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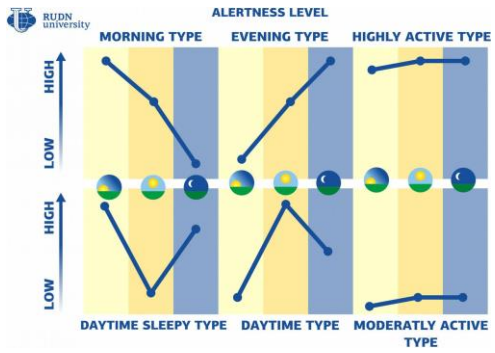
Doctors confirm the existence of multiple chronotypes

Having conducted a large-scale study, a team of scientists improved the classification of human diurnal activity and suggested using 6 chronotypes instead of just 'early birds' and 'night owls'.



Credit: RUDN University

Two thousand participants, including the employees of the Institute of Medicine of RUDN University, were tested in the course of the research. The results of the work were published in the *Personality and Individual Differences* journal.

The physiological functions of our bodies are subject to diurnal rhythms. It means that a person can be more or less active and efficient depending on the time of the day. The two widely known chronotypes are 'early birds' that are most active in the morning and 'night owls' for which evenings are the most productive time. However, these two types are not clearly distinguished: about 60% of all people fail to fit into one of the categories. A team of scientists from the Institute of Medicine of RUDN University together with the leading Russian and foreign chronobiologists carried out a large-scale study and identified 4 additional chronotypes, thus expanding the common classification.

"The research of individual chronobiological and chronopsychological differences is predominantly focused on the morning and evening chronotypes. However, recent studies suggest that the existing classification needs to be reconsidered and expanded. Our team conducted a test and asked the participants to choose their diurnal activity types from six suggested options. Based on the results of the test, we studied the dynamics of sleep-wake patterns throughout the day," said Dmitry S. Sveshnikov, MD, an Assistant Professor at the Department of Human Physiology, Institute of Medicine of RUDN University.

The team suggested a new classification that includes 6 chronotypes characterized by different criteria: sleep duration, excessive diurnal drowsiness, ability to wake up and fall asleep as and when required, and so on. The four new chronotypes in the classification are highly active type (that remains active throughout the day), daytime sleepy type (that is active in the mornings and evenings, not in the afternoon), daytime active type (that is active in the afternoon), and moderately active type (with reduced activity throughout the day).

The team conducted a number of online tests with a total of 2,283 participants, and 95% of the respondents identified with one of the six chronotypes. Only 1/3 of them chose either a morning or an evening type (13% and 24%, respectively). The majority of the participants went for the other four types: 15% chose the daily type; 18%--daytime sleepy type, 9%--highly active type, and 16%--moderately active type.

"Taking into account the incidence of the types in question, we consider our hypothesis about the existence of additional chronotypes fully confirmed," added Dmitry S. Sveshnikov.

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Moderna Filing for FDA Emergency COVID Vaccine Approval, Reports 94.1% Efficacy

Moderna announced that the vaccine prevented serious cases of infection.

Damian McNamara

The Moderna COVID-19 vaccine in development was 94.1% effective in the final analysis of its 30,000-participant phase 3 study. Bolstered by the new findings, the company plans to file for an

emergency use authorization (EUA) from the Food and Drug Administration (FDA) today, according to a company release.

A total of 11 people in the mRNA-1273 vaccinated group later tested positive for COVID-19, compared with 185 participants given two placebo injections, resulting in a point estimate of 94.1% efficacy. This finding aligns with the 94.5% efficacy in interim trial results announced on November 16, as reported by *Medscape Medical News*. Furthermore, Moderna announced that the vaccine prevented serious cases of infection. All 30 severe infections occurred among those people randomly assigned to placebo.

The FDA plans to review the Moderna vaccine safety and efficacy data at the next Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting scheduled for December 17. If and when approved, healthcare providers can use the new 91301 CPT code specific to mRNA-1273 vaccination.

"This positive primary analysis confirms the ability of our vaccine to prevent COVID-19 disease with 94.1% efficacy and, importantly, the ability to prevent severe COVID-19 disease," said Stéphane Bancel, MBA, MEng, chief executive officer of Moderna, in the news release. "We believe that our vaccine will provide a new and powerful tool that may change the course of this pandemic and help prevent severe disease, hospitalizations, and death."

Vaccine efficacy remained consistent across different groups analyzed by age, race/ethnicity, and gender. The 196 COVID-19 cases in the trial included 33 adults older than 65 years and 42 people from diverse communities, including 29 Hispanic or Latinx, six Black or African Americans, four Asian Americans, and three multiracial participants, the company reported.

No Serious Vaccine-Related Safety Issues

The mRNA-1273 vaccine was generally well tolerated and no serious safety concerns with the vaccine have been identified to date, the company reported.

Injection site pain, fatigue, myalgia, arthralgia, headache, and erythema/redness at the injection site were the most common solicited adverse events in a prior analysis. The company noted that these solicited adverse reactions increased in frequency and severity after the second vaccine dose. A continuous review of safety data is ongoing. One COVID-19-related death in the study occurred in the placebo group.

Ready to Start Shipping

Moderna expects to have approximately 20 million doses of mRNA-1273 available in the United States by the end of this year. The company reports that it's on track to manufacture 500 million to 1 billion doses globally in 2021.

The company also is seeking approval from nations and organizations worldwide, including a conditional approval from the European Medicines Agency (EMA). The study is being conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services.

Moderna will be the second company to file an EUA with the FDA for a COVID vaccine, after Pfizer requested one for its mRNA vaccine earlier this month.

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HIV-like virus edited out of primate genome

Breakthrough brings Temple researchers and their collaborators closer to a cure for human HIV infection

Philadelphia, PA - Taking a major step forward in HIV research, scientists at the Lewis Katz School of Medicine at Temple University have successfully edited SIV - a virus closely related to HIV, the cause of AIDS - from the genomes of non-human primates. The breakthrough brings Temple researchers and their collaborators

closer than ever to developing a cure for human HIV infection.

"We show for the first time that a single inoculation of our CRISPR gene-editing construct, carried by an adeno-associated virus, can edit out the SIV genome from infected cells in rhesus macaque monkeys," said Kamel Khalili, PhD, Laura H. Carnell Professor and Chair of the Department of Neuroscience, Director of the Center for Neurovirology, and Director of the Comprehensive NeuroAIDS Center at the Lewis Katz School of Medicine at Temple University (LKSOM).

Dr. Khalili was a senior co-investigator on the new study, with Tricia H. Burdo, PhD, Associate Professor and Associate Chair of Education in the Department of Neuroscience at LKSOM, who is an expert on the utilization of the SIV (simian immunodeficiency virus)-infected antiretroviral therapy (ART)-treated rhesus macaque model for HIV pathogenesis and cure studies; and with Andrew G. MacLean, PhD, Associate Professor at the Tulane National Primate Research Center and the Department of Microbiology and Immunology at Tulane University School of Medicine, and Binhua Ling, PhD, Associate Professor at the Southwest National Primate Research Center, Texas Biomedical Research Institute. Dr. Ling was previously Associate Professor at the Tulane National Primate Research Center and the Department of Microbiology and Immunology at Tulane University School of Medicine. Pietro Mancuso, PhD, an Assistant Scientist in Dr. Khalili's laboratory in the Department of Neuroscience at LKSOM, was first author on the report, which was published online November 27 in the journal *Nature Communications*.

Of particular significance, the new work shows that the gene-editing construct developed by Dr. Khalili's team can reach infected cells and tissues known to be viral reservoirs for SIV and HIV. These reservoirs, which are cells and tissues where the viruses integrate into host DNA and hide away for years, are a major barrier to curing infection. SIV or HIV in these reservoirs lies beyond the reach of ART, which suppresses viral replication and clears the virus from the blood. As soon as ART is stopped, the viruses emerge from their reservoirs and renew replication.

In non-human primates, SIV behaves very much like HIV. "The SIV-infected rhesus macaque model studied in Dr. Burdo's lab is an ideal large animal model for recapitulating HIV infection in humans," explained Dr. Khalili.

For the new study, the researchers began by designing an SIV-specific CRISPR-Cas9 gene-editing construct. Experiments in cell culture confirmed that the editing tool cleaved integrated SIV DNA at the correct location from host cell DNA, with limited risk of potentially harmful gene editing at off-target sites. The research team then packaged the construct into an adeno-associated virus 9 (AAV9) carrier, which could be injected intravenously into SIV-infected animals.

Dr. Burdo, in collaboration with colleagues at Tulane National Primate Research Center, randomly selected three SIV-infected macaques to each receive a single infusion of AAV9-CRISPR-Cas9, with another animal serving as a control. After three weeks, the researchers harvested blood and tissues from the animals. Analyses showed that in AAV9-CRISPR-Cas9-treated macaques, the gene-editing construct had been distributed to a broad range of tissues, including the bone marrow, lymph nodes, and spleen, and had reached CD4+ T cells, which are a significant viral reservoir.

Moreover, the Temple researchers demonstrated that the SIV genome was effectively cleaved from infected cells, based on genetic analyses of tissues from treated animals. "The step-by-step excision of SIV DNA occurred with high efficiency from tissues and blood cells," Dr. Mancuso explained. Excision efficiency varied by tissue but reached notably high levels in the lymph nodes.

The new study is a continuation of efforts by Dr. Khalili and

colleagues to develop a novel gene-editing system using CRISPR-Cas9 technology - the subject of the 2020 Nobel Prize in Chemistry - to specifically remove HIV DNA from genomes harboring the virus. The researchers have shown previously that their system can effectively eliminate HIV DNA from cells and tissues in HIV-infected small animal models, including HIV-1 humanized mice.

Co-corresponding author Dr. MacLean is encouraged by the findings. "This is an important development in what we hope will be an end to HIV/AIDS," says MacLean. "The next step is to evaluate this treatment over a longer period of time to determine if we can achieve complete elimination of the virus, possibly even taking subjects off of ART."

Dr. MacLean is hopeful that this treatment strategy will translate to the human population. The biotech company Excision BioTherapeutics, of which Dr. Khalili is a scientific founder and where Dr. Burdo contributes to preclinical research and development and serves on the Scientific Advisory Board, will assist with funding and infrastructure for larger scale studies and future clinical trials after approval by the Food and Drug Administration.

"We hope to soon move our work into clinical studies in humans as well," Dr. Khalili added. "People worldwide have been suffering with HIV for 40 years, and we are now very near to clinical research that could lead to a cure for HIV infection."

Other researchers contributing to the study include Chen Chen, Dr. Rafal Kaminski, Dr. Jennifer Gordon, Dr. Shuren Liao, Jake A. Robinson, Mandy D. Smith, Dr. Hong Liu, Dr. Ilker K. Sariyer, Rahsan Sariyer, and Dr. Martina Donadoni, Department of Neuroscience, Center for Neurovirology, Lewis Katz School of Medicine at Temple University; the late Dr. Tiffany A. Peterson, Jaclyn B. Williams, and Summer Siddiqui, Division of Comparative Pathology at the Tulane National Primate Research Center; and Dr. Bruce A. Bunnell, Division of Comparative Pathology at the Tulane National Primate Research Center, the Tulane Brain Institute, the Department of Pharmacology at Tulane University School of Medicine, and the Department of Microbiology, Immunology and Genetics at the University of North Texas Health Science Center, Fort Worth.

The research was supported in part by National Institutes of Health grants P51OD11104, P30MH092177, R01NS104016, R56AI143647, R56AI150772, U42OD024282, and U42OD010568.

Editor's Note: Kamel Khalili is Co-Founder and Chief Scientific Consultant, and holds equity in Excision Biotherapeutics, which has licensed the viral gene editing technology from Temple University. Kamel Khalili and Rafal Kaminski are named inventors on patents that cover the viral gene editing technology. Tricia Burdo and Jennifer Gordon hold equity in Excision Biotherapeutics. These named researchers are employed by Temple University, and conduct research activities sponsored by the company.

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Stone Age 'Venus Figurines' Have a New Explanation, And It's Surprisingly Touching

Alternative explanation for mystery of the figurines' exaggerated physiques as symbols of survival

Peter Dockrill

***Venus of Willendorf*. (Bjørn Christian Tørrissen/Wikimedia Commons/CC BY-SA 4.0)**

They rank among some of the oldest known art in the world. Strange statuettes of female figures dating back to the Late Stone Age, many with heavily rounded breasts, buttocks, thighs, hips, and stomachs.

