at different locations to see if there are some convergent behaviors," says Jiguet. "That would definitely say it's worth continuing to tag and to develop local systems to better analyze this."

Tsunami scientist Eddie Bernard, the former head of the US National Oceanic and Atmospheric Administration's Pacific Tsunami Warning Center and Pacific Marine Environmental Laboratory, has seen his fair share of ideas for forecasting tsunamis. He thinks the real hope for tsunami-warning technology is the one he helped develop, and which already dots coastlines today. Known as deep-ocean assessment and reporting of tsunamis (DART), the system relies on a highly sensitive pressure sensor anchored to the seafloor, which communicates with a surface buoy and satellite. DART detects differences in tsunami waves as small as a centimeter, a level of sensitivity that Bernard says solves the issue of false alarms that plagued past tsunami forecasting technology.

Bernard commends the Kivi Kuaka team's research. "The only thing I would say is don't overstress the tsunami warning aspect of this project," he says, noting that besides the importance of detection, measuring the wave's size is critical because most tsunamis are harmlessly small, and false alarms cause economic damage and erode public trust.

Jiguet is up front that the idea is uncharted. "I am at a point in my career when I can take such risks," he says. Even if the attempt to develop a bird-based tsunami early warning system fails, the project will still help scientists protect birds and benefit the French Ministry for the Armed Forces' mission of aiding climate change and biodiversity initiatives in the Pacific. In that sense, the research has already yielded results. Jiguet says their first season's tracking data highlights Hawai'i as an important stepping stone for the birds they tagged—a useful clue for conserving these species amid rising seas and an uncertain future.

https://bit.ly/3kQaIbZ

Atomic-scale imaging reveals ants use zinc to sharpen their teeth

Tiny creatures have a built-in set of tools that would be the envy of any carpenter or surgeon

Ever wonder how tiny creatures can so easily slice, puncture, or sting? New research reveals that ants, worms, spiders, and other tiny creatures have a built-in set of tools that would be the envy of any carpenter or surgeon.

Ant mandibles pack a powerful bite, thanks to embedded atoms of zinc.
Credit: Robert Schofield, University of Oregon

A recent study, published in the Nature journal *Scientific Reports*, shows for the first time how individual atoms of zinc are arranged to maximize cutting efficiency and maintain the sharpness of these exquisitely constructed tiny animal tools. A collaboration between a research team at the University of Oregon and the U.S. Department of Energy's (DOE's) Pacific Northwest National Laboratory (PNNL) revealed nature's solution to enable tiny creatures to cut and puncture with relative ease.

When the ant bites

Consider the ant tooth. Yes, ants have teeth, as anyone who has ever stepped on an ant mound can attest. These specialized structures, technically called "mandibular teeth" because they are attached outside of their mouths, are made of a network of material that tightly binds individual atoms of zinc. The total effect is a mandible that packs more than 8 percent of the tooth weight with zinc.

These kinds of specialized critter tools have been a decades-long fascination for University of Oregon associate professor Robert Schofield, who led this study. His team of biophysicists has developed techniques to measure the hardness, elasticity, energy of fracture, abrasion resistance, and impact resistance on a miniature scale.

But they couldn't actually see the structure of the materials that make up ant teeth and other microscopic animal tools, especially at the atomic scale. That's where PNNL materials scientist Arun Devaraj and doctoral intern Xiaoyue Wang entered the picture. Devaraj is an expert in the use of a specialized microscope technique called atom probe tomography. He used a focused ion beam microscope to take a tiny needle sample from the tip of an ant tooth and then imaged that needle sample using atom probe tomography, allowing the team to identify how individual atoms are arranged near the tip of an ant tooth.

Using this technique, Devaraj and Wang recorded for the first time the nanoscale distribution of zinc atoms in the ant tooth.

"We could see that the zinc is uniformly distributed in the tooth, which was a surprise," said Devaraj. "We were expecting the zinc to be clustered in nano-nodules."

The research team estimated that, because these biomaterials can be sharper, they make it possible for the animals to use 60 percent or even less of the force that they would have to use if their tools were made of materials similar to that found in human teeth. Because less force is required, their smaller muscles spend less energy. These advantages may explain why every spider, ant, other insects, worms, crustaceans, and many other groups of organisms have these specialized tools.

Ouch! Ant teeth at work

"Human engineers might also learn from this biological trick," said Schofield. "The hardness of ant teeth, for example, increases from about the hardness of plastic to the hardness of aluminum when the zinc is added. While there are much harder engineering materials, they are often more brittle."

Learning from nature is one way of understanding what makes materials stronger and more damage-resistant, added Devaraj. He is currently using a DOE Early Career Award to study, at the atomic scale, principles that make some materials strong and damage resistant. "By studying steel microstructure also at the atomic scale, we can better understand how altering the composition of materials changes its damage resistance, specifically stress corrosion resistance and behavior over time," he said. "This is especially important for designing structures like nuclear power plants that need to withstand aging for many decades."

More information: *The homogenous alternative to biomineralization: Znand Mn-rich materials enable sharp organismal "tools" that reduce force requirements, Scientific Reports (2021).* *DOI: 10.1038/s41598-021-91795-y*

https://bit.ly/3h1MVEJ

Israel's COVID-19 boosters are preventing infections, new studies suggest

Protection increases in the weeks following a third dose, but it's unclear how long the effect will last

By Gretchen Vogel

Israel's nationwide campaign to provide its population with COVID-19 vaccine boosters appears to benefit recipients. A third

dose of the Pfizer-BioNTech vaccine significantly lowers the risk of infection, according to two new studies.

A report for the country's Ministry of Health, posted Friday, showed a third dose reduced recipients' risk of testing positive for SARS-CoV-2 by more than 10-fold 2 weeks later. And in a preprint posted yesterday, researchers used data from a health maintenance organization (HMO) to calculate that a third dose roughly halves a person's chances of testing positive for the virus starting 1 week after the shot and further reduces it after the second week.

Israel's case numbers and hospitalizations continue to climb as the Delta variant spreads. The country recorded 10,947 new cases on Monday, more than on any other day since the start of the pandemic. But the number of cases in older people began to slow in the weeks after 31 July, when third doses of the messenger RNA vaccine were offered to people ages 60 and older—a sign that boosters may be working. On 29 August, Israel announced it would expand the booster program to everyone over the age of 12 whose second dose was at least 5 months earlier. More than 2.1 million people have already received a third dose, the government said yesterday.

That boosters can reduce infections is not a surprise, says David Dowdy, an epidemiologist at Johns Hopkins University. "If your goal is to provide someone with high levels of short-term immunity, there's no question that a good way to do this is … through a booster shot," he says. The findings also add to evidence that the current vaccines are still effective against the Delta variant. But Dowdy warns that because the studies only cover a short period after the booster shot, it remains unclear how long the increase in protection will last.

Researchers from Israel's Ministry of Health and several universities analyzed information about more than 1.1 million Israelis over the age of 60 in the ministry's database, correlating COVID-19 diagnoses between 30 July and 22 August with whether and when people had received a booster. Twelve days after people received a third dose, they found, the risk of infection was reduced more than 10-fold. That brings protection back up to the 95% range seen shortly after the second dose. The effect against severe disease was even larger, reducing the risk 15 times, but the authors caution that small numbers of patients with severe disease and the study's short time frame mean the result has a large uncertainty.

The other study comes from researchers at KSM Research and Innovation at Maccabi Healthcare Services (MHS), Israel's second largest HMO. They teamed up with researchers at Yale School of Public Health to see whether they could tease out an early effect from the booster in health records from MHS's 2.5 million members, just more than one-quarter of the Israeli population.

The team analyzed results from 182,076 polymerase chain reaction tests performed on 153,753 MHS members over the age of 40 during the first 3 weeks of August, comparing those who tested negative with those who tested positive. Between 7 and 13 days after a booster, a person's chance of testing positive fell by 48% compared with someone who had received only two doses, the analysis showed; from 14 to 21 days after the shot, the chance fell by 70%. The study did not look at severe disease, only at new infections.

Dowdy says the result are good news, but don't prove that making boosters widely available is wise. "The question is not, 'Does a booster shot ramp up your immune system in the short term?'" he says. "But rather 'Does a booster shot provide a meaningful increase in longer term immunity over months? And if so, what is the right interval for providing booster shots?'" The answers to those crucial questions, he says, are still "completely unknown."

Yale's Daniel Weinberger, who helped lead the study, agrees. "Our study looked at a very narrow question," he says. Short-term protection "is really only one piece of the puzzle."

If the booster's additional immunity fades quickly, or if the booster campaign distracts from surveillance efforts or from reaching people who have not been vaccinated at all, Dowdy says, the effort will have little long-term impact: "We need longer term data before we can say that giving people boosters at any given interval is the right strategy."

https://wb.md/3BEczr3

Moderna's Vaccine Creates Twice as Many Antibodies as Pfizer's

Moderna's COVID-19 vaccine generates more than double the antibodies seen from Pfizer's COVID-19 vaccine, according to a new research letter published Monday in JAMA.

Carolyn Crist

The study compared the levels of antibodies produced against the coronavirus spike protein. However, the research didn't measure the levels of neutralizing antibodies or whether the differences correlated with vaccine efficacy over time.

"I would urge caution in making the conclusion that because Moderna demonstrated a slightly higher peak on average that its efficacy will be slower to wane," David Benkeser, a biostatistician at Emory University, told Bloomberg News.

"Such a conclusion requires a host of assumptions that have not yet been evaluated," he said.

The study evaluated antibody levels in 1,647 workers at a major Belgium hospital system. The researchers analyzed blood samples about 6-10 weeks after vaccination.

Among those who had not been previously infected, the Moderna recipients average 2,881 units per milliliter, as compared with Pfizer recipients who averaged 1,108 units per milliliter.

Those who previously contracted COVID-19 had higher antibody levels, with Moderna recipients averaging 3,836 units per milliliter and Pfizer recipients averaging 1,444 units per milliliter.

Across all ages, those who weren't previously infected with COVID-19 and were vaccinated with the Moderna vaccine had higher antibodies than those vaccinated with the Pfizer vaccine, although the highest antibodies were seen in ages 35 and younger.

The differences could be explained by the higher amount of active ingredient in the Moderna vaccine, the researchers wrote. The Moderna vaccine has 100 micrograms of active ingredient, as compared with 30 micrograms in the Pfizer vaccine.

The slightly longer interval between doses could lead to differences as well, the researchers wrote. The Moderna shots are taken four weeks apart, while the Pfizer shots are taken three weeks apart.

Now the study team wants to determine whether the different antibody levels correlate with vaccine efficacy and longer protection, and if so, whether the Moderna vaccine may be better for immunocompromised people who don't respond as well to vaccines, Bloomberg reported.

Sources

JAMA: "Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b6 and mRNA-1273."

Bloomberg News: "Moderna Makes Twice as Many Antibodies as Pfizer, Study Says."

https://bit.ly/2WQHeSY

Solving a long-standing biological search problem

How the cell can mend broken DNA using another DNA copy as template has puzzled researchers for years.

How is it possible to find the correct sequences in the busy interior of the cell? Researchers from Uppsala university have now discovered the solution; it is easier to find a rope than a ball if you are blindfolded.

When a DNA molecule breaks in two, the fate of the cell is threatened. From the perspective of a bacterium, fixing the break quickly is a matter of life and death. But to mend the DNA without introducing mistakes in the sequence is challenging; the repair machinery needs to find a template. The process of healing broken

DNA using a template from a sister chromosome is known as homologous recombination and is well described in the literature.

However, the description usually disregards the daunting task of finding the matching template among all the other genome sequences.

The chromosome is a complex structure with several million base pairs of genetic code and it is quite clear that simple diffusion in 3D would not be sufficiently fast by a long shot.

But then, how is it done? This has been the mystery of homologous recombination for 50 years.

From previous studies, it is clear that the molecule RecA is involved and important in the search process, but, up until now, this has been the limit of our understanding of this process.

Now, a group of Uppsala researchers headed by Professor Johan Elf has finally found the solution to this search enigma.

In a study that is published in *Nature*, they use a CRISPR-based technique to make controlled DNA breaks in bacteria.

By growing the cells in a microfluidic culture chip and tracking labeled RecA molecules with fluorescence microscopy, the researchers can image the homologous recombination process from start to finish. "The microfluidic culture chip allows us to follow the fate of thousands of individual bacteria simultaneously and to control CRISPR-induced DNA breaks in time.

It is very precise, almost like having a pair of tiny DNA scissors," says Jakub Wiktor, one of the researchers behind the study.

The label on RecA together with fluorescent markers on the DNA allows the researchers to follow every step of the process accurately; for example, they conclude that the whole repair is finished in 15 minutes, on average, and that the template is located in about nine.

Using microscopy, Elf and his team investigate the fate of the break site and its homologous copy in real-time.

They also find that the cell responds by rearranging RecA to form thin filaments that span the length of the cell.

"We can see the formation of a thin, flexible structure that protrudes from the break site just after the DNA damage.

Since the DNA ends are incorporated into this fiber, it is sufficient that any part of the filament finds the precious template and thus the search is theoretically reduced from three to two dimensions.

Our model suggests that this is the key to fast and successful homology repair," says Arvid Gynnå, who has worked on the project throughout his Ph.D. studies.

Going from a 3D to a 2D search is indeed a considerable improvement regarding the probability of finding the homologous sequence quickly enough, or in fact, at all.

As the Japanese mathematician, Shizuo Kakutani puts it: "A drunk man will find his way home, but a drunk bird may be lost forever".

With these words, he tried to explain a curious fact; an object that explores a 2D surface by a random walk will sooner or later find its way back to its starting point while in a 3D space, it is likely that it will never return "home".

The Uppsala researchers performed their study in the model organism E. coli, but the process of homology repair is nearly identical for higher organisms such as ourselves, or doves for that matter.

DNA damage occurs frequently in our bodies, and without the ability to heal broken DNA, we would be extremely vulnerable to, for example, UV light and reactive oxygen species, and more likely to develop cancer.

In fact, most oncogenes are related to DNA repair and the new mechanistic insights might help us understand the causes of tumor growth.

More information: *Wiktor, J. et al. RecA finds homologous DNA by reduced dimensionality search. Nature (2021).* *doi.org/10.1038/s41586-021-03877-6*

https://bit.ly/2Yjapi1

Huge, gold-standard study shows unequivocally that surgical masks work to reduce coronavirus spread

Surgical masks are better than cloth ones.

By Yasemin Saplakoglu 1 day ago

Results from a massive study in Bangladesh unequivocally show that surgical masks reduce the spread of SARS-CoV-2, scientists say.

The results — from the highest-quality, gold-standard type of clinical trial, known as a randomized controlled trial — should "end any scientific debate" on whether masks are effective in battling the spread of COVID-19, Jason Abaluck, an economist at Yale and one of the authors who helped lead the study, told The Washington Post. "This is an incredibly challenging but important study to pull off," Megan Ranney, an emergency medicine physician and a professor at Brown University who was not part of the study, told the Post. "Anti-mask people keep saying, 'Where's the randomized controlled trial?' Well, here you go."