These iconic, stylised depictions of women from the Upper Palaeolithic – often called Venus figurines, in a loose reference to the Roman goddess of beauty – have been found scattered across Europe and Eurasia.

Over 200 of these mysterious figurines have been uncovered, dated between 38,000 to 14,000 years ago, with most of those recovered from about 26,000-21,000 years ago.

While there is much academic debate about what the Venus figurines represented in the eyes of their ancient carvers, many researchers have interpreted the statues' voluptuous characteristics as symbols of fertility, sexuality, beauty, and motherhood.

Others have also noted, however, that the enlarged bodies offer a

very realistic depiction of what human obesity looks like. Obesity is a grave problem for people in the 21st century, although why it would have been on the minds of our ancient ancestors 30,000 years ago isn't entirely clear.

"Some of the earliest art in the world are these mysterious figurines of overweight women from the time of hunter gatherers in Ice Age Europe, where you would not expect to see obesity at all," says medical researcher Richard Johnson from the University of Colorado.

In a new study, Johnson and fellow researchers offer an alternative explanation for mystery of the figurines' exaggerated physiques: the bodies are not swollen as symbols of sex, they say, but as symbols of survival.

The researchers analysed dozens of the figures with obese features from various chapters in the period, measuring the statues' waist-to-hip and waist-to-shoulder ratios. When those measurements are compared to where the statues were found – specifically, noting distances to ancient glaciers that existed – an interesting connection was found.

Many of the Venus figurines were carved during an extreme window of climate change called the Last Glacial Maximum, in which temperatures plummeted and ice masses expanded throughout many parts of the world.

Amidst the hardship, the statues were carved; it's possible, the researchers say, that their shapely forms were created in a sort-of response to the creeping cold. "During this period, humans faced advancing glaciers and falling temperatures that led to nutritional stress, regional extinctions, and a reduction in the population," the researchers explain in the study, noting the strange relationship they found.

"Figurines are less obese as distance from the glaciers increases… Specifically, the body size proportions were largest when the glaciers were advancing, whereas obesity decreased when the climate warmed and glaciers retreated."

In the team's hypothesis, the full-figured Venuses existed as a symbol of survival in the face of an unrelenting winter, exemplifying the virtues of over-nourished women, whose larger, fattier bodies could better withstand the harsh, freezing conditions.

"We propose they conveyed ideals of body size for young women, and especially those who lived in proximity to glaciers," Johnson says. The researchers contend that obese women would have been better at carrying pregnancies during the Last Glacial Maximum, and also at breastfeeding.

"The figurine would represent a desired likeness of the woman in which the image had power to bring about a healthier mother and child, spanning conception, a precarious pregnancy, childbirth, and nursing," the authors write.

"Increased fat would provide both a source of energy during gestation through the weaning of a baby as well as much needed insulation." It's a fascinating argument, although it's worth noting that not everybody in the archaeology community has welcomed their findings.

Still, if the researchers are right, these iconic statuettes – many worn down, as if they had been handled as heirlooms over successive generations – could have played a greater symbolic role than ever known, in shepherding humanity through one of its bleakest climatic challenges.

"During this period, the figurines emerged as an ideological tool to help improve fertility and survival of the mother and newborns," the researchers conclude. "The aesthetics of art thus had a significant function in emphasising health and survival to accommodate increasingly austere climatic conditions."

The findings are reported in *Obesity*.

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Glucosamine may reduce overall death rates as effectively as regular exercise

Glucosamine supplements may reduce the risk of cardiovascular-related death--and death overall

Glucosamine supplements may reduce overall mortality about as well as regular exercise does, according to a new epidemiological study from West Virginia University.

"Does this mean that if you get off work at five o'clock one day, you should just skip the gym, take a glucosamine pill and go home instead?" said Dana King, professor and chair of the Department of Family Medicine, who led the study. "That's not what we suggest. Keep exercising, but the thought that taking a pill would also be beneficial is intriguing."

He and his research partner, Jun Xiang--a WVU health data analyst--assessed data from 16,686 adults who completed the National Health and Nutrition Examination Survey from 1999 to 2010. All of the participants were at least 40 years old. King and Xiang merged these data with 2015 mortality figures.

After controlling for various factors--such as participants' age, sex, smoking status and activity level--the researchers found that taking glucosamine/chondroitin every day for a year or longer was associated with a 39 percent reduction in all-cause mortality.

It was also linked to a 65 percent reduction in cardiovascular-related deaths. That's a category that includes deaths from stroke, coronary artery disease and heart disease, the United States' biggest killer. "Once we took everything into account, the impact was pretty significant," King said. The results appear in the *Journal of the American Board of Family Medicine*.

King himself takes glucosamine/chondroitin, one of the most common formulations of glucosamine supplements.

"I'm in a local cyclists' club, and we go for rides on weekends," he said. "One day I asked the other cyclists if they took glucosamine, and everyone did. And I thought, 'Well, I wonder if this is really helpful?' That's how I got curious about it."

He explains that because this is an epidemiological study--rather than a clinical trial--it doesn't offer definitive proof that glucosamine/chondroitin makes death less likely. But he does call the results "encouraging."

"In my view, it's important that people know about this, so they can discuss the findings with their doctor and make an informed choice," he said. "Glucosamine is over the counter, so it is readily available."

Citation *Title: Glucosamine chondroitin and overall mortality in a US NHANES cohort*

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Telomere shortening protects against cancer

Long viewed as an unwanted side-effect of aging, study shows it is in fact good for you

As time goes by, the tips of your chromosomes--called telomeres--become shorter. This process has long been viewed as an unwanted side-effect of aging, but a recent study shows it is in fact good for you.

"Telomeres protect the genetic material," says Titia de Lange, Leon Hess Professor at Rockefeller. "The DNA in telomeres shortens when cells divide, eventually halting cell division when the telomere reserve is depleted."

New results from de Lange's lab provide the first evidence that telomere shortening helps prevent cancer in humans, likely because of its power to curtail cell division. Published in *eLife*, the findings were obtained by analyzing mutations in families with exceptional cancer histories, and they present the answer to a decades-old question about the relationship between telomeres and cancer.

A longstanding controversy

In stem cells, including those that generate eggs and sperm,

telomeres are maintained by telomerase, an enzyme that adds telomeric DNA to the ends of chromosomes.

Telomerase is not present in normal human cells, however, which is why their telomeres wither away. This telomere shortening program limits the number of divisions of normal human cells to about 50.

The idea that telomere shortening could be part of the body's defense against cancer was first proposed decades ago. Once an early-stage tumor cell has divided 50 times, scientists imagined, depletion of the telomere reserve would block further cancer development. Only those cancers that manage to activate telomerase would break through this barrier.

Clinical observations seemed to support this hypothesis. "Most clinically detectable cancers have re-activated telomerase, often through mutations," de Lange says. Moreover, mouse experiments showed that shortening telomeres can indeed protect against cancer. Nonetheless, evidence for the telomere tumor suppressor system remained elusive for the past two decades, and its existence in humans remained controversial.

The solution to a decades-old problem

The telomere tumor suppressor pathway can only work if we are born with telomeres of the right length; if the telomeres are too long, the telomere reserve would not run out in time to stop cancer development.

Longer telomeres will afford cancer cells additional divisions during which mutations can creep into the genetic code, including mutations that activate telomerase.

For decades, de Lange's lab has been studying the complex process by which telomeres are regulated. She and others identified a set of proteins that can limit telomere length in cultured human cells, among them a protein called TIN2.

When TIN2 is inhibited, telomerase runs wild and over-elongates telomeres. But it was not known whether TIN2 also regulated telomere length at birth.

The stalemate on the telomere tumor suppressor continued until physicians at the Radboud University Medical Center in Holland reached out to de Lange about several cancer-prone families. The doctors found that these families had mutations in TINF2, the gene that encodes the TIN2 protein instrumental to controlling telomere length. That's when they asked de Lange to step in.

Isabelle Schmutz, a *Women&Science* postdoctoral fellow in the de Lange lab, used CRISPR gene-editing technology to engineer cells with precisely the same mutations as those seen in the Dutch families and examined the resulting mutant cells.

She found that the mutant cells had fully functional telomeres and no genomic instability. They were, for all intents and purposes, normal healthy cells.

But there was one thing wrong with the cells. "Their telomeres became too long, " de Lange says. Similarly, the patient's telomeres were unusually long. "These patients have telomeres that are far above the 99th percentile," de Lange says.

"The data show that if you're born with long telomeres, you are at greater risk of getting cancer, " says de Lange.

"We are seeing how the loss of the telomere tumor suppressor pathway in these families leads to breast cancer, colorectal cancer, melanoma, and thyroid cancers. These cancers would normally have been blocked by telomere shortening. The broad spectrum of cancers in these families shows the power of the telomere tumor suppressor pathway."

The study is demonstration of the power of basic science to transform our understanding of medicine. "How telomeres are regulated is a fundamental problem," de Lange says. "And by working on a fundamental problem, we were eventually able to understand the origins of a human disease."

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Cannabidiol (CBD) in cannabis does not impair driving, landmark study shows

Research shows cannabidiol safe for driving and THC effects fade in hours

A landmark study on how cannabis affects driving ability has shown that cannabidiol (CBD), a cannabis component now widely used for medical purposes, does not impair driving, while moderate amounts of the main intoxicating component tetrahydrocannabinol (THC) produce mild driving impairment lasting up to four hours.

The study was led the Lambert Initiative for Cannabinoid Therapeutics at the University of Sydney and conducted at Maastricht University in the Netherlands. It was published today in the prestigious *Journal of the American Medical Association*.

Lead author Dr Thomas Arkell said: "These findings indicate for the first time that CBD, when given without THC, does not affect a subject's ability to drive. That's great news for those using or considering treatment using CBD-based products."

There has been substantial growth in medical treatment using cannabis-related products in Australia and overseas. This includes increasing use of CBD-containing products for conditions such as epilepsy, anxiety, chronic pain and addictions. Many currently available products also contain a mixture of THC and CBD.

The research involved people inhaling vaporised cannabis containing different mixes of THC and CBD, then going for a 100-kilometre drive under controlled conditions on public highways both 40 minutes and four hours later. Cannabis containing mainly CBD did not impair driving while cannabis containing THC, or a THC/CBD mixture, caused mild impairment measured at 40 minutes later but not after four hours.

Dr Arkell said: "With cannabis laws changing globally, jurisdictions are grappling with the issue of cannabis-impaired driving. These results provide much needed insights into the magnitude and duration of impairment caused by different types of cannabis and can help to guide road-safety policy not just in Australia but around the world".

"Road safety is a primary concern," Dr Arkell said. "These results should allow for evidence-based laws and regulation for people receiving medical cannabis."

The Academic Director of the Lambert Initiative, Professor Iain McGregor, said: "We were delighted to have the opportunity to collaborate with Professor Jan Ramaekers and his team on this study. Studying the effects of cannabis on driving with such precision in a real-world context is incredibly important.

"The results should reassure people using CBD-only products that they are most likely safe to drive, while helping patients using THC-dominant products to understand the duration of impairment."

METHOD

The study involved giving 26 healthy participants four different types of cannabis in a random order to vaporise on four separate occasions. Each participant's driving performance was then assessed on the road in real-world conditions along a 100-kilometre stretch of public highway in a dual control car with a driving instructor present.

The tests were done at Maastricht University in the Netherlands using a well-established scientific test that measures standard deviation of vehicle position (SDLP), an index of lane weaving, swerving and overcorrecting. SDLP increases under the influence of alcohol and drugs such as Valium and Stilnox.

Participants vaporised cannabis containing mainly THC, mainly CBD, THC and CBD in combination, or placebo cannabis (no active components). The amount of THC vaporised by participants was enough to cause strong feelings of intoxication.

To test how the different types of cannabis affect driving,

participants completed two one-hour, on-road highway driving tests commencing at 40 minutes and at four hours after inhaling vaporised cannabis.

Professor McGregor said: "With rapidly changing attitudes towards medical and non-medical use of cannabis, driving under the influence of cannabis is emerging as an important and somewhat controversial public health issue.

"While some previous studies have looked at the effects of cannabis on driving, most have focused on smoked cannabis containing only THC (not CBD) and have not precisely quantified the duration of impairment. "This is the first study to illustrate the lack of CBD effects on driving and to also provide a clear indication of the duration of THC impairment."

DOWNLOAD *the paper, research images and photos of the researchers at this link.*
DOWNLOAD *b-roll footage that recreates test conditions and lab tests at this link.*

https://bit.ly/39QzRzr

Drug reverses age-related cognitive decline within days

Rapid mental rejuvenation in old mice suggests age-related losses may be broadly reversible

Just a few doses of an experimental drug can reverse age-related declines in memory and mental flexibility in mice, according to a new study by UC San Francisco scientists. The drug, called ISRIB, has already been shown in laboratory studies to restore memory function months after traumatic brain injury (TBI), reverse cognitive impairments in Down Syndrome , prevent noise-related hearing loss, fight certain types of prostate cancer , and even enhance cognition in healthy animals.

In the new study, published December 1, 2020 in the open-access journal *eLife* , researchers showed rapid restoration of youthful cognitive abilities in aged mice, accompanied by a rejuvenation of brain and immune cells that could help explain improvements in brain function.

"ISRIB's extremely rapid effects show for the first time that a significant component of age-related cognitive losses may be caused by a kind of reversible physiological "blockage" rather than more permanent degradation," said Susanna Rosi , PhD, Lewis and Ruth Cozen Chair II and professor in the departments of Neurological Surgery and of Physical Therapy and Rehabilitation Science (http://ptrehab.ucsf.edu/) .

"The data suggest that the aged brain has not permanently lost essential cognitive capacities, as was commonly assumed, but rather that these cognitive resources are still there but have been somehow blocked, trapped by a vicious cycle of cellular stress," added Peter Walter , PhD, a professor in the UCSF Department of Biochemistry and Biophysics and a Howard Hughes Medical Institute investigator. "Our work with ISRIB demonstrates a way to break that cycle and restore cognitive abilities that had become walled off over time."

Could Rebooting Cellular Protein Production Hold the Key to Aging and Other Diseases?

Walter has won numerous scientific awards, including the Breakthrough , Lasker and Shaw prizes, for his decades-long studies of cellular stress responses. ISRIB, discovered in 2013 in Walter's lab, works by rebooting cells' protein production machinery after it gets throttled by one of these stress responses -- a cellular quality control mechanism called the integrated stress response (ISR; ISRIB stands for ISR InhiBitor).

The ISR normally detects problems with protein production in a cell -- a potential sign of viral infection or cancer-promoting gene mutations -- and responds by putting the brakes on cell's protein-synthesis machinery.

This safety mechanism is critical for weeding out misbehaving cells, but if stuck in the on position in a tissue like the brain, it can lead to serious problems, as cells lose the ability to perform their normal

activities, Walter and colleagues have found.

In particular, recent animal studies by Walter and Rosi, made possible by early philanthropic support from The Rogers Family Foundation, have implicated chronic ISR activation in the persistent cognitive and behavioral deficits seen in patients after TBI, by showing that, in mice, brief ISRIB treatment can reboot the ISR and restore normal brain function almost overnight.

The cognitive deficits in TBI patients are often likened to premature aging, which led Rosi and Walter to wonder if the ISR could also underlie purely age-related cognitive decline. Aging is well known to compromise cellular protein production across the body, as life's many insults pile up and stressors like chronic inflammation wear away at cells, potentially leading to widespread activation of the ISR.

"We've seen how ISRIB restores cognition in animals with traumatic brain injury, which in many ways is like a sped-up version of age-related cognitive decline," said Rosi, who is director of neurocognitive research in the UCSF Brain and Spinal Injury Center and a member of the UCSF Weill Institute for Neurosciences. "It may seem like a crazy idea, but asking whether the drug could reverse symptoms of aging itself was just a logical next step."

ISRIB Improves Cognition, Boosts Neuron and Immune Cell Function

In the new study, researchers led by Rosi lab postdoc Karen Krukowski , PhD, trained aged animals to escape from a watery maze by finding a hidden platform, a task that is typically hard for older animals to learn. But animals who received small daily doses of ISRIB during the three-day training process were able to accomplish the task as well as youthful mice, much better than animals of the same age who didn't receive the drug.

The researchers then tested how long this cognitive rejuvenation lasted and whether it could generalize to other cognitive skills. Several weeks after the initial ISRIB treatment, they trained the same mice to find their way out of a maze whose exit changed daily -- a test of mental flexibility for aged mice who, like humans, tend to get increasingly stuck in their ways. The mice who had received brief ISRIB treatment three weeks before still performed at youthful levels, while untreated mice continued to struggle.

To understand how ISRIB might be improving brain function, the researchers studied the activity and anatomy of cells in the hippocampus, a brain region with a key role in learning and memory, just one day after giving animals a single dose of ISRIB. They found that common signatures of neuronal aging disappeared literally overnight: neurons' electrical activity became more sprightly and responsive to stimulation, and cells showed more robust connectivity with cells around them while also showing an ability to form stable connections with one another usually only seen in younger mice.

The researchers are continuing to study exactly how the ISR disrupts cognition in aging and other conditions and to understand how long ISRIB's cognitive benefits may last. Among other puzzles raised by the new findings is the discovery that ISRIB also alters the function of the immune system's T cells, which also are prone to age-related dysfunction.

The findings suggest another path by which the drug could be improving cognition in aged animals, and could have implications for diseases from Alzheimer's to diabetes that have been linked to heightened inflammation caused by an aging immune system.

"This was very exciting to me because we know that aging has a profound and persistent effect on T cells and that these changes can affect brain function in the hippocampus," said Rosi. "At the moment, this is just an interesting observation, but it gives us a very exciting set of biological puzzles to solve.

ISRIB May Have Wide-Ranging Implications for Neurological Disease

It turns out that chronic ISR activation and resulting blockage of cellular protein production may play a role in a surprisingly wide array of neurological conditions. Below is a partial list of these conditions, based on a recent review by Walter and colleague Mauro Costa-Mattioli of Baylor College of Medicine, which could potentially be treated with an ISR-resetting agent like ISRIB:

- ***Frontotemporal Dementia***
- ***Alzheimer's Disease***
- ***Amyotrophic Lateral Sclerosis (ALS)***
- ***Age-related Cognitive Decline***
- ***Multiple Sclerosis***
- ***Traumatic Brain Injury***
- ***Parkinson's Disease***
- ***Down Syndrome***
- ***Vanishing White Matter Disorder***
- ***Prion Disease***

ISRIB has been licensed by Calico, a South San Francisco, Calif. company exploring the biology of aging, and the idea of targeting the ISR to treat disease has been picked up by other pharmaceutical companies, Walter says.

One might think that interfering with the ISR, a critical cellular safety mechanism, would be sure to have serious side effects, but so far in all their studies, the researchers have observed none. This is likely due to two factors, Walter says. First, it takes just a few doses of ISRIB to reset unhealthy, chronic ISR activation back to a healthier state, after which it can still respond normally to problems in individual cells. Second, ISRIB has virtually no effect when applied to cells actively employing the ISR in its most powerful form -- against an aggressive viral infection, for example.

Naturally, both of these factors make the molecule much less likely to have negative side effects -- and more attractive as a potential therapeutic. According to Walter: "It almost seems too good to be true, but with ISRIB we seem to have hit a sweet spot for manipulating the ISR with an ideal therapeutic window.

Authors: Other authors on the study were Amber Nolan, Elma S. Frias, Morgane Boone, Katherine Grue, Maria-Serena Paladini, and Edward Elizarraras of UCSF; and Gonzalo Ureta, Luz Delgado and Sebastian Bernales of Fundación Ciencia & Vida in Santiago, Chile; Fundación Ciencia & Vida. Bernales is also an employee of Praxis Biotech, LLC.

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Disclosures: Gonzalo Ureta works at Fundacion Ciencia & Vida and receives partial funding from Praxis Biotech. Sebastian Bernales is an employee of Praxis Biotech. Peter Walter is an inventor on U.S. Patent 9708247 held by the Regents of the University of California that describes ISRIB and its analogs. Rights to the invention have been licensed by UCSF to Calico.

https://bit.ly/37BDrL0

KU Leuven vaccine candidate protects against Covid-19 and yellow fever

Vaccine candidate against Covid-19 based on yellow fever vaccine, which as a result also works against yellow fever

Virologists at the Rega Institute at KU Leuven (Belgium) have developed a vaccine candidate against Covid-19 based on the yellow fever vaccine, which as a result also works against yellow fever. Results published today in *Nature* show that the vaccine protects hamsters from infection with the SARS-CoV-2 coronavirus after a single dose. The vaccine is also effective in monkeys. The team is currently preparing for clinical trials.

To engineer their vaccine, tentatively named RegaVax, the team led by Professor Johan Neyts and Kai Dallmeier inserted the genetic code of the SARS-CoV-2 spikes into the genetic code of the yellow fever vaccine. The researchers tested the vaccine in healthy hamsters and monkeys. Another group of the animals received a

placebo.

The researchers first vaccinated the hamsters and then dripped the virus into their noses. Ten days after a single vaccine dose, most of the hamsters were protected against the virus. Three weeks after vaccination, all hamsters were protected. "They also didn't develop any lung infections. The lungs of the hamsters in the control groups, by contrast, showed clear signs of infection and disease," Neyts explains.

The team also tested the vaccine in monkeys. "In some of the monkeys, we observed neutralising antibodies already seven days after vaccination. After fourteen days, high titers of neutralizing antibodies were measured in all animals. This is very fast. Moreover, in the vaccinated animals, the virus was completely or nearly completely gone from their throats."

Long-lasting immunity

"Ours is the only vaccine currently in development against Covid-19 that also protects against yellow fever," explains professor Neyts. Previously, the Rega team used the yellow fever vaccine as the foundation for vaccine candidates against Zika, Ebola, and rabies. "The effectiveness and safety of the yellow fever vaccine, which has been in use for 80 years, is well-established. More than 500 million people have already received this vaccine. One dose offers fast protection against yellow fever that in nearly all cases lasts for life."

"A vaccine that works against Covid-19 and yellow fever could offer an important contribution to the WHO's campaign to eradicate yellow fever by 2026," Neyts continues. "Especially now that we know there are mosquito species present in Asia that can transmit the yellow fever virus."

RegaVax works after one dose, unlike many of the front-runners in the race today, which require a repeat vaccination after one month. "This has important logistical implications, in particular for countries with a less advanced medical system," explains professor Neyts.

"Additionally, we expect that the vaccine will offer long-lasting immunity to Covid-19. It could therefore be an ideal candidate for repeat vaccinations when immunity decreases in people who have received one of the first-generation vaccines."

Finally, the vaccine can be stored at 2-8 °C, while some vaccines require a cold chain with temperatures down to -70 °C. That's already challenging in the Western world, but it may be nearly impossible to vaccinate large populations in remote tropical and subtropical regions," Neyts explains.

"An inexpensive, single-dose vaccine that rapidly protects against infection, that can be stored and transported at fridge temperature, and that may, like the yellow fever vaccine on which it is based, result in long-lasting immunity, provides an important and much-needed diversification of the Covid-19 vaccine landscape," Neyts concludes.

His team is now preparing for clinical trials next year and has joined forces with a specialised and accredited company that will produce the vaccine candidate for testing in humans.

New technique

RegaVax is a vector vaccine: it uses the genetic code of the yellow fever vaccine virus as a carrier (or vector) for the genetic code of the coronavirus spikes. "When working with a related virus, such as the Zika virus, pieces of the genetic code of the yellow fever vaccine virus are swapped with a similar piece of the code of the targeted virus.

Using this strategy the team recently developed a Zika vaccine candidate. However, since SARS-CoV-2 is unrelated to yellow fever, a new technology had to be developed to insert an entirely unrelated genetic sequence in the yellow fever vaccine backbone. This concerns an important innovation in the vaccine field."