For the past year and a half, scientists have said that masks reduce the spread of the virus. But it's very difficult to study how much masks help to curb transmission in the real world, where not everyone is masking, using the same quality of masks or even wearing masks properly.

Observational studies, which simply compare mask wearing behaviors to infection rates in different areas, can be muddied by so many other factors. Randomized trials — in which people are randomly assigned to receive a medical intervention or not — are the most robust form of evidence. But those are expensive and difficult to conduct, especially for a behavior like masking.

In the new study, researchers from Bangladesh and the U.S. tested the effectiveness of mask promotion and usage across 600 villages in Bangladesh. The study, which involved more than 342,000 adults, is the largest randomized trial ever conducted on mask usage, according to the Post.

The study was posted as a preprint to the Innovations for Poverty Action nonprofit website on Sept. 1 while it is being peer-reviewed for publication in the journal Science, according to the Post.

In the trial, which ran from November 2020 to April 2021, about 178,000 people received the "intervention" and about 164,000 people did not.

Everyone in the intervention group received free masks, were provided ample information on the importance of mask wearing, had community leaders as role models and received in-person reminders for eight weeks, according to the study.

People in the control group received none of these interventions. The researchers then placed observers throughout the community who tracked, on a weekly basis, how many people properly wore masks and physically distanced themselves at mosques, markets and main entrance roads to villages and tea stalls.

Five and nine weeks after the trials started, the researchers surveyed the participants for COVID-19-like symptoms. Then, about 10 to 12 weeks after the trial start, they took blood samples from the participants who were symptomatic and tested them for SARS-CoV-2 antibodies.

The masking interventions tripled proper mask use, from 13.3% in the control group observations to 42.3% in the masking intervention group. They also found that physical distancing was about 24.1% in the control group observations compared with 29.2% in the treatment group. Five months after the trial, the "impact of the intervention faded," meaning that less people wore masks properly, but mask wearing remained 10% higher in the intervention group compared with the control group, the researchers wrote.

In the intervention group, 7.62% of people had COVID-19-like symptoms, compared with 8.62% in the control group. The

researchers collected blood samples from nearly 11,000 participants, and found that the intervention reduced symptomatic COVID-19 infection by 9.3%.

"Our results should not be taken to imply that masks can prevent only 10% of COVID-19 cases, let alone 10% of COVID-19 mortality," the authors wrote in the paper. That's because the intervention only led to 29 more people out of every 100 people to wear masks.

"The total impact with near-universal masking–perhaps achievable with alternative strategies or stricter enforcement–may be several times larger than our 10% estimate," they wrote.

Villages were given either cloth masks or surgical masks. In villages that were given surgical masks, symptomatic infection was reduced by 11.2% compared with the control group.

That percentage was even higher in older adults: In those who were 60 years or older and who were given free surgical masks along with the other interventions, symptomatic infection was reduced by 34.7% compared with the control group.

They did not find that cloth masks reduced symptomatic infection compared with control groups.

The study is one of many that show the benefits of masking, but it has some limitations.

For example, although they were told to remain discreet and wear plain clothing, researchers who were surveying the participants on how well they wore masks and physically distanced themselves may have been recognized by the study participants, who then may have changed their behaviors, the authors wrote. The study also couldn't explain whether masks made symptoms less severe by reducing the viral load people were exposed to, or whether they reduced new infections completely.

https://bit.ly/3mZFmlH

Beer Was Drunk in China 9,000 Years Ago, But It Likely Wasn't For Recreation

Points to the drinking having been part of a ritual ceremony relating to the burial of the dead

David Nield

Archaeologists have discovered some of the oldest artifacts ever found to be associated with beer, in a haul from Qiaotou in southern China dating back 9,000 years. However, it appears the ancient drinkers in question weren't in it simply for a buzz.

Some of the painted pottery vessels recovered for the study. **(Jiajing Wang)**

The find consisted of two human skeletons surrounded by scores of ceramic pots – actually some of the earliest painted pottery ever found – in what appears to be a burial mound in a non-residential area. Of all 50 intact vessels uncovered, the researchers took 20 to analyze.

Previous research has established criteria for identifying socially valued food items in the archaeological record, such as whether the ingredients are hard to collect or take time to produce. The beer in this case would tick most of those boxes, leading archaeologists to conclude the beverages in these containers weren't just a part of a regular meal.

All that points to the drinking having been part of a ritual ceremony relating to the burial of the dead, the researchers think. Some of the pots were similar in size to the drinking glasses of today, while seven of them appeared to be long-necked Hu pots, used for drinking alcohol in later historical periods.

"Through a residue analysis of pots from Qiaotou, our results revealed that the pottery vessels were used to hold beer, in its most

general sense," says anthropologist Jiajing Wang from Dartmouth College, New Hampshire.

"This ancient beer though would not have been like the IPA that we have today. Instead, it was likely a slightly fermented and sweet beverage, which was probably cloudy in color."

The analysis of the pots looked at samples of starch, phytoliths (preserved plant residue) and fungi recovered from the inside of the uncovered items, which were then compared with control samples taken from the surrounding soil.

The traces of starch granules, phytoliths, mold and yeast found in the pots were all consistent with the process of beer fermentation. It appears that rice, grain, and unknown tubers were used to cook up the booze. Rice husks and other plant parts may have been added to aid fermentation.

As the remains are from so long ago – back when rice was just beginning to be used as a staple food – it's difficult for the researchers to say for certain how the alcohol might have been produced by this ancient community.

"We don't know how people made the mold 9,000 years ago, as fermentation can happen naturally," says Wang. "If people had some leftover rice and the grains became moldy, they may have noticed that the grains became sweeter and alcoholic with age."

"While people may not have known the biochemistry associated with grains that became moldy, they probably observed the fermentation process and leveraged it through trial and error."

Mold acts as an agent in both stages of the beer-making process: saccharification (transforming starch into sugar with enzymes) and fermentation (converting sugar into alcohol and other states with yeasts).

The researchers have also tried to slot the discovery of these beer pots with the wider picture of society in China at the time. Today, this area of southern China is the country's rice heartland, but then it would have been populated by hunter-gatherers relying on foraging for food.

More advanced rice farming communities wouldn't form for another several thousand years, and the team behind this new study thinks that beer might have helped oil the wheels of cooperation and society back then, just as it can do today.

"The findings suggest that beer drinking was an essential element in prehistoric funerary rituals in southern China, contributing to the emergence of complex farming societies four millennia later," write the researchers in their published paper.

The study has been published in *PLOS One*.

https://bit.ly/3h4F3Cy

New evidence supports idea that America's first civilization was made up of 'sophisticated' engineers

Early Indigenous people were highly skilled engineers capable of building massive earthen structures in a matter of months

by Sara Savat

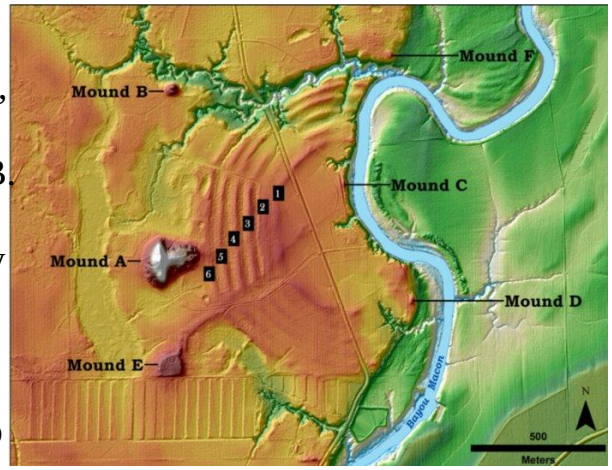
The Native Americans who occupied the area known as Poverty Point in northern Louisiana more than 3,000 years ago long have been believed to be simple hunters and gatherers. But new Washington University in St. Louis archaeological findings paint a drastically different picture of America's first civilization.