Virus inhibitors

"Mind you: vaccines are not a solution for people who are already ill. That is why we are also developing a cure to help Covid-19 patients," Neyts concludes. "We recently published on the protective activity of the Japanese flu drug favipiravir in hamsters. We have identified some other existing medicines or combinations thereof that inhibit the virus. We are now first exploring their effect in infected hamsters. At the same time, we aim to develop new and powerful virus inhibitors against SARS-CoV-2. For this purpose, we have already tested more than 1.6 million molecules in our fully automated high biosafety laboratory. We're looking for a needle in a haystack."

https://go.nature.com/2IiSGji

Cracking the meat-allergy mystery with the tick-bite link

An unusual reaction to mammalian meat is challenging the immunological understanding of allergies.

Bianca Nogrady

Peter Moore woke up in the middle of the night with his throat so tight he struggled to breathe, his torso covered with huge red welts, and no idea why. Earlier that evening in June 2001, Moore — then a 25-year-old teacher living in a coastal suburb of Sydney, Australia — had eaten pork spare ribs at a neighbour's house, then gone to bed content and in perfect health. Until he woke in a panic.

Moore's partner, Christine, immediately called an ambulance. She and the neighbour bundled him into a boat and ferried him across the short stretch of coastal waters to Church Point, where an ambulance could pick him up.

As they waited, seated on a sandstone wall under a street light, Moore remembers watching tiny black ants run back and forth on the ground in front of his feet. "There are certain moments in your life which are super vivid, and that one of the street lights, the ants, the sound of the ambulance, it doesn't dissipate," he says.

The medical team at the hospital where Moore was taken were puzzled. They treated him with adrenaline, antihistamine and steroids, and he recovered. A couple of months later, it happened again, this time after a dinner of spaghetti and meatballs. And again in November that year, after eating beef nachos. Each time, he was hospitalized. Each time, no one was sure what it was he was reacting to.

The allergist he saw after his third episode suggested it might be some kind of additive in the meat, so he started avoiding meat altogether. Then, around six years later, he discovered that a neighbour had experienced similar reactions after eating meat. The chance conversation led him to allergist and clinical immunologist Sheryl van Nunen at Sydney's Royal North Shore Hospital.

Van Nunen diagnosed him with mammalian-meat allergy, a rare condition that she had first seen in a patient in 1987. Since then, she has managed more than 400 cases — and noticed something common among them. "After you've seen a couple of people and the story's the same, I like to know what's happening to them, so I always take a family history of allergy," she says. These patients said they had experienced a large, localized reaction, or a more extreme systemic reaction, when they'd been bitten by a tick.

As more and more patients arrived at her clinic with similar stories, van Nunen deduced that it wasn't just any tick causing these reactions: it was a specific type from Sydney's northern beaches.

Breakthrough

Half the world away, in North Carolina and Tennessee, researchers conducting clinical trials of a monoclonal antibody treatment for colorectal cancer — cetuximab — were seeing unprecedented rates of severe allergic reactions to the drug. Just over one in five people who had received the intravenous drug were experiencing full anaphylaxis[1] — something that hadn't been seen in cetuximab

clinical trials in other parts of the world.

What was especially strange — aside from the high frequency of the reaction — was that many of these people had no history of allergies or previous exposure to the drug. Typically, an allergic reaction to a drug is built up over multiple exposures. “The patients were reacting on the first infusion, which made you think something had to be there ahead of time,” says Scott Commins, an allergist and immunologist at the University of North Carolina at Chapel Hill who was among those investigating.

After studying the molecular structure of cetuximab and the immunological markers of the response, researchers hypothesized that the sugar molecules attached to the monoclonal antibody might be important. The manufacturer provided an alternative form of the drug without those sugars, and it was tested. Suddenly, all the previously positive antibody responses turned negative. “We had played this hunch, and then for the data to be so clean, and really support that hunch — it was a good day,” Commins says.

Further analysis revealed the exact culprit: a sugar called galactose-α-1,3-galactose, or α-gal. Many mammals produce α-gal, but humans and some other primates do not, having lost the ability to do so around 28 million years ago. This is a major barrier to transplantation of organs between animals and humans, because humans produce substantial quantities of natural antibodies against α-gal. Cetuximab was produced using a mouse cell line, which was the source of the α-gal.

This was a breakthrough, but it still didn’t explain why the rate of hypersensitivity reactions to cetuximab was so high in that particular part of the United States. So researchers dug deeper. Using a newly developed test for the type of immunoglobulin E (IgE) antibodies that target α-gal, they discovered that α-gal sensitivity was surprisingly common in the southeastern United States compared with other parts of the country.

Then came the second breakthrough. In 2009, Commins and his colleagues found that 24 patients at the University of Virginia allergy clinic in Charlottesville had IgE antibodies against α-gal[2] — and all of them had shown allergic reactions within three to six hours of eating mammalian meat. Just a few months later, van Nunen and her colleagues published a paper on the association between mammalian-meat allergy and tick bites[3], and the pieces of this food-allergy puzzle finally fell into place. In the southeastern United States, just as in Sydney, a tick was the key.

“The tick is altering us,” van Nunen says. When a tick bites a person, it introduces α-gal to the human immune system, which in some people leads to the development of an allergy to mammalian meat products. Exactly how this happens, however, is still shrouded in mystery.

Tick link

The tick is a cunning parasite. It has to be, because unlike other blood-sucking arthropods, it needs to stay attached to its host for a long time — in some cases, for up to ten days.

Ixodes ricinus, the castor bean tick, has been linked to mammalian-meat allergy in Europe. **Credit: London Scientific Films/Getty**

To suck blood for such a prolonged period, the ticks need a way to manipulate the defences of their host so that they remain unrecognized, says Mária Kazimírová, an entomologist at the Slovak Academy of Sciences in Bratislava. The key to this lies in their saliva, which contains anticoagulants to keep the blood flowing, anaesthetics to dull the skin around the bite, and immunosuppressants and immunomodulators to stop the host’s skin from initiating an inflammatory reaction that might prematurely end the tick’s feeding.

This sialome — the proteins expressed in the salivary glands of

ticks and other blood-sucking parasites — varies between species as well as between individual ticks. It can even vary in one tick over the course of a single feeding, as a mechanism to avoid immune detection. The source of the α-gal is still being investigated: it could be produced by the tick or its microbiome, or ingested from a host.

Not all species of tick produce α-gal, says Shahid Karim, a vector biologist at the University of Southern Mississippi in Hattiesburg. In Australia, the main culprit in mammalian-meat allergy is *Ixodes holocyclus*, which is also known as the paralysis tick. It is found across the east coast, but especially around Sydney's northern beaches, where Moore lived and where so many of van Nunen's patients come from.

In the United States, *Amblyomma americanum*, or lone star tick, is the species whose bite is most commonly associated with the develop-ment of mammalian-meat allergy. The tick is distributed across the east and central United States, including North Carolina, Tennessee and New York.

Allergist Erin McGintee had only just started up her practice a decade ago at the east end of Long Island, New York, when she saw a man who thought he had a shellfish allergy. "He would wake up in the middle of the night, usually with severe abdominal symptoms, like he was going to have diarrhoea or he was going to vomit," says McGintee. "He'd jump up out of bed, run to the bathroom and break out in hives. And with his couple of most severe episodes, he actually lost consciousness."

But before some of these episodes, the man hadn't knowingly eaten shellfish. He'd been at a steakhouse, then at a barbecue. McGintee recalled seeing an abstract about mammalian-meat allergy, so she looked into it. When she tested the man for α-gal antibodies, the results came back positive.

"Now that I am an expert in this allergy and I've taken care of it for so many years, his presentation was absolutely classic," McGintee says. She has since seen around 600 people with the allergy, which fits with the high prevalence of the lone star tick in east Long Island. But the condition is not solely caused by lone star ticks and paralysis ticks in the United States and Australia. In Europe, it can be triggered by *Ixodes ricinus* (the castor bean tick), *Rhipicephalus bursa* (the brown ear tick) and *Hyalomma marginatum*. In Japan, it's linked to *Haemaphysalis longicornis* (the Asian longhorned tick), and in Brazil it's caused by *Amblyomma sculptum*.

There are also clusters of cases in South Africa. However, Tshegofatso Mabelane, an allergist in Pretoria who has been studying a large cohort of people with mammalian-meat allergy, says the cause there has yet to be identified. The cases are clustered in rural areas, which suggests that the people affected would have had the opportunity to come into contact with ticks. But Mabelane's patients don't necessarily report the history of tick-bite reactions that van Nunen has observed. Mabelane speculates that there could be another type of blood-sucking arthropod that is sensitizing these people to α-gal.

The clinical presentation of mammalian-meat allergy also varies between locations. Mabelane conducted a food-challenge trial (in which a person is intentionally exposed to the allergen) in 131 South Africans who had experienced adverse reactions to meat[4], giving them a meal of beef sausage. She expected the reaction to take a few hours to manifest, on the basis of what had been reported in other parts of the world. But that wasn't the case. "I had people presenting within 45 minutes," she says. Furthermore, they predominantly showed gastrointestinal symptoms. "I'm expecting skin manifestations, and I'm running around [with] buckets."

Van Nunen has identified two other forms of allergic presentation in tick-bite-induced mammalian-meat allergy — food protein-induced enterocolitis syndrome and the much rarer food

carbohydrate-induced enterocolitis syndrome. She is also investigating a possible third presentation, T cell systemic contact dermatitis, in a person whose contact dermatitis resolved when they took mammalian meat out of their diet.

"Now the spectrum of mammalian-meat allergy is across all of the known descriptions of hypersensitivity to food," van Nunen says. "This allergen can do everything any other allergen can do." And it presents across all ages, from children to elderly people; McGintee has seen it in a child aged three.

Paradigm shift

Most humans happily consume mammalian meat throughout their life without becoming allergic, despite our lack of α-gal. But the number of cases of α-gal syndrome is growing: it is estimated to affect more than 5,000 people in the United States, and it is a leading cause of anaphylaxis in the southeast of the country.

Why this allergy has emerged in such numbers only relatively recently, when ticks have been around for a long time, is unclear. One theory is that the ticks themselves have changed. Karim is investigating whether the tick's complement of microbes has altered in response to environmental factors, and this has led to ticks producing α-gal in response. Van Nunen also suggests that the tick might be producing α-gal as a defence mechanism against microorganisms that live in and on it.

Researchers also don't know why the allergy develops only in some people bitten by ticks bearing α-gal, or even why it develops at all. "It really breaks this whole paradigm that tolerance is established in early childhood and is therefore never bendable or breakable," says Commins. The immunological understanding has been that once tolerance to a food is established, IgG antibodies are made to record that. "So what we're really talking about is a new set of IgE antibodies that seem to somehow override the IgG that you've made for years."

There are relatively few clues in the patients themselves as to what might be predisposing them to developing mammalian-meat allergy. Some clinicians have observed that it runs in families, and that individuals of blood group B are less susceptible than those of blood groups O or A. Studies have also shown that although people with mammalian-meat allergy have high levels of IgE antibodies against α-gal, not all people with high levels of those antibodies have mammalian-meat allergy.

McGintee theorizes that there might be a window after a tick bite in which the conditions exist for mammalian-meat allergy to develop, and that it is exposure to additional stimulating factors during that window that determines whether a person will become allergic. When someone is bitten by an α-gal-producing tick, they begin to manufacture antibodies against α-gal over a period of a month or two, she says. At that point, the person might not be producing enough antibodies to have a noticeable reaction to any α-gal that they consume. But if, during that time, they were to eat a substantial quantity of red meat, or be bitten by another tick, the cumulative effect on levels of α-gal antibodies in their system might be enough to provoke an allergic response.

"My theory is that there's probably a lot of people who make some α-gal antibodies following a lone star tick bite, but maybe they never hit that threshold," she says. "They miss the window, and they never have a reaction."

Support for this comes from the observation that the allergy does seem to wane over time if patients are not exposed to any more tick bites. "In quite a few people, you can get them back onto meat within three to four years, but the secret to that is no more tick bites," van Nunen says. Another tick bite can send antibody levels — and allergic responses — soaring again.

This is why van Nunen has focused some of her attention on identifying methods of preventing tick bites, such as treating

clothing with insecticide, as well as techniques for removing embedded ticks in a way that reduces the amount of saliva they discharge into their host. “Tick-bite prevention and management strategies have been proven to work,” she says.