Far from the simplicity of life sometimes portrayed in anthropology books, these early Indigenous people were highly skilled engineers capable of building massive earthen structures in a matter of months—possibly even weeks—that withstood the test of times, the findings show.

"We as a research community—and population as a whole—have undervalued native people and their ability to do this work and to do it quickly in the ways they did," said Tristram R. "T.R." Kidder, lead author and the Edward S. and Tedi Macias Professor of Anthropology in Arts & Sciences.

"One of the most remarkable things is that these earthworks have held together for more than 3,000 years with no failure or major erosion. By comparison, modern bridges, highways and dams fail with amazing regularity because building things out of dirt is more complicated than you would think. They really were incredible engineers with very sophisticated technical knowledge."

The findings were published in *Southeastern Archaeology* on September, 1, 2021. Washington University's Kai Su, Seth B. Grooms, along with graduates Edward R. Henry (Colorado State) and Kelly Ervin (USDA Natural Resources Conservation Service) also contributed to the paper.



***The illustration above shows the core features of the Poverty Point site in northern Louisiana. The green to the right is the Mississippi River flood plain. The orange is Macon Ridge, the higher ground on which the site is located. Six C-shaped ridges are visible at the site. Parts of the ridges have been damaged by historic and modern activities. The pattern south of Mound E is the result of farm activity. Many of the low areas around the site – lighter yellow – are thought to be places where soil was mined to make ridges and mounds.1 of 3The illustration above shows the core features of the Poverty Point site in northern Louisiana. The green to the right is the Mississippi River flood plain. The orange is Macon Ridge, the higher ground on which the site is located. Six C-shaped ridges are visible at the site. Parts of the ridges have been damaged by historic and modern activities. The pattern south of Mound E is the result of farm activity. Many of the low areas around the site – lighter yellow – are thought to be places where soil was mined to make ridges and mounds.* Credit: T.R. Kidder**

The Poverty Point World Heritage site consists of a massive 72-foot-tall earthen mound and concentric half circle ridges. The structures were constructed by hunter-gatherers approximately 3,400 years ago from nearly 2 million cubic yards of soil. Amazingly, this was done without the luxury of modern tools, domesticated animals or even wheeled carts.

An excavation before sampling. Note the color changes between layers. The darker layers have carbon-rich deposits made by humans, such as midden or garbage that was scraped up and dumped to form the ridge structure during construction. There is little organic garbage in the upper third section. Credit: T.R. Kidder

According to Kidder, the site was likely an important religious site where Native Americans came in pilgrimage, similar to Mecca. It was abandoned abruptly between 2,000-2,200 years ago—most likely due to documented flooding in the Mississippi Valley and climate change.

The ridges at Poverty Point contain vast amounts of artifacts around the edges and within, suggesting that people lived there. Kidder and team re-excavated and re-evaluated a site on Ridge West 3 at the Poverty Point Site that was originally excavated by renowned archaeologist Jon Gibson in 1991.

Using modern research methods including radiocarbon dating, microscopic analysis of soils and magnetic measurements of soils, the research provides conclusive evidence that the earthworks were built rapidly. Essentially, there is no evidence of boundaries or signs of weathering between the various levels, which would have occurred if there was even a brief pause in construction. Kidder believes the construction was completed in lifts, or layers of sediment deposited to increase the ridge height and linear dimensions before another layer was placed to expand the footprint vertically and horizontally.

Why does that matter? According to Kidder, the findings challenge previous beliefs about how pre-modern hunters and gatherers

behaved. Building the enormous mounds and ridges at Poverty Point would have required a large labor pool that was well organized and would have required leadership to execute. Hunters and gathers were believed to shun politics.

"Between the speed of the excavation and construction, and the quantity of earth being moved, these data show us native people coming to the site and working in concert. This in and of itself is remarkable because hunter-gatherers aren't supposed to be able to do these activities," Kidder said.

What's even more impressive than how quickly the people built the earthen structures is the fact that they're still intact. Due to its proximity to the Gulf of Mexico, this area receives immense amounts of rain that makes earthworks especially prone to erosion. Microscopic analysis of soils shows that the Native Americans mixed different types of soil—clays, silts and sand—in a calculated recipe to make the structures stronger.

"Similar to the Roman concrete or rammed earth in China, Native Americans discovered sophisticated ways of mixing different types of materials to make them virtually indestructible, despite not being compacted. There's some magic there that our modern engineers have not been able to figure out yet," Kidder said.

More information: *Tristram R. Kidder et al, Multi-method geoarchaeological analyses demonstrates exceptionally rapid construction of Ridge West 3 at Poverty Point, Southeastern Archaeology (2021). DOI: 10.1080/0734578X.2021.1958445*

https://bit.ly/38FGMtj

New 'mu' coronavirus variant could escape vaccine-induced immunity, WHO says

The World Health Organization has added "mu" to it's list of "variants of interest."

By Rachael Rettner

Health officials are watching another new coronavirus variant, dubbed "mu," which they say has concerning mutations that could allow it to escape vaccine-induced immunity.

The variant, also known as B.1.621, was first detected in Colombia in January 2021, according to the World Health Organization (WHO). On Monday (Aug. 30), WHO classified it as a "variant of interest," or VOI, and named it mu.

The VOI label means the variant is increasing in prevalence in multiple areas and has mutations that are likely to affect viral characteristics, such as transmissibility or disease severity, Live Science previously reported. In contrast, officials use the term "variant of concern," or VOC, once reliable data show that the variant has increased transmissibility — such as what's been seen with the delta variant — or other worrisome features, such as the ability to evade vaccines.

The mu variant "has a constellation of mutations that indicate potential properties of immune escape," WHO officials wrote in the agency's weekly epidemiological report on COVID-19, published Tuesday (Aug. 31). Early data in lab dishes show that antibodies generated in response to COVID-19 vaccination or previous infection are less able to "neutralize," or bind to and disable, the mu variant, the report said. However, this finding still needs to be confirmed by future studies. Mu shares some mutations with the beta variant (a VOC), including mutations known as E484K and K417N, according to Medpage Today.

So far, the mu variant has been detected in 39 countries, including in some large outbreaks in South America and Europe. The variant has also been detected in the U.S. — a study from the University of Miami detected the variant in 9% of cases at the Jackson Memorial Health System in Miami, according to Medpage Today. Although the variant makes up less than 0.1% of all COVID-19 cases worldwide that undergo genetic sequencing, it accounts for 39% of sequenced cases in Colombia and 13% in Ecuador, and has been increasing in prevalence in these areas, the report said.

More studies are needed to better understand the mu variant and keep an eye on its spread, WHO said.

Exactly how transmissible mu is has not been determined, but Public Health England recently noted that the variant doesn't seem to be spreading particularly rapidly, and that it appears "unlikely" to be more transmissible than the delta variant. As a result "there is no indication that [mu] is out-competing delta" at this time, the agency said in a risk assessment of the variant. But the variant's ability to escape vaccine-induced immunity "may contribute to future changes in growth," the assessment said.

WHO is currently monitoring five variants of interest (eta, iota, kappa, lambda and mu) and four variants of concern (alpha, beta, gamma and delta).

https://go.nature.com/38Dy12L

India's DNA COVID vaccine is a world first – more are coming

The ZyCoV-D vaccine heralds a wave of DNA vaccines for various diseases that are undergoing clinical trials around the world.

Smriti Mallapaty

India has approved a new COVID vaccine that uses circular strands of DNA to prime the immune system against the virus SARS-CoV-2. Researchers have welcomed news of the first DNA vaccine for people to receive approval anywhere in the world, and say many other DNA vaccines may soon be hot on its heels.

ZyCoV-D, which is administered into the skin without an injection, has been found to be 67% protective against symptomatic COVID-19 in clinical trials, and will likely start to be administered in India this month. Although the efficacy is not particularly high compared to that of many other COVID-19 vaccines, the fact that it is a DNA vaccine is significant, say researchers.

It is proof of the principle that DNA vaccines work and can help in controlling the pandemic, says Peter Richmond, a paediatric immunologist at the University of Western Australia in Perth. "This is a really important step forward in the fight to defeat COVID-19 globally, because it demonstrates that we have another class of vaccines that we can use."

Close to a dozen DNA vaccines against COVID-19 are in clinical trials globally, and at least as many again are in earlier stages of development. DNA vaccines are also being developed for many other diseases.

"If DNA vaccines prove to be successful, this is really the future of vaccinology" because they are easy to manufacture, says Shahid Jameel, a virologist at Ashoka University in Sonipat, India.

Fast-tracked development

The urgency of combating COVID-19 has fast-tracked the development of vaccines that use genetic technology, such as messenger RNA and DNA vaccines, says David Weiner, director of the Vaccine & Immunotherapy Center at the Wistar Institute in Philadelphia, Pennsylvania.

RNA vaccines were quicker to show strong immune responses in clinical trials; they have now been delivered to hundreds of millions of people around the world. But DNA vaccines have a number of benefits, because they are easy to produce and the finished products are more stable than mRNA vaccines, which typically require storage at very low temperatures.

ZyCoV-D was developed by Indian pharmaceutical firm Zydus Cadila, headquartered in Ahmedabad. On 20 August, India's drug regulator authorized the vaccine for people aged 12 and older. The efficacy figure of 67% came from trials involving more than 28,000 participants, which saw 21 symptomatic cases of COVID-19 in the vaccinated group and 60 among people who received a placebo.

ZyCoV-D contains circular strands of DNA known as plasmids, which encode the spike protein of SARS-CoV-2, together with a promoter sequence for turning the gene on. Once the plasmids enter

the nuclei of cells, they are converted into mRNA, which travels to the main body of the cell, the cytoplasm, and is translated into the spike protein itself. The body's immune system then mounts a response against the protein, and produces tailored immune cells that can clear future infections. Plasmids typically degrade within weeks to months, but the immunity remains.

Both DNA and mRNA vaccines have been under development since the 1990s, says Weiner. The challenge for DNA vaccines is that they need to make it all the way to the cell nucleus, unlike mRNA vaccines, which just need to get to the cytoplasm, says Jameel. So, for a long time, DNA vaccines struggled to induce potent immune responses in clinical trials, which is why they had been approved for use as vaccines only in animals, such as horses, until now.

Injection-free vaccine

To solve this problem, ZyCoV-D is deposited under the skin, as opposed to deep in muscle tissue. The area under the skin is rich in immune cells that gobble up foreign objects, such as vaccine particles, and process them. "This helps capture the DNA far more efficiently than in the muscle," Jameel says. Unusually, the vaccine is delivered using a needle-free device pressed against the skin, which creates a fine, high-pressure stream of fluid that punctures the surface and is less painful than an injection.

But despite being more potent than previous DNA vaccines, ZyCoV-D requires a minimum of three doses to achieve its initial efficacy. This is likely to add to the logistical challenge of administering the vaccine during the current pandemic, says Jameel. Although ZyCoV-D's efficacy seems to be lower than the 90% or higher achieved by some mRNA vaccines, the figures are not comparable, says Jameel. The ZyCoV-D trials in India earlier this year were conducted while the Delta variant of SARS-CoV-2 was the dominant variant in circulation, whereas earlier mRNA vaccine trials were conducted when less transmissible variants were circulating. "The efficacy is essentially against the Delta variant, so that is pretty good," he says.

Some researchers have criticized a lack of transparency in the approval process, because no late-stage trial results have yet been published. Zydus Cadila says the trial is still under way and it will submit the full analysis for publication shortly. The company says the first doses will start to be administered in India in September and it plans to produce up to 50 million doses by early next year.

DNA vaccines in clinical trials

Many DNA vaccines against COVID-19 are currently undergoing clinical trials around the world.

Vaccine	Developer	Location	Route	Stage of trial
ZyCoV-D	Zydus Cadila	India	Skin	Approved for emergency use
INO-4800	Inovio and partners	United States	Skin	Phase II/III
AG0302-COVID19	AnGes, Osaka University, Takara Bio	Japan	Muscle	Phase II/III
GX-19N	Genexine	South Korea	Muscle	Phase I/II
GLS-5310	GeneOne Life Science	South Korea	Skin	Phase I/II
COVID-eVax	Takis, Rottapharm Biotech	Italy	Muscle	Phase I/II
AG0301-COVID19	AnGes, OSaka University, Takara Bio	Japan	Muscle	Phase I/II
Covigenix VAX-001	Entos Pharmaceuticals	Canada	Muscle	Phase I
CORVax12	OncoSec, Providence Cancer Institute	United States	Skin	Phase I
bacTRL-Spike	Symvivo	Canada	Oral	Phase I
COVIGEN	BioNet, Technovalia, University of Sydney	Thailand, Australia	Skin or muscle	Phase I

***World Health Organization.* *COVID-19 Vaccine Tracker and Landscape* (WHO, 2021).**

Vaccine pipeline

Several other DNA vaccines are being developed against COVID-19, using a variety of antigens and delivery mechanisms (see 'DNA

vaccines in clinical trials'). Two have entered late-stage trials: one by Japanese company AnGes, based in Osaka; the other, which Weiner helped to develop, by Inovio Pharmaceuticals in Plymouth Meeting, Pennsylvania. Inovio is injected under the skin and uses a device that hits the skin with short electric pulses to form pores in the cells that the vaccine can slip through.

More than half a dozen DNA vaccines for COVID-19 are in early-stage trials, including one by the South Korean biotech company GeneOne Life Science in Seoul, and another that Richmond is involved in, developed by the Thai firm BioNet in Bangkok. This vaccine is undergoing a phase I trial in Australia.

But Richmond expects many more DNA vaccines to emerge, targeting diseases for which there are currently no vaccines — from cytomegalovirus, which can be passed on to babies during pregnancy, to respiratory syncytial virus. DNA vaccines are also being trialled or developed for influenza, human papillomavirus, HIV and Zika.

DNA vaccines can store lots of information, which means they can encode large, complex proteins or even multiple proteins. Weiner says that gives them promise as anti-cancer vaccines, a possibility he is exploring in his own research.

"It's a very exciting time for genetic technologies. They have finally gotten a chance to show what they can do," he says.

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https://bit.ly/3DKY4U5

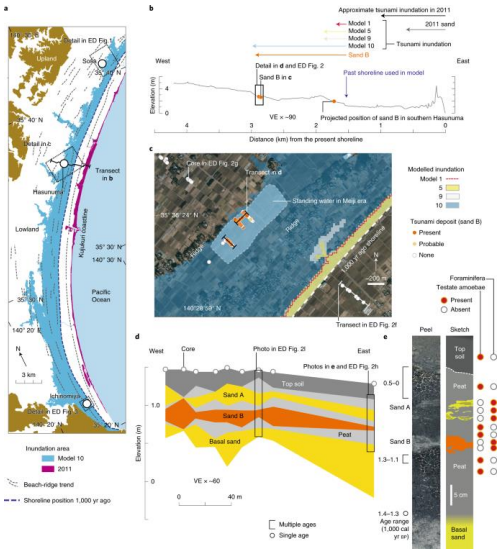
New source for earthquakes and tsunamis in the Greater Tokyo Region identified

Sandy deposits from the Boso Peninsula region (50 km east of Tokyo) attributed to an unusually large tsunami that occurred about 1,000 years ago

Researchers have discovered geologic evidence that unusually large earthquakes and tsunamis from the Tokyo region—located near tectonic plate boundaries that are recognized as a seismic hazard source—may be traceable to a previously unconsidered plate boundary. The team, headed by Simon Fraser University Earth scientist Jessica Pilarczyk, has published its research today in *Nature Geoscience.*

The team's ground-breaking discovery represents a new and unconsidered seismic risk for Japan with implications for countries lining the Pacific Rim, including Canada. Pilarczyk points to low-lying areas like Delta, Richmond and Port Alberni as potentially vulnerable to tsunamis originating from this region.