Moore, who left Australia for the United States in 2009 and is now a teacher in North Carolina, had a close encounter with a lone star tick in the summer. It was crawling across his arm but hadn’t yet attached, so he was able to flick it off. He is careful to avoid meat, and he uses his personal experience to help students with food allergies, their parents and other teachers understand the risks and realities of potentially fatal food allergies.

Despite his awareness, he has had a couple of allergic episodes in recent years after being inadvertently exposed to mammalian meat products. Moore says he still lives in fear of another severe reaction that might land him in hospital. “People say is it hard, not eating red meat or pork? And I say, when you know something could kill you, it’s really easy to avoid.”

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Incredible vision in ancient marine creatures drove an evolutionary arms race

Ancient deep sea creatures called radiodonts had incredible vision that likely drove an evolutionary arms race according to new research published today.

The international study, led by Professor John Paterson from the University of New England's Palaeoscience Research Centre, in collaboration with the University of Adelaide, the South Australian Museum and The Natural History Museum (UK), found that radiodonts developed sophisticated eyes over 500 million years ago, with some adapted to the dim light of deep water.

An artist's reconstruction of 'Anomalocaris' briggsi swimming within the twilight zone. **Credit: Katrina Kenny**

"Our study provides critical new information about the evolution of the earliest marine animal ecosystems," Professor Paterson said. "In particular, it supports the idea that vision played a crucial role during the Cambrian Explosion, a pivotal phase in history when most major animal groups first appeared during a rapid burst of evolution over half a billion years ago."

Radiodonts, meaning "radiating teeth", are a group of arthropods that dominated the oceans around 500 million years ago.

The many species share a similar body layout comprising of a head with a pair of large, segmented appendages for capturing prey, a circular mouth with serrated teeth, and a squid-like body.

It now seems likely that some lived at depths down to 1000 metres and had developed large, complex eyes to compensate for the lack of light in this extreme environment.

"When complex visual systems arose, animals could better sense their surroundings," Professor Paterson explained. "That may have fuelled an evolutionary arms race between predators and prey.

Once established, vision became a driving force in evolution and helped shape the biodiversity and ecological interactions we see

today."

Some of the first radiodont fossils discovered over a century ago were isolated body parts, and initial attempts at reconstructions resulted in "Frankenstein's monsters".

But over the past few decades many new discoveries -- including whole radiodont bodies -- have given a clearer picture of their anatomy, diversity and possible lifestyles.

Co-author, Associate Professor Diego García-Bellido from the University of Adelaide and South Australian Museum, said the rich treasure trove of fossils at Emu Bay Shale on South Australia's Kangaroo Island in particular has helped to build a clearer picture of Earth's earliest animals.

"The Emu Bay Shale is the only place in the world that preserves eyes with lenses of Cambrian radiodonts.

The more than thirty specimens of eyes we now have, has shed new light on the ecology, behaviour and evolution of these, the largest animals alive half-a-billion years ago," A/Prof. García-Bellido said.

In 2011, the team published two papers in the journal Nature on fossil compound eyes from the 513-million-year-old Emu Bay Shale on Kangaroo Island.

The first paper on this subject documented isolated eye specimens of up to one centimetre in diameter, but the team were unable to assign them to a known arthropod species.

The second paper reported the stalked eyes of Anomalocaris, a top predator up to one metre in length, in great detail.

"Our new study identifies the owner of the eyes from our first 2011 paper: 'Anomalocaris' briggsi --representing a new genus that is yet to be formally named," Prof. Paterson said.

"We discovered much larger specimens of these eyes of up to four centimetres in diameter that possess a distinctive 'acute zone', which is a region of enlarged lenses in the centre of the eye's surface that enhances light capture and resolution."

The large lenses of 'Anomalocaris' briggsi suggest that it could see in very dim light at depth, similar to amphipod crustaceans, a type of prawn-like creature that exists today. The frilly spines on its appendages filtered plankton that it detected by looking upwards.

Dr Greg Edgecombe, a researcher at The Natural History Museum, London and co-author of the study, added that the South Australian radiodonts show the different feeding strategies previously indicated by the appendages - either for capturing or filtering prey - are paralleled by differences in the eyes.

"The predator has the eyes attached to the head on stalks but the filter feeder has them at the surface of the head.

The more we learn about these animals the more diverse their body plan and ecology is turning out to be," Dr Edgecombe said. "The new samples also show how the eyes changed as the animal grew.

The lenses formed at the margin of the eyes, growing bigger and increasing in numbers in large specimens - just as in many living arthropods. The way compound eyes grow has been consistent for more than 500 million years."

The study "Disparate compound eyes of Cambrian radiodonts reveal their developmental growth mode and diverse visual ecology" was published today in the prestigious journal *Sciences Advances*.

https://bit.ly/3quyzQr

Cretaceous Titanosaur Suffered from Blood Parasites and Severe Bone Inflammation

A giant sauropod dinosaur that lived 85.2 million years ago (Cretaceous period) in what is now Brazil had an aggressive case of osteomyelitis in its leg and soft-bodied parasitical microorganisms in its vascular canals.

by Sergio Prostak

“The occurrence of osteomyelitis in dinosaurs is rare, but recent studies have corroborated the occurrence of this form of bone

inflammation in Sauropodomorpha," said lead author Dr. Tito Aureliano and his colleagues from the University of Campinas, the Federal University of Rio Grande do Norte, and the Federal University of Sao Carlos.

"Evidence of fossil endoparasites of vertebrates has already been found in coprolites and invertebrate vectors preserved in amber."

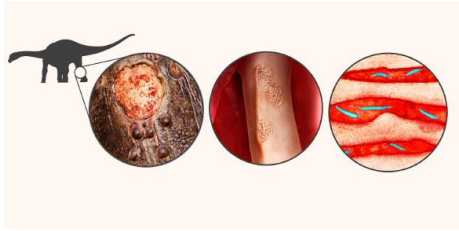
"However, fossil parasites preserved directly in vertebrate tissues were unknown until the present date."

Life reconstruction of the titanosaur from the Upper Cretaceous Adamantina Formation in São Paulo backcountry, southeastern Brazil. The animal was reconstructed based on associated saltasaurid specimens in the area. **Image credit: Hugo Cafasso.**

In the study, the researchers looked at the 85.2-million-year-old fragmentary fibula of a titanosaur from Brazil's Adamantina Formation.

They used CT scanning to create a 3D model of the full fossil. They also examined the specimen with petrographic and non-filtered optical microscopes.

They identified tens of fossil parasites preserved inside the specimen's vascular canals — the first clear example of a parasite preserved inside fossilized bone tissue. The dinosaur fibula also showed acute osteomyelitis with elliptical ulcerations, present throughout all the bone.Bone inflammation was either caused by the referred parasites or facilitated its infestation.



Ulcerations reconstructed based on pathologies in the 85.2-million-year-old titanosaurs fibula. **Image credit: Hugo Cafasso.**

"Our research documents for the first time the detailed histological description of severe bone inflammation and the exceptional preservation of soft-bodied parasitical microorganisms inside the vascular canals of a non-avian dinosaur," the scientists said.

"The results bring new insights into the fields of parasitology, pathology, and histology in the fossil record."

The team's paper was published in the journal *Cretaceous Research*.

Tito Aureliano et al. 2021. Blood parasites and acute osteomyelitis in a non-avian dinosaur (Sauropoda, Titanosauria) from the Upper Cretaceous Adamantina Formation, Bauru Basin, Southeast Brazil. Cretaceous Research 118: 104672; doi: 10.1016/j.cretres.2020.104672

https://wb.md/39MRvnx

Colchicine a Case Study for What's Wrong With US Drug Pricing

Centuries-old drug sold for pennies in the United States before increasing 50-fold to about $5 per pill in 2009

Patrice Wendling

Public spending on colchicine has grown exponentially over the past decade despite generics suggesting an uphill slog for patients seeking access to long-term therapy for gout or cardiac conditions.

Medicaid spending on single-ingredient colchicine jumped 2833%, from $1.1 million in 2008 to $32.2 million in 2017, new findings show. Medicaid expansion likely played a role in the increase, but 58% was due to price hikes alone.

The centuries-old drug sold for pennies in the United States before increasing 50-fold to about $5 per pill in 2009 after the first FDA-approved colchicine product, Colcrys, was granted 3 years' market exclusivity for the treatment of acute gout based on a 1-week trial.

If prices had remained at pre-Colcrys levels, Medicaid spending in 2017 would have totaled just $2.1 million rather than $32.2 million according to the analysis, published online November 30 in *JAMA Internal Medicine*.

The study was motivated by difficulties gout patients have in accessing colchicine, but also last year's COLCOT trial, which

reported fewer ischemic cardiovascular events in patients receiving colchicine after myocardial infarction (MI), observed Natalie McCormick, PhD, Massachusetts General Hospital and Harvard Medical School, Boston.

"They were suggesting it could be a cost-effective way for secondary prevention and it is fairly inexpensive in most countries, but not the US," she told *theheart.org | Medscape Cardiology*. "So there's really a potential to increase public spending if more and more patients are then taking colchicine for prevention of cardiovascular events and the prices don't change."

The current pandemic could potentially further increase demand. Results initially slated for September are expected this month from the COLCORONA trial, which is testing whether the anti-inflammatory agent can prevent hospitalizations, lung complications, and death when given early in the course of COVID-19.

University of Oxford researchers also announced last week that colchicine is being added to the massive RECOVERY trial, which is studying treatments for hospitalized COVID-19 patients.

Notably, the Canadian-based COLCOT trial did not use Colcrys, but rather a colchicine product that costs just 26 cents a pill in Canada, roughly the price of most generics available worldwide.

Authorized generics typically drive down drug prices when competing with independent generics, but this competition is missing in the United States, where Colcrys holds patents until 2029, McCormick and colleagues note. More than a half dozen independent generics have FDA approval to date, but only authorized generics with price points set by the brand-name companies are available to treat acute gout, pericarditis, and potentially millions with MI.

"One of the key takeaways is this difference between the brand names and the authorized generics and the independents," she said. "The authorized [generics] have really not saved money. The list prices were just slightly lower and patients can also have more difficulty in getting those covered."

For this analysis, the investigators used Medicaid and Medicare data to examine prices for all available forms of colchicine from 2008 through 2017, including unregulated/unapproved colchicine (2008–2010), generic combination probenecid–colchicine (2008–2017), Colcrys (2009–2017), brand-name single-ingredient colchicine Mitigare (approved in late 2014 but not marketed until 2015), and their authorized generics (2015–2017). Medicare trends from 2012 to 2017 were analyzed separately because pre-Colcrys Medicare data were not available.

Based on the results, combined spending on Medicare and Medicaid claims for single-ingredient colchicine exceeded $340 million in 2017.

Inflation- and rebate-adjusted Medicaid unit prices rose from $0.24 a pill in 2008, when unapproved formulations were still available, to $4.20 a pill in 2011 (Colcrys only), and peaked at $4.66 a pill in 2015 (Colcrys plus authorized generics).

Prescribing of lower-priced probenecid–colchicine ($0.66/pill in 2017) remained stable throughout. Medicaid rebate-adjusted prices in 2017 were $3.99/pill for all single-ingredient colchicine products, $5.13/pill for Colcrys, $4.49/pill for Mitigare, and $3.88/pill for authorized generics.

Medicare rebate-adjusted 2017 per pill prices were $5.81 for all single-ingredient colchicine products, $6.78 for Colcrys, $5.68 for Mitigare, $5.16 for authorized generics, and $0.70 for probenecid–colchicine. "Authorized generics have still driven high spending," McCormick said. "We really need to encourage more competition in order to improve access."

In an accompanying commentary, B. Joseph Guglielmo, PharmD, University of California, San Francisco, pointed out that the

estimated median research and development cost to bring a drug to market is between $985 and $1335 million, which inevitably translates into a high selling price for the drug. Such investment and its resultant cost, however, should be associated with potential worth to society.

"Only a fraction of an investment was required for Colcrys, a product that has provided no increased value and an unnecessary, long-term cost burden to the health care system," he writes. "The current study findings illustrate that we can never allow such an egregious case to take place again."

McCormick reported grants from Canadian Institutes of Health Research during the conduct of the study. Guglielmo reported having no relevant conflicts of interest.