In 2011, eastern Japan was hit with a massive magnitude 9 quake—creating the largest rupture area of any earthquake originating from the Japan Trench. It triggered the Fukushima Daiichi nuclear disaster and a tsunami that traveled thousands of miles away—impacting the shores of British Columbia, California, Oregon, Hawaii and Chile.



For the past decade, Pilarczyk and an international team of collaborators have been working with the Geological Survey of Japan to study Japan's unique geologic history. Together, they uncovered and analyzed sandy deposits from the Boso Peninsula region (50 km east of Tokyo) that they attribute to an unusually large tsunami that occurred about 1,000 years ago.

Until now, scientists did not have historical records to ascertain if a portion of the Philippine Sea/Pacific plate boundary near the Boso Peninsula was capable of generating large tsunamis similar in size as the Tohoku event in 2011.

Using a combination of radiocarbon dating, geologic and historical records, and paleoecology, the team used 13 hypothetical and historical models to assess each of the three plate boundaries, including the Continental/Philippine Sea plate boundary (Sagami Trough), the Continental/Pacific plate boundary (Japan Trench) and the Philippine Sea/Pacific plate boundary (Izu-Bonin Trench) as sources of the 1,000-year-old earthquake.

Pilarczyk reports that the modeled scenarios suggest that the source of the tsunami from 1,000 years ago originated from the offshore area off the Boso Peninsula—the smallest of which (for example, possible earthquakes with the lowest minimum magnitude), are linked to the previously unconsidered Izu-Bonin Trench at the boundary of the Philippine Sea and Pacific plates.

"Earthquake hazard assessments for the Tokyo region are complicated by the' trench-trench triple junction', where the oceanic Philippine Sea Plate not only underthrusts a continental plate but is also being subducted by the Pacific Plate. "says Pilarczyk, an assistant professor of Earth sciences at SFU who holds a Canada Research Chair in Natural Hazards. "Great thrust earthquakes and associated tsunamis are historically recognized hazards from the Continental/Philippine Sea (Sagami Trough) and Continental/Pacific (Japan Trench) plate boundaries but not from the Philippine Sea/Pacific boundary alone."

Pilarczyk hopes that these findings will be used to produce better informed seismic hazard maps for Japan. She also says that this information could be used by far-field locations, including Canada, to inform building practices and emergency management strategies that would help mitigate the destructive consequences of an earthquake similar to the one of 1,000 years ago.

More information: *Jessica E. Pilarczyk et al, A further source of Tokyo earthquakes and Pacific Ocean tsunamis, Nature Geoscience (2021). DOI: 10.1038/s41561-021-00812-2 , www.nature.com/articles/s41561-021-00812-2*

https://bit.ly/38KSx1q

Extensive Chains of Volcanoes Provides Safety Valve for Earth's Long-Term Climate

Extensive chains of volcanoes have been responsible for both emitting and then removing atmospheric carbon dioxide (CO2), stabilizing temperatures at Earth's surface.

An international research team explored the combined impact of processes in the Earth, oceans, and atmosphere over the past 400 million years. Their findings are published in the journal *Nature Geoscience*.

The researchers included scientists from the University of Leeds, University of Southampton, University of Sydney, Australian National University (ANU), and the University of Ottawa.

Co-author Dr. Andrew Merdith, of Leeds' School of Earth and Environment, said: "The work understates the importance of the connectivity and dependence between different Earth systems, each occurring on different scales in time and space.

"Unfortunately, the connectivity and response between the different systems isn't necessarily instantaneous, and effects can lag their processes by millions of years."

Locking up CO2

Natural breakdown and dissolution of rocks on Earth's surface is called chemical weathering. The process is critically important because the products of weathering – elements such as calcium and magnesium – are flushed via rivers to the oceans, where they form minerals that lock up CO2.

This feedback mechanism regulates atmospheric CO2 levels, and in turn global climate, over geological time.

Lead author of the report is Dr. Tom Gernon, Associate Professor in Earth Science at the University of Southampton, and a Fellow of the Turing Institute. He said: "In this respect, weathering of the Earth's surface serves as a geological thermostat. "But the

underlying controls have proven difficult to determine due to the complexity of the Earth system."

Eelco Rohling, Professor in Ocean and Climate Change at ANU and co-author of the study, said: "Many Earth processes are interlinked, and there are some major time lags between processes and their effects. "Understanding the relative influence of specific processes within the Earth system response has therefore been an intractable problem."

To unravel the complexity, the team constructed a novel 'Earth network', incorporating machine-learning algorithms and state-of-the-art plate tectonic reconstructions.

This enabled them to identify the dominant interactions within the Earth system, and how they evolved through time. The team found that continental volcanic arcs were the most important driver of weathering intensity over the past 400 million years.

Chains of volcanoes

Today, continental arcs comprise chains of volcanoes in, for example, the Andes in South America, and the Cascades in the US.

These volcanoes are some of the highest and fastest eroding features on Earth.

Because the volcanic rocks are fragmented and chemically reactive, they are rapidly weathered and flushed into the oceans.

Leeds' Dr. Merdith added: "The plate-tectonic reconstructions, which describe the position and motion of Earth's tectonic plates through time, provided a foundation within which our analysis could not only be performed, but also make sense.

"This is because we can extract and approximate a number of tectonic parameters, such as volcanic degassing along arcs, as well as the storage of carbon in oceans through the alteration of new oceanic crust at mid-ocean ridges."

Martin Palmer, Professor of Geochemistry at the University of Southampton and co-author of the study, said: "It's a balancing act. On one hand, these volcanoes pumped out large amounts of CO2 that increased atmospheric CO2 levels.

"On the other hand, these same volcanoes helped remove that carbon via rapid weathering reactions."

The study casts doubt on a long-held concept that Earth's climate stability over tens to hundreds of millions of years reflects a balance between weathering of the seafloor and continental interiors.

Geological tug of war

Lead author Dr. Gernon added: "The idea of such a geological tug of war between the landmasses and the seafloor as a dominant driver of Earth surface weathering is not supported by the data.

"Unfortunately, the results do not mean that nature will save us from climate change.

"Today, atmospheric CO2 levels are higher than at any time in the past three million years, and human driven emissions are about 150 times larger than volcanic CO2 emissions.

"The continental arcs that appear to have saved the planet in the deep past are simply not present at the scale needed to help counteract present-day CO2 emissions."

But the team's findings still provide critical insights into how society might manage the current climate crisis.

Artificially enhanced rock weathering—where rocks are pulverized and spread across land to speed up chemical reaction rates—could play a key role in safely removing CO2 from the atmosphere.

The team's findings suggest that such schemes may be deployed optimally by using calc-alkaline volcanic materials (those containing calcium, potassium, and sodium), like those found in continental arc environments.

Dr Gernon added: "This is by no means a silver bullet solution to the climate crisis—we urgently need to reduce CO2 emissions in line with IPCC mitigation pathways, full stop.

“Our assessment of weathering feedbacks over long timescales may help in designing and evaluating large-scale enhanced weathering schemes, which is just one of the steps needed to counteract global climate change.”

For more on this research, see Volcanoes Act as a Safety Valve for Earth’s Long-Term Climate – Stabilizing Surface Temperatures.

Reference: “Global chemical weathering dominated by continental arcs since the mid-Palaeozoic” by Thomas M. Gernon, Thea K. Hincks, Andrew S. Merdith, Eelco J. Rohling, Martin R. Palmer, Gavin L. Foster, Clément P. Bataille and R. Dietmar Müller, 23 August 2021, Nature Geoscience.

DOI: 10.1038/s41561-021-00806-0

https://bit.ly/2WTdHIB

A Unique Mixture of Salts Could Have Sparked Life on Primordial Earth, Study Hints

Mixture of salts, mixed with heat flows from molten rock, could have contributed to formation of self-replicating biomolecules

David Nield

None of us would be around if organisms hadn't been sparked into life billions of years ago. The question of just *how* that spark came about continues to fascinate scientists.

New research looking at how the conditions on primordial Earth might have produced life has identified a mixture of salts that, mixed with heat flows from molten rock, could potentially have contributed to the formation of self-replicating biomolecules.

This self-replication is a key part of the 'RNA world' hypothesis: the idea that ribonucleic acids (RNA) can both store biological information and perform the required structure folding for life to grow and evolve into the state it is today.

In this case, scientists looked at the mixture of magnesium (Mg) and sodium (Na) as it might have been on Earth in its earliest years: for RNA folding to work, a relatively high concentration of doubly charged magnesium ions and a lower concentration of singly charged sodium is required.

"Accordingly, the question arises as to which environments on early Earth might have provided suitable salt conditions for such prebiotic processes. One geologically probable process that produces saline environments is the leaching of salts from basalt," the international team of researchers writes in their study.

"As a primary partial melt of the Earth's mantle, basalt is one of the most abundant rock types to be expected in the Earth's early crust, as well as the crust of other terrestrial planets in our Solar System."

The team synthesized basaltic glass – which naturally occurs on Earth when melted basalt is rapidly cooled (by contact with ocean water, for instance) – and characterized it in its various forms, including both rock and glass.

An analysis of the amount of magnesium and sodium extracted from the glass, under a variety of temperatures and with a variety of grain sizes, always showed significantly more sodium than magnesium.

What's more, the levels of magnesium were always significantly lower than necessary for prebiotic RNA folding to properly function. The missing part of the process, the researchers discovered, was convective flows of heat.

"This situation changed considerably when heat currents – which are very likely to have been present, owing to the high levels of geological activity expected in prebiotic environments – were added," says biophysicist Christof Mast, from the Ludwig Maximilians University of Munich in Germany.

"We have shown that a combination of basaltic rocks and simple convection currents can give rise to the optimal relationship between Mg and Na ions under natural conditions."

The temperature gradients that feature in the narrow cracks and pores of basaltic glass create the convective flows required for salt optimization and also move more ions against the current – creating what's known as thermophoresis.

Together, convection and thermophoresis increase the number of magnesium ions in the mix, creating conditions where self-replicating RNA can occur, the study shows. The same sort of chemical reactions may have played out on Earth 4 billion years ago.

This leaching of salts from basalt – found in abundance in Earth's mantle – fits the template for the RNA world hypothesis to work, the research shows. What's more, it widens out the possibilities in terms of salt mixes that may have helped spark life.

"The principle demonstrated here is applicable to a broad range of salt concentrations and compositions, and, as such, highly relevant to various origin-of-life scenarios," write the researchers in their published paper.

The research has been published in *Nature Chemistry*.

https://bit.ly/3h39n05

New Concept Drug Successfully Hunts Down Late-Stage Prostate Cancer

A new class of drug successfully targets treatment-resistant prostate cancers and prolongs the life of patients.

The treatment delivers beta radiation directly to tumor cells, is well tolerated by patients and keeps them alive for longer than standard care, found a phase 3 trial to be presented at the European Association of Urology congress, EAU21.

Despite progress in medicine in recent years, metastatic castration-resistant prostate cancer remains untreatable and fatal. The new treatment, known as Lu-PSMA-617, takes a new approach, targeting a molecule called PSMA, which is known to be increased on the surfaces of the tumor cells, destroying them and their surrounding microenvironment.

Professor Johann de Bono, Professor of Experimental Cancer Medicine at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, and Professor Ken Herrmann, Director of the Clinic for Nuclear Medicine at University Hospital Essen, Germany, and an international team of researchers set out to see whether Lu-PSMA-617 was more effective than standard care and recruited 831 patients with metastatic castration-resistant prostate cancer between June 2018 and October 2019. Patients were randomly assigned to receive the treatment plus standard care or standard care alone.

They report that the treatment significantly improved survival of patients by an average of four months, compared with standard treatment. Median survival time was 15.3 for the treatment group and 11.3 months for those receiving standard care. Progression-free survival, or the time before a patient's tumor became worse, was also longer with the treatment: a median of 8.7 months compared with 3.4 months for those with standard care.

The trial also compared side effects, finding that health-related quality of life was not negatively affected, and the team concludes that it is an effective and safe medicine that can improve standard of care for patients with this advanced prostate cancer.

Professor Ken Herrmann says: "This is a completely new therapeutic concept; a precision medicine that delivers radiation directly to a high incidence tumor. The treatment was well tolerated by patients and they had an average of four months' longer survival with good quality of life. Lu-PSMA-617 can improve the lives of many men with advanced prostate cancer and their families."

Professor Johann de Bono says: "Our findings show that this potent radioactive medicine can deliver radiation precisely to cancer cells and destroy them, extending patients' lives. I hope men whose tumors have high levels of PSMA can soon benefit from this highly innovative treatment. Currently, the treatment is being appraised by the National Institute for Health and Care Excellence (NICE) for use in the NHS in England and Wales."

"Using the PSMA molecule to directly target prostate cancer cells

is the beginning of a new era of precision medicine in urology diagnostics as well as therapy", says Professor Peter Albers, Head of the Department of Urology, Dusseldorf University, and Chair of the Scientific Office of the EAU.

"LU-PSMA-617 was tested in so-called end-stage disease and still showed superiority and this paves the way for studies to treat patients in earlier stages. We have seen similar success in the diagnostic setting, using this molecule to improve the way we stage tumors. This targeted approach will revolutionize the way we approach the treatment of men with prostate cancer in the future."

https://bit.ly/3jHN95A

Study reveals threat of catastrophic supervolcano eruptions ever-present

Prompts the need for a rethink of how these potentially catastrophic events are predicted

Curtin scientists are part of an international research team that studied an ancient supervolcano in Indonesia and found such volcanoes remain active and hazardous for thousands of years after a super-eruption, prompting the need for a rethink of how these potentially catastrophic events are predicted.

Associate Professor Martin Danišík, lead Australian author from the John de Laeter Centre based at Curtin University, said supervolcanoes often erupted several times with intervals of tens of thousands of years between the big eruptions but it was not known what happened during the dormant periods.

"Gaining an understanding of those lengthy dormant periods will determine what we look for in young active supervolcanoes to help us predict future eruptions," Associate Professor Danišík said.

"Super-eruptions are among the most catastrophic events in Earth's history, venting tremendous amounts of magma almost instantaneously.

They can impact global climate to the point of tipping the Earth into a 'volcanic winter', which is an abnormally cold period that may result in widespread famine and population disruption.

"Learning how supervolcanoes work is important for understanding the future threat of an inevitable super-eruption, which happen about once every 17,000 years."