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https://bit.ly/2JJbQiO

Lab-Grown Chicken Meat Is Finally Going on Sale in a World First

Lab-grown chicken will soon be available in restaurants in Singapore after the country became the first to green-light meat created without slaughtering any animals.

US start-up Eat Just said Wednesday that its meat had been approved for sale in the city-state as an ingredient in chicken nuggets. The news marks a "breakthrough for the global food industry", said the company, as firms increasingly try to find less environmentally harmful ways of producing meat.

"I'm sure that our regulatory approval for cultured meat will be the first of many in Singapore and in countries around the globe," said Josh Tetrick, co-founder and CEO of Eat Just.

Consumption of regular meat is an environmental threat as cattle produce methane, a potent greenhouse gas, while logging forests to make way for animals destroys natural barriers against climate change. Demand for sustainable meat alternatives is rising due to growing pressure from consumers about the environment and animal welfare, but other products in the market are plant-based.

There were concerns that lab-grown varieties would be too expensive, but a spokesman for Eat Just said the company had made "considerable progress" in lowering the cost.

"Right from the start, we will be at price parity for premium chicken at a high-end restaurant," he told AFP.

He did not reveal the price of the nuggets but said they would be launched soon at a Singapore restaurant before other products – including chicken breasts with lab-grown meat – are rolled out.

Eat Just hopes to bring down the cost to below that of conventional chicken in the coming years, the spokesman added.

Soaring meat consumption

The company conducted more than 20 production runs in 1,200-litre bioreactors to make the chicken alternative, and checks on safety and quality showed that its "cultured" product – the term for meat grown in labs from animal cells – met food standards.

Meat consumption is projected to increase more than 70 percent by 2050, and lab-grown alternatives have a role to play in ensuring a secure food supply, Eat Just said.

"Working in partnership with the broader agriculture sector and forward-thinking policymakers, companies like ours can help meet the increased demand for animal protein as our population climbs to 9.7 billion by 2050," said company CEO Tetrick.

The Singapore Food Agency, the city-state's regulator, confirmed it had approved the sale of Eat Just's lab-grown chicken in nuggets after concluding it was safe for consumption. The high-tech city-state has become a hub for the development of sustainable foods, with start-ups producing goods ranging from lab-grown "seafood" to dumplings made with tropical fruit instead of pork.

William Chen, a Singapore-based scientist and member of an expert panel that advises the regulator, said food security was a key concern in the city-state's drive for developing meat alternatives.

Singapore "has virtually no agriculture, we import more than 90 percent of our food from overseas," said Chen, director of Nanyang Technological University's food, science and technology programme. "Finding ways to enhance food availability locally would be one very sustainable, viable option."

https://bit.ly/3qhfj41

Cluster of Alaskan islands could be single, interconnected giant volcano

A small group of volcanic islands in Alaska's Aleutian chain might be part of a single, undiscovered giant volcano

Washington--A small group of volcanic islands in Alaska's Aleutian chain might be part of a single, undiscovered giant volcano, say scientists presenting the findings Monday, 7 December at AGU's Fall Meeting 2020. If the researchers' suspicions are correct, the newfound volcanic caldera would belong to the same category of volcanoes as the Yellowstone Caldera and other volcanoes that have had super-eruptions with severe global consequences.

The Islands of the Four Mountains in the central Aleutians is a tight group of six stratovolcanoes named Carlisle, Cleveland, Herbert, Kagamil, Tana and Uliaga. Stratovolcanoes are what most people envision when they think of a volcano: a steep conical mountain with a banner of clouds and ash waving at the summit. They can have powerful eruptions, like that of Mount St. Helens in 1980, but these are dwarfed by far less frequent caldera-forming eruptions.

Researchers from a variety of institutions and disciplines have been studying Mount Cleveland, the most active volcano of the group, trying to understand the nature of the Islands of the Four Mountains. They have gathered multiple pieces of evidence showing that the islands could belong to one interconnected caldera.

Unlike stratovolcanoes, which tend to tap small- to modestly-sized reservoirs of magma, a caldera is created by tapping a huge reservoir in the Earth's crust. When the reservoir's pressure exceeds the strength of the crust, gigantic amounts of lava and ash are released in a catastrophic episode of eruption.

Caldera-forming eruptions are the most explosive volcanic eruptions on Earth and they often have had global effects. The ash and gas they put into the atmosphere can affect Earth's climate and trigger social upheaval. For example, the eruption of nearby Okmok volcano in the year BCE 43 has been recently implicated in the disruption of the Roman Republic. The proposed caldera underlying the Islands of the Four Mountains would be even larger than Okmok. If confirmed, it would become the first in the Aleutians that is hidden underwater, said Diana Roman of the Carnegie Institution for Science in Washington, D.C., co-author of the study.

"We've been scraping under the couch cushions for data," said Roman, referring to the difficulty of studying such a remote place. "But everything we look at lines up with a caldera in this region."

Despite all these signs, Roman along with John Power, a researcher with the U.S. Geological Survey at the Alaska Volcano Observatory and the study's lead author, maintain that the existence of the caldera is not by any means proven. To do that the study team will need to return to the islands and gather more direct evidence to fully test their hypothesis.

"Our hope is to return to the Islands of Four Mountains and look more closely at the seafloor, study the volcanic rocks in greater detail, collect more seismic and gravity data, and sample many more of the geothermal areas," Roman said.

The caldera hypothesis might also help explain the frequent explosive activity seen at Mount Cleveland, Roman said. Mount Cleveland is arguably the most active volcano in North America for at least the last 20 years. It has produced ash clouds as high as 15,000 and 30,000 feet above sea level. These eruptions pose hazards to aircraft traveling the busy air routes between North

America and Asia.

"It does potentially help us understand what makes Cleveland so active," said Power, who will present the work. "It can also help us understand what type of eruptions to expect in the future and better prepare for their hazards."

https://bit.ly/33QMGFQ

How Dinosaurs Thrived in the Snow

Discoveries made in the past decades help show how many species coped with cold temperatures near both poles

By Riley Black

Imagine a tyrannosaur striding through the snow, leaving three-toed footprints in the powder as flurries fall on the fuzz along the dinosaur's back. The vision might seem fit for fantasy, vastly different than the steamy and plant-choked settings we typically think of dinosaurs inhabiting. Yet such scenes truly transpired millions of years ago, with an entire spiky, feathery and beaked menagerie of dinosaurs thriving in polar habitats marked by greater swings between the seasons and prolonged winter darkness.

Dinosaurs found in Alaska's Prince Creek formation likely remained in the region when it snowed during the winter. **Julio Lacerda**

The finds are coming fast and furious. A tiny jaw found in Alaska's ancient rock record, and written about in July, indicates that dinosaurs nested in these places and stayed year-round. In 2018, paleontologists published a study describing how microscopic details of polar dinosaur bones show that some dinosaurs slowed their growth during harsh seasons to get by with less. The ongoing identification of new species, not found anywhere else, highlighted how some dinosaurs adapted to the cold. Each thread comes together to underscore how wonderfully flexible dinosaur species were, adapting to some of the harshest habitats of their time.

Understanding when and where polar dinosaurs roamed takes a little geological imagination. Earth's continents are always shifting, so the climates where fossils are found were once different. The environments recorded in the strata of southern Australia, for example, were further south and within the Antarctic Circle when dinosaurs thrived there in the Cretaceous. But in reconstructing the tectonic jigsaw and tracking where fossils have been uncovered, paleontologists have found dinosaurs that lived near both the northern and southern poles at different times.

Some of the oldest polar dinosaurs are found among the rocks of southern Australia's aptly-named Dinosaur Cove. Over 110 million years ago, says Monash University paleontologist Patricia Rich, this area was a temperate rainforest carpeted with ferns and bushy-looking conifers called podocarps. And while the Cretaceous world was a bit warmer, with no polar icecaps, winter could still be harsh. "There would have been ice and snow in the three-month-long, dark winters," Rich says. Still, a variety of dinosaurs thrived here, including small, feathery predators, parrot-like oviraptors and *Leaellynasaura*, a small herbivore that walked on two legs and had one of the longest tails for its body size of any dinosaur.

Some dinosaurs might have dug in to survive the harshest months. Paleontologists working in southern Australia's strata have found burrow-like structures from the age of *Leaellynasaura*, and elsewhere these structures actually contain small, herbivorous dinosaurs. "It's possible that dinosaurs might have burrowed as a way to escape the cold," says paleontologist Adele Pentland of the Australian Age of Dinosaurs Museum of Natural History.

"The clearest evidence we have of polar adaptations, or not, is the composition of the fauna," adds Monash University paleontologist

Steve Poropat. Which types of dinosaurs are found in cooler places, as opposed to those that are missing, offers some insights into which dinosaurs were better able to cope with or adapt to the long polar nights. "Theropods, ornithopods, ankylosaurs? No problem. You find them at heaps of sites throughout Victoria," Poropat notes, referencing the state in southeastern Australia. These types of dinosaurs could withstand the cold and dark months. But long-necked, plant-eating dinosaurs called sauropods that lived at the same time are missing from the same sites, which suggests that they were not able to survive or adapt to the colder environments.

The Antarctic Circle wasn't the only place to host chill-adapted dinosaurs. The 70 million-year-old rock of Alaska's Prince Creek Formation contains the fossils of horned dinosaurs, tyrannosaurs, duckbilled dinosaurs, raptors and more that lived within the Arctic Circle. And when these dinosaurs began to catch researcher's attention during the 1980s, they presented some challenges to what paleontologists thought about dinosaur lives.

"When dinosaurs were first found in the Arctic, they presented some serious problems to our understanding of dinosaurian physiology," Perot Museum of Nature and Science paleontologist Tony Fiorillo says. Even as paleontologists considered that dinosaurs might keep warmer body temperatures, the harshness of the Arctic cold was thought to be too much. Some experts proposed that dinosaurs might migrate, drawing an analogy to modern-day caribou, which don't migrate long distances north and south, Fiorillo says. Various lines of evidence indicate that the dinosaurs remained in their home habitat through the winter. Just this past year, Fiorillo and colleagues were the ones who published on a jaw from a very young raptor—evidence that dinosaurs were nesting in the region and not just passing through.

The landscape would have looked a little familiar. At the time the Prince Creek Formation was being laid down, Fiorillo says, the area was similar to what it's like today—a coastal plain dominated by stands of conifers and flowering plants low to the ground. And while overall warmer than the same spot today, it still got cold enough to snow during the winters.

Alaska's dinosaurs had to contend with some of the same stresses as their southern counterparts—such as harsher changes in seasons and months of darkness—but evidence from their bones indicate that these dinosaurs stayed year-round. Much like their relatives elsewhere, polar dinosaurs grew fast when they were young but switched to more of a stop-and-start growth pattern as they got older. This means that polar dinosaurs were already biologically predisposed to surviving on less during the cold months, with the dinosaurs growing faster again during the lush summers. While certainly chilly during the winter, the ground did not freeze in these places, providing enough vegetation to support an ecosystem of resident dinosaurs.

There may have been no one way that dinosaurs adjusted to the comparative harshness of life near the pole. The local tyrannosaur in the Prince Creek Formation was not a familiar species seen elsewhere, but a unique and smaller predator—roughly the size of a polar bear— that Fiorillo and colleagues dubbed *Nanuqsaurus*. The comparatively small stature of this dinosaur, as well as the downsized species of horned dinosaur called *Pachyrhinosaurus* in the area, hints that types of dinosaurs that grew big elsewhere adapted to become smaller and thereby get by on less food in the cool of ancient Alaska.

But some polar dinosaurs truly thrived. The raptor-relative *Troodon* was a feathery, eight-foot-long dinosaur with large eyes. While rare elsewhere, Fiorillo says, "it is the overwhelmingly abundant theropod dinosaur." The small-carnivore's large eyes may have given it an advantage, especially during the dark months.

Our visions of polar dinosaurs are still relatively new. Determining

which species lived in cooler areas is part of that task. Some, like *Nanuqsaurus* which was named in 2014, are new. Others turn out to be familiar—a duckbill dinosaur previously thought to be a new species has turned out to be *Edmontosaurus*, a wide-ranging hadrosaur found elsewhere. “For me,” Fiorillo says, “the story is even more fascinating knowing that some Arctic dinosaurs became specialists within the ancient north while others were generalists capable of surviving a wide array of environmental conditions.”

Many finds are left to be made, not just among the dinosaurs but about the big picture of the habitats where they lived. “Discoveries are being made every day,” Rich says, noting that fieldwork just this year in the time of *Leaellynasaura* has uncovered dinosaur tracks, turtle shells, tree trunks with termite damage and more, all parts of a lost polar world. Finds like these will continue to highlight just how successful dinosaurs were, a testament to their prehistoric versatility. In virtually any ancient landscape, dinosaurs found a way.

https://bit.ly/3qxx43Y

'Oldest' Baby Ever Born Is a 28-Year-Old Record-Breaker Almost as Old as Her Mother

A baby born in Tennessee can lay claim to being the oldest baby ever born, in that she is believed to be the longest-frozen embryo ever successfully delivered in a live birth.

Peter Dockrill

Molly Everette Gibson was born on October 26, but her birthday was an event literally decades in the making. She was born from an embryo frozen in October 1992 – a mind-boggling 28 years ago.

And effectively a lifetime ago, too. Molly's mother, Tina, is now 29, and was herself only born about 18 months earlier than when Molly was frozen in her embryonic form.

In a manner of speaking, they've both been on this planet for about the same amount of time, even though they're a generation apart.

"It's hard to wrap your head around it," Tina Gibson told the *New York Post*. "But, as far as we're concerned, Molly is our little miracle."

The incredible strangeness of this story gets even stranger.

When Molly was born, she broke the record held by another child who was previously the longest-frozen embryo ever delivered. That child – Emma Wren Gibson – was frozen as an embryo for 24 years before being born in 2017.

Emma also happens to be Molly's older sister, meaning this single family's two children were the two longest-frozen embryos ever to be born.

That might sound weird – as if the Gibson family, who previously struggled with infertility for several years, were vying for a spot in the Guinness World Records – but it makes perfect sense when you know the entire story.

Molly and Emma are full genetic siblings that were frozen at the same time, after being anonymously donated by their biological parents, whose identity has not been disclosed.

In other words, the two sisters are actual sisters – in addition to being adopted sisters – who were both carried and delivered by their adoptive mother, Tina.

It's just that it took a little longer than usual, decades in fact, for these patient little ones to have their time in the sun.

"We're over the moon," Tina Gibson told the BBC.

"I still get choked up. If you would have asked me five years ago if I would have not just one girl, but two, I would have said you were crazy."

The births were facilitated by staff at the National Embryo Donation Centre (NEDC), in Knoxville, a Christian-based nonprofit that receives donated embryos from biological parents who have gone through in vitro fertilisation (IVF), but who have decided, for whatever reason, not to go through with using the embryo for a

pregnancy.

In such cases, rather than letting the embryos be discarded, the parents can donate their frozen embryos to the NEDC, which stores them for later use, working with would-be parents (most of them with infertility), who apply to adopt, carry, and deliver an embryo.

The centre has facilitated over 1,000 successful deliveries, but Emma and Molly represent the most scientifically remarkable cases, in that they are the longest-frozen embryos ever to become babies.

Beyond the novelty of their record-breaking status, their successful births are providing unique proof of how long frozen embryos can actually last, which has never been fully understood.

"As long as the embryos are maintained correctly in the liquid nitrogen storage tank at minus 396 degrees, we feel they may be good indefinitely," NEDC lab director Carol Sommerfelt told the *New York Post*. "With the birth of Molly, we know they can survive at least 27 and a half years and probably longer."

While Molly and Emma are testament to the possibilities, there is still much risk and uncertainty in the process.

About 75 percent of donated embryos survive the freezing and thawing process, the NEDC says, and about 49 percent of transfers result in a live birth.

Fortunately, IVF success rates with frozen embryos have caught up in recent years, and are now thought to be about as successful as treatments using fresh embryos.

For the embryos that make it to birth, a loving family awaits. For some, like Molly and Emma – born whole decades after nature otherwise intended – there's that and more.

When going through the process the first time, Tina Gibson only found out on the day of the transfer that the embryo she would be receiving had been frozen since about the time of her own birth.

"What does that mean?" she asked the specialist. He replied. "Well, it could be a world record."

https://bit.ly/2VLeS8I

Common tire chemical implicated in mysterious deaths of at-risk salmon

6PPD-quinone, leaches out of the particles that tires shed onto pavement

By Erik Stokstad

For decades, something in urban streams has been killing coho salmon in the U.S. Pacific Northwest. Even after Seattle began to restore salmon habitat in the 1990s, up to 90% of the adults migrating up certain streams to spawn would suddenly die after rainstorms. Researchers suspected the killer was washing off nearby roads, but couldn't identify it. "This was a serious mystery," says Edward Kolodziej, an environmental engineer at the University of Washington's (UW's) Tacoma and Seattle campuses.

Online today in *Science*, researchers led by Kolodziej report the primary culprit comes from a chemical widely used to protect tires from ozone, a reactive atmospheric gas. The toxicant, called 6PPD-quinone, leaches out of the particles that tires shed onto pavement. Even small doses killed coho salmon in the lab. "It's a brilliant piece of work," says Miriam Diamond, an environmental chemist at the University of Toronto. "They've done a tremendous job at sleuthing out a very challenging problem."

Manufacturers annually produce some 3.1 billion tires worldwide. Tire rubber is a complex mixture of chemicals, and companies closely guard their formulations. Because tire particles are a common component of water pollution, researchers have been examining how they affect aquatic life.

After Kolodziej arrived at UW's Center for Urban Waters in 2014, he joined the effort to solve the coho salmon mystery. The group created a mixture of particles from nine tires—some bought new, others provided by two undergraduates who moonlight as mechanics—to mimic what might wash off typical highways. They

found several thousand unidentified chemicals in the mixture. Postdoc Zhenyu Tian spent more than 2 years narrowing down the list, separating the molecules based on their electrical charge and other properties. By May 2019, he had narrowed the focus to about 50 unknown chemicals, and then further work revealed the chemical formula of a prime suspect. “If you’re looking for an unexplained toxicant that’s killing fish, we had the perfect instruments and expertise,” Kolodziej recalls.

But what was it? A 2019 report from the Environmental Protection Agency on chemicals in recycled tires mentioned 6PPD, which has a similar formula. The final clue was buried in an industry report from 1983, which contained the exact formula of 6PPD-quinone, the molecule created when 6PPD reacts with ozone. The team synthesized 6PPD-quinone and found it was highly lethal to coho salmon.

Now, the team is working to understand how the chemical kills fish. Kolodziej and colleagues say other species of fish should also be evaluated for sensitivity. Because you can’t buy the molecule, Kolodziej’s team is making it. “My lab might even be the only place that actually has this,” he says.

The researchers suspect the compound is present on busy roads everywhere. They’ve found it washes off pavement and into streams in Los Angeles and San Francisco, for example. The simplest solution might be for tire manufacturers to switch to an environmentally benign alternative. But Sarah Amick, vice president of environment, health, safety, and sustainability at the U.S. Tire Manufacturers Association, says it’s too early to discuss alternatives. “It’s important that additional research be done to validate and verify these results.”

Another way to protect salmon is to filter stormwater through soil, but installing enough infiltration basins to treat road runoff before it reaches spawning streams would be very expensive, says co-author Jenifer McIntyre, an ecotoxicologist at Washington State University’s Puyallup Research and Extension Center. In the meantime, Kolodziej says he “can’t walk along a street without staring at all the skid marks,” thinking about tire chemicals, and “wondering what’s there.”

https://bit.ly/3qkQeFE

Oral drug blocks SARS-CoV-2 transmission, Georgia State biomedical sciences researchers find

"This is the first demonstration of an orally available drug to rapidly block SARS-CoV-2 transmission"

Atlanta--Treatment of SARS-CoV-2 infection with a new antiviral drug, MK-4482/EIDD-2801 or Molnupiravir, completely suppresses virus transmission within 24 hours, researchers in the Institute for Biomedical Sciences at Georgia State University have discovered.

The group led by Dr. Richard Plemper, Distinguished University Professor at Georgia State, originally discovered that the drug is potent against influenza viruses.

"This is the first demonstration of an orally available drug to rapidly block SARS-CoV-2 transmission," said Plemper. "MK-4482/EIDD-2801 could be game-changing."

Interrupting widespread community transmission of SARS-CoV-2 until mass vaccination is available is paramount to managing COVID-19 and mitigating the catastrophic consequences of the pandemic.

Because the drug can be taken by mouth, treatment can be started early for a potentially three-fold benefit: inhibit patients' progress to severe disease, shorten the infectious phase to ease the emotional and socioeconomic toll of prolonged patient isolation and rapidly silence local outbreaks.

"We noted early on that MK-4482/EIDD-2801 has broad-spectrum activity against respiratory RNA viruses and that treating infected

animals by mouth with the drug lowers the amount of shed viral particles by several orders of magnitude, dramatically reducing transmission," said Plemper.

"These properties made MK-4482/EIDD/2801 a powerful candidate for pharmacologic control of COVID-19."

In the study published in *Nature Microbiology*, Plemper's team repurposed MK-4482/EIDD-2801 against SARS-CoV-2 and used a ferret model to test the effect of the drug on halting virus spread.

"We believe ferrets are a relevant transmission model because they readily spread SARS-CoV-2, but mostly do not develop severe disease, which closely resembles SARS-CoV-2 spread in young adults," said Dr. Robert Cox, a postdoctoral fellow in the Plemper group and a co-lead author of the study.

The researchers infected ferrets with SARS-CoV-2 and initiated treatment with MK-4482/EIDD-2801 when the animals started to shed virus from the nose.

"When we co-housed those infected and then treated source animals with untreated contact ferrets in the same cage, none of the contacts became infected," said Josef Wolf, a doctoral student in the Plemper lab and co-lead author of the study.

By comparison, all contacts of source ferrets that had received placebo became infected.

If these ferret-based data translate to humans, COVID-19 patients treated with the drug could become non-infectious within 24 hours after the beginning of treatment.

MK-4482/EIDD-2801 is in advanced phase II/III clinical trials against SARS-CoV-2 infection.

Co-authors of the study include R.M. Cox, J.D. Wolf and R.K. Plemper at Georgia State.

The study was funded by public health service grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases to Georgia State.

To read the study, visit https://www.nature.com/articles/s41564-020-00835-2.

https://bit.ly/2VIarLM

Ancient migration was choice, not chance

Paleolithic people likely colonized the Ryukyu Islands intentionally

The degree of intentionality behind ancient ocean migrations, such as that to the Ryukyu Islands between Taiwan and mainland Japan, has been widely debated. Researchers used satellite-tracked buoys to simulate ancient wayward drifters and found that the vast majority failed to make the contested crossing. They concluded that Paleolithic people 35,000-30,000 years ago must therefore have made the journey not by chance but by choice.

A candidate bamboo craft for the Ryukyu migration built for a re-enactment of that crossing. **Credit: © 2020 Yosuke Kaifu**

Human migration over the last 50,000 years is an essential part of human history. One aspect of this story that fascinates many is the ways in which ancient people must have crossed between separate land masses. Professor Yosuke Kaifu from the University Museum at the University of Tokyo and his team explore this subject, in particular a crossing known to have taken place 35,000-30,000 years ago from Taiwan to the Ryukyu Islands, including Okinawa, in southwestern Japan.

"There have been many studies on Paleolithic migrations to Australia and its neighboring landmasses, often discussing whether these journeys were accidental or intentional," said Kaifu. "Our study looks specifically at the migration to the Ryukyu Islands, because it is not just historically significant, but is also very difficult to get there. The destination can be seen from the top of a coastal mountain in Taiwan, but not from the coast. In addition, it is on the opposite side of the Kuroshio, one of the strongest currents

in the world. If they crossed this sea deliberately, it must have been a bold act of exploration."

This issue of the intentionality of this journey is less straightforward to solve than you might imagine. To investigate the likelihood of the journey occurring by chance, the effect of the Kuroshio on drifting craft needed measuring. To do this, Kaifu and his team used 138 satellite-tracked buoys to trace the path of a would-be drifter caught on this journey.