Associate Professor Danišík said the team investigated the fate of magma left behind after the Toba super-eruption 75,000 years ago, using the minerals feldspar and zircon, which contain independent records of time based on the accumulation of gasses argon and helium as time capsules in the volcanic rocks.

"Using these geochronological data, statistical inference and thermal modeling, we showed that magma continued to ooze out within the caldera, or deep depression created by the eruption of magma, for 5000 to 13,000 years after the super-eruption, and then the carapace of solidified left-over magma was pushed upward like a giant turtle shell," Associate Professor Danišík said.

"The findings challenged existing knowledge and studying of eruptions, which normally involves looking for liquid magma under a volcano to assess future hazard.

We must now consider that eruptions can occur even if no liquid magma is found underneath a volcano—the concept of what is 'eruptible' needs to be re-evaluated.

"While a super-eruption can be regionally and globally impactful and recovery may take decades or even centuries, our results show the hazard is not over with the super-eruption and the threat of further hazards exists for many thousands of years after.

"Learning when and how eruptible magma accumulates, and in what state the magma is in before and after such eruptions, is critical for understanding supervolcanoes."

The study was led by researchers from Oregon State University, and co-authored by researchers from Heidelberg University, the Geological Agency of Indonesia, and by Dr.

Jack Gillespie from Curtin's School of Earth and Planetary Sciences and The Institute for Geoscience Research (TIGeR), Curtin's flagship earth sciences research institute.

The paper, "Resurgence initiation and subsolidus eruption of cold carapace of warm magma at Toba Caldera, Sumatra," was published in journal *Nature—Earth and Environmental Sciences*.

More information: *Resurgence initiation and subsolidus eruption of cold carapace of warm magma at Toba Caldera, Sumatra, Nature—Earth and Environmental Sciences, DOI: 10.1038/s43247-021-00260-1*

https://bit.ly/3n3OB4l

Coronavirus epidemics first hit more than 21,000 years ago

The most recent common ancestor of these viruses existed more than 21,000 years ago

Sarbecoviruses have crossed into humans twice in the last decade, leading to the deadly SARS-CoV-1 outbreak in 2002-04 and the current COVID-19 pandemic, caused by the SARS-CoV-2 virus.

A new Oxford University study, published today, shows that the most recent common ancestor of these viruses existed more than 21,000 years ago, nearly 30 times older than previous estimates.

Despite having a very rapid rate of evolution over short timescales, to survive, viruses must remain highly adapted to their hosts—this imposes severe restrictions on their freedom to accumulate mutations without reducing their fitness.

This causes the apparent rate of evolution of viruses to slow down over time. The new research, for the first time, successfully recreates the patterns of this observed rate decay in viruses.

"We developed a new method that can recover the age of viruses over longer timescales and correct for a kind of 'evolutionary relativity," where the apparent rate of evolution depends on the timescale of measurement.

Our estimate based on viral sequence data, of more than 21,000 years ago, is in remarkable concordance with a recent analysis on human genomic dataset that suggests infection with an ancient coronavirus around the same time," said Mahan Ghafari, from Oxford University.

The study also demonstrates that while existing evolutionary models have often failed to measure the divergence between virus species over periods—from a few hundred to a few thousands of years—the evolutionary framework developed in this study will enable the reliable estimation of virus divergence across vast timescales, potentially over the entire course of animal and plant evolution.

The new model enables us to not only reconstruct the evolutionary history of viruses related to SARS-CoV-2, but also a much wider range of RNA and DNA viruses during more remote periods in the past.

The model predictions for hepatitis C virus—a leading global cause of liver disease—are consistent with the idea that it has circulated for nearly a half a million years. HCV may thus have spread worldwide as an intrinsic part of the "Out-of-Africa" migration of modern humans around 150,000 years ago.

The different genotypes of HCV indigenous to human populations in South and South-East Asia and Central Africa may have originated over this prolonged period and this revised timescale may resolve the longstanding riddle of their global distributions.

"With this new technique we can look much more widely at other viruses; re-evaluate the timescales of their deeper evolution and gain insights into host relationships that are key to understanding their ability to cause disease," says Prof Simmonds, Oxford University.

More information: *Mahan Ghafari et al, A mechanistic evolutionary model explains the time-dependent pattern of substitution rates in viruses, Current Biology (2021). DOI: 10.1016/j.cub.2021.08.020*

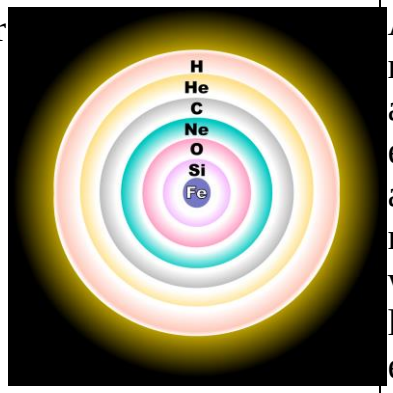
https://bit.ly/3DO58iT

Heavier Stars Might not Explode as Supernovae, Just Quietly Implode Into Black Holes

New study suggests it isn't the case that all stars above about ten solar masses will end as a supernova, as generally thought

by Brian Koberlein

A supernova is a brilliant end to a giant star For a brief moment of cosmic time, a star makes one last effort to keep shining, only to fade and collapse on itself. The end result is either a neutron star or a stellar-mass black hole. We've generally thought that all stars above about ten solar masses will end as a supernova, but a new study suggests that isn't the case.



The onion-skin model of a dying star, not to scale. **Credit: R. J. Hall**

Unlike the famous Type Ia supernovae, which can be caused by the merger or interaction of two stars, large stars undergo what is known as a core-collapse supernova. Stars survive through a balance of heat and pressure against gravity. As more elements are fused, a large star must generate heat by fusing ever heavier elements. Eventually, this forms a layer of regions where different elements are fused. But that chain can only be carried up to iron. After that, fusing heavier elements costs you energy rather than releases it. So, the core collapses, creating a shock wave that rips the star apart.

In models of large dying stars, core-collapse supernovae occur for stars above 9 – 10 solar masses, up to about 40 – 50 solar masses. Above that mass, stars are so massive that they likely collape into a black hole directly, without becoming a supernova. Extremely massive stars, on the order of 150 solar masses or more, might explode as a hypernova. These beasts don't explode because of a core-collapse, but rather an effect known as pair instability, where colliding photons created in the core create pairs of electrons and positrons.

This new study suggests that the upper mass limit for core-collapse supernovae might be much lower than we thought. The team looked at the elemental abundances of a pair of colliding galaxies known as Arp 299. Because the galaxies are in the process of colliding, the region is a hotbed of supernovae. As a result, the elemental abundances of Arp 299 should be largely dependent on the elements cast off in supernova explosions. They measured the abundance ratio of iron to oxygen, and the ratios of neon and magnesium to oxygen. They found that the Ne/O and Mg/O ratios were similar to that of the Sun, while the Fe/O ratio was much lower than solar levels. Iron is cast into the universe most efficiently by large supernovae.

The ratios the team observed didn't match standard core-collapse models, but they found that the data matched supernova models well if you excluded any supernova over about 23 – 27 solar masses. In other words, if stars collapse into black holes above about 27 solar masses, then models and observations agree.

This work doesn't conclusively prove that the upper mass limit for supernovae is smaller than we thought. It's also possible that supernovae produce higher levels of neon and magnesium than models predict. Either way, it is clear that we still have much to learn about the last dying gasps of large stars.

Reference: *Mao, Junjie, et al. "Elemental Abundances of the Hot Atmosphere of Luminous Infrared Galaxy Arp 299." The Astrophysical Journal Letters 918.1 (2021): L17.*