"The results were clearer than I would have expected," said Kaifu. "Only four of the buoys came within 20 kilometers of any of the Ryukyu Islands, and all of these were due to adverse weather conditions. If you were an ancient mariner, it's very unlikely you would have set out on any kind of journey with such a storm on the horizon. What this tells us is that the Kuroshio directs drifters away from, rather than towards, the Ryukyu Islands; in other words, that region must have been actively navigated."

You might wonder how we can be so sure the current itself is the same now as it was over 30,000 years ago. But existing evidence, including geological records, tell researchers that currents in the region have been stable for at least the last 100,000 years. As for the researchers' confidence that Paleolithic voyagers would not dare face stormy conditions that might otherwise explain chance migrations, prior research suggests that these voyagers were groups including families, whose modern-day analogues do not take such risks.

"At the beginning, I had no idea how to demonstrate the intentionality of the sea crossings, but I was lucky enough to meet my co-authors in Taiwan, leading authorities of the Kuroshio, and came across the idea of using the tracking buoys," said Kaifu. "Now, our results suggest the drift hypothesis for Paleolithic migration in this region is almost impossible. I believe we succeeded in making a strong argument that the ancient populations in question were not passengers of chance, but explorers."

Journal article

Kaifu, Y., Kuo, T.-H., Kubota, Y., Jan, S. Palaeolithic voyage for invisible islands beyond the horizon. Scientific Reports. DOI: 10.1038/s41598-020-76831-7

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https://bit.ly/33PDLEW

New study debunks blood type diet

ABO blood types benefit similarly from plant-based diet, according to research published in the Journal of the Academy of Nutrition and Dietetics

Washington--A study published in the *Journal of the Academy of Nutrition and Dietetics* by researchers with the Physicians Committee for Responsible Medicine--a nonprofit of 12,000 doctors--debunks the "blood type diet" by finding that blood type was not associated with the effects of a plant-based diet on body weight, body fat, plasma lipid concentrations, or glycemic control.

This new study is based on a randomized control trial whose main findings were published in *JAMA Network Open* on Nov. 30. That trial randomly assigned overweight participants with no history of diabetes to an intervention or control group on a 1:1 ratio for 16 weeks.

Participants in the intervention group followed a low-fat, plant-based diet. The control group made no diet changes. The key finding is that a plant-based diet ramps up metabolism as measured by an increase in after-meal calorie burn of 18.7%, on average, for the intervention group over the control.

To consider a potential connection between blood type and diet, researchers took the additional step of conducting a secondary analysis among intervention-group participants of the 16-week

randomized clinical trial.

They considered whether the effects of a plant-based dietary intervention on body weight, blood lipids, and glycemic control are associated with ABO blood type. The "blood type diet" recommends a mainly plant-based diet for those with blood type A, while it recommends a diet heavy in meat for people with blood type O.

"We found that blood type made no difference," says study author Neal Barnard, MD, president of the Physicians Committee. "While the blood type diet says that a plant-based diet should be better for blood type A and less so for blood type O, it turned out to be beneficial for people of all blood types, and there was no evidence that meaty diets are good for anyone.

"Our research shows that all blood types benefit equally from a vegan diet based on the consumption of fruits and vegetables, legumes and whole grains, looking specifically at weight loss and cardiometabolic health in overweight adults," he says.

Main outcomes that were measured were body weight, fat mass, visceral fat volume, blood lipids, fasting plasma glucose, and HbA1c. T-tests compared participants with blood type A to all other participants (non-A), and individuals with blood type O to all other participants (non-O).

There were no significant differences in any outcome between individuals of blood type A and non-A, or between individuals of blood type O and non-O. Mean body weight change was -5.7 kg for blood type A participants and -7.0 kg for non-A participants, and was -7.1 kg for type O participants and -6.2 kg for non-O participants. Mean total cholesterol decreased 17.2 mg/dl in the type A group and 18.3 mg/dl for non-A participants, and decreased 17.4 mg/dl among type O participants and 18.4 mg/dl for non-O participants.

https://bit.ly/3n300OU

Here's what happens when a bee stings you directly in your eyeball

You think 2020 is pretty horrible, but it could always be worse.

Beth Mole

There are precious few things that could truly make 2020 worse than it already is. But a rare bee sting right to the eyeball might be one of them.

Doctors this week published an image of just such an uncommon ocular impaling. The image, appearing in the New England Journal of Medicine, also included a brief report of the patient's condition and recovery. The details confirm that although reading about this horror show of a year may sometimes feel like getting repeatedly stabbed in the peepers, the real thing is actually far more unpleasant.

The patient was a 22-year-old male who showed up at a hospital's emergency department with redness, pain, and decreased vision in his left eye, which had taken a bee sting about an hour earlier. Though the man had 20/20 vision in his right eye, he reported only being able to see hand movements close to his face with his left eye. With a closer look (see here), the doctors reported seeing diffuse haziness in his left eye due to swelling, and—most obvious—a bee stinger still jutting out from his eyeball, surrounded by some eye gunk. Specifically, the small spear was embedded in the man's cornea—the clear, dome-shaped outer layer of tissue at the front of the eye that helps focus light.

Corneal run-throughs with a bee stinger are rare, the doctors note. But when they do occur, there's a risk of the corneal tissue failing and becoming cloudy (corneal decompensation). There's also the possibility of secondary glaucoma, in which pressure inside the eye increases and causes optic nerve damage and vision loss.

The doctors gave the man some antibiotic eye drops and a local anesthetic before pulling the stinger out. They then thoroughly

cleaned the puncture wound and closed it up with corneal sutures. Finally, they gave the man two weeks' worth of prescriptions for glucocorticoids, antibiotics, and eye medications that together tried to prevent inflammation, pain, and secondary infection.

In a relatively happy ending, a three-month follow-up visit revealed that the man's eye largely recovered. The corneal swelling had gone down completely, and the man's vision in his left eye was 20/40.

https://bit.ly/36N7YpY

Research inspired by COVID-19: 'COVID toes' likely a sign of successful viral response

This may be because patients develop COVID toes as a delayed response after the virus is no longer detectable

Yvonne Kim | The Capital Times

Data collected from patients who have developed "COVID toes," a dermatological immune response that is most likely a symptom of COVID-19, may be key in solving longer-term mysteries about viral immunity and genetic skin conditions.

Prior to the pandemic, dermatologists usually saw about one to two cases a year of chilblains, inflamed blood vessels in the skin that are often a result of cold weather. But international reports of COVID toes began surfacing in early spring when patients — usually young, with mild to no viral symptoms — noticed bruised and painful or itchy toes.

Over a few weeks, there was nearly a 300% increase of patients in Wisconsin exhibiting the condition compared to 2019, said Lisa Arkin, director of pediatric dermatology at the University of Wisconsin-Madison. Trends were similar across the United States.

"This was a real pivot because there aren't so many dermatologists doing COVID-19 research," Arkin said. "Suddenly, in the spring, there was an avalanche of patients, many of whom had had symptoms for several weeks."

The data on COVID toes had so far been retrospective, so Arkin and a team of scientists started a database in June to follow patients and collect blood at various points, from the initial onset of COVID toes to the resolution of symptoms months later. They became interested in COVID toes as the potential manifestation of underlying autoimmune conditions, specifically "type I interferonopathies."

In some people, genetic mutations can lead to increased production of type I interferons, proteins that are pivotal in responding to viral infections. COVID toes are likely a manifestation of this exaggerated protective response among patients who successfully control the virus and do not develop severe COVID-19.

Conversely, Arkin said, evidence indicates that gene mutations producing too few type I interferons may cause extreme susceptibility to respiratory viruses. This explains why some people become very ill later into the infection period as an attenuated, delayed response.

"It's this idea that it's not the virus that's killing people; it's the failed control of the virus," Arkin said.

But, according to the American Association of Dermatology's national registry, only about 15% of patients who developed COVID toes received positive antigen tests and about 30% produced antibodies, which Arkin said "leaves a big chunk of patients who still have no clear link." This may be because patients develop COVID toes as a delayed response after the virus is no longer detectable, or because they fought the virus off so immediately and successfully that they never even created antibodies.

Researchers hope to more definitively link COVID toes to the virus. Arkin said the research has already detected strong Type I interferon responses in the skin, leading her to expect there will be similar findings in the blood: "The speculation is, if this is all Type I interferon … then it is a response to some viral exposure. And, of

course, pinning the donkey with which is the most commonly circulating virus in Wisconsin, it's COVID."

She added that the research implications go beyond this pandemic. In the past, an infant with chilblains would warrant a genetic evaluation for a Type I interferonopathy, but with adolescents or adults, there was never a clear diagnosis, other than that they were likely triggered by some kind of viral infection. Examining COVID-specific cases may help "disentangle the mystery" among patients, who may develop the skin condition not only from COVID-19, but also the flu or other viral infections.

An improved understanding of COVID toes may have hopeful implications on therapeutic responses, both for this pandemic and future ones. If they are, in fact, a protective immune response against COVID-19, Arkin said interferon-based, topical treatments like nasal drops may be an effective preventative response among high-risk populations.

"SARS-CoV-2 is the only thing we're thinking about right now, but unfortunately this is not going to be the last pandemic," Arkin said. "Just as these other patients who had chilblains once or twice a year may be triggered by some other virus, getting some other insight into the immune response to this virus in patients … can really help us in the future."

https://bit.ly/3mQqDqz

Microwave energy likely behind illnesses of American diplomats in Cuba and China

Radio frequency energy of radiation that includes microwaves likely caused American diplomats in China and Cuba to fall ill

Rebecca Falconer

A radio frequency energy of radiation that includes microwaves likely caused American diplomats in China and Cuba to fall ill with neurological symptoms over the past four years, a report published Saturday finds.

Why it matters: The National Academies of Sciences, Engineering, and Medicine's report does not attribute blame for the suspected attacks, but it notes there "was significant research in Russia/USSR into the effects of pulsed, rather than continuous wave [radio frequency] exposures."

Personnel at the U.S. Embassy in Cuba in Havana in 2017. **Photo: Sven Creutzmann/Mambo photo/Getty Images**

- ***It also states that military personnel in "Eurasian communist countries" were exposed to non-thermal radiation.***

Driving the news: The State Department commissioned the report after government personnel and their families began falling ill at the U.S. Embassy in Havana, Cuba, in late 2016 and the U.S. Consulate in Guangzhou, China, in early 2017.

- ***There were reports of 40 State Department staff experiencing symptoms including ear pain, intense head pressure or vibration, dizziness, visual problems, and cognitive difficulties.***
- ***"Many still continue to experience these or other health problems," the study authors note in a statement.***
- ***Canada's government has confirmed 14 of its citizens also fell ill in Cuba's capital, in what became known as "Havana syndrome," the Ottawa Citizen notes.***

Of note: The report, first obtained by NBC News, recommends that the State Department act promptly to establish plans and protocols to enable future investigations if required.

- ***"The larger issue is preparedness for new and unknown threats that might compromise the health and safety of U.S. diplomats serving abroad," the report states.***
- ***"The next event may be even more dispersed in time and place, and even more difficult to recognize quickly."***

For the record: Russia has denied it's behind the suspected attack,

and CIA director Gina Haspel "has not concluded the Kremlin was responsible," but some Russia experts at the agency noted to the New York Times it fits with Moscow's "long history of experimenting with the technology."

- ***Mark Lenzi, a diplomatic security officer who fell ill with the symptoms when he was working in Guangzhou, China, in 2018, has filed a lawsuit against the State Department for disability discrimination.***
- ***"My government looked the other way when they knew I and my family were injured," he told the NYT. "This report is just the beginning and when the American people know the full extent of this administration's cover-up of the radiofrequency attacks in China in particular they will be outraged."***
- ***The Office of Special Counsel has launched two investigations into the State Department over the matter.***

What they're saying: The State Department said in an emailed statement, "We are pleased this report is now out and can add to the data and analyses that may help us come to an eventual conclusion as to what transpired."

- ***Sen. Jeanne Shaheen (D-N.H.), a senior member of the Senate Foreign Relations and Armed Services Committees, who led bipartisan calls for the report to be released, said in a statement: "The health effects from these mysterious injuries have tormented those afflicted. Their illnesses and suffering are real and demand a response from Congress."***

"American public servants and their families — who have been targeted — have requested that Congress receive and review this report, so I'm glad the State Department heeded our bipartisan call so we can get to work."

Read the report, via DocumentCloud: