http://bit.ly/34NMHIr

Consumption of chili pepper cuts down the risk of death from a heart or cerebral attack

An Italian study, conducted on twenty-three thousand people and published in the Journal of the American College of Cardiology, shows that regular consumption of this spice is linked to a reduction of death risk for cardiac and cerebrovascular causes

Chili pepper is a common guest in Italians kitchens, and over the centuries it has been praised for its supposed therapeutic virtues. Now an Italian research shows that people who consume it on a regular basis have a mortality risk for every cause reduced by 23% compared to those who do not like it.

The study, published in the Journal of the American College of Cardiology (JACC), has been conducted by the Department of Epidemiology and Prevention of I.R.C.C.S. Neuromed in Pozzilli, Italy, in collaboration with the Department of Oncology and Molecular Medicine of the Istituto Superiore di Sanità in Rome, the University of Insubria in Varese and the Mediterranean Cardiocentro in Naples.

The research examined 22,811 citizens of Molise region, in Italy, participating in the Moli-sani study. Following their health status for an average period of about 8 years, and comparing it with their eating habits, Neuromed researchers observed that, in people regularly consuming chili pepper (4 times a week or more), the risk of dying of a heart attack was cut down by 40%. Risk reduction for cerebrovascular mortality was even higher since it resulted more than halved.

"An interesting fact - says Marialaura Bonaccio, Neuromed epidemiologist and first author of the publication - is that protection from mortality risk was independent of the type of diet people followed. In other words, someone can follow the healthy Mediterranean diet, someone else can eat less healthily, but for all of them chili pepper has a protective effect".

The Moli-sani study is the first to explore the properties of this spice in relation to the risk of death in a European and Mediterranean population.

"Chili pepper - comments Licia Iacoviello, Director of the Department of Epidemiology and Prevention at the I.R.C.C.S. Neuromed and Professor of Hygiene and Public Health at the Università dell'Insubria of Varese - is a fundamental component of our food culture.

We see it hanging on Italian balconies, and even depicted in jewels. Over the centuries, beneficial properties of all kinds have been associated with its consumption, mostly on the basis of anecdotes or traditions, if not magic.

It is important now that research deals with it in a serious way, providing rigor and scientific evidence. And now, as already observed in China and in the United States, we know that the various plants of the capsicum species, although consumed in different ways throughout the world, can exert a protective action towards our health".

New researches will be now necessary to understand the biochemical mechanisms through which the chili pepper and its "relatives" (all united by the presence of a substance called capsaicin), scattered in all the corners of the globe, act. But for the time being, spicy food lovers surely have one more reason to maintain their habit.

The Moli-sani Study

Started in March 2005, it involves about 25,000 citizens living in the Molise region. The aim is to learn about environmental and genetic factors underlying cardiovascular disease, cancer and degenerative pathologies. The Moli-sani Study, now based in the I.R.C.C.S. Neuromed, has transformed an entire Italian region in a large research lab.

http://bit.ly/2MkhIqM

Celebrated ancient Egyptian woman physician likely never existed, says researcher

Merit Ptah is often called the first woman doctor, CU Anschutz researcher calls it a case of mistaken identity

AURORA, Colo. For decades, an ancient Egyptian known as Merit Ptah has been celebrated as the first female physician and a role model for women entering medicine. Yet a researcher from the University of Colorado Anschutz Medical Campus now says she never existed and is an example of how misconceptions can spread.

Vezir Ramose and spouse Merit-Ptah **Wikimedia Commons, the free media repository**

"Almost like a detective, I had to trace back her story, following every lead, to discover how it all began and who invented Merit Ptah," said Jakub Kwiecinski, PhD, an instructor in the Dept. of Immunology and Microbiology at the CU School of Medicine and a medical historian.

His study was published last week in the *Journal of the History of Medicine and Allied Sciences*.

Kwiecinski's interest in Merit Ptah (`beloved of god Ptah') was sparked after seeing her name in so many places.

"Merit Ptah was everywhere. In online posts about women in STEM, in computer games, in popular history books, there's even a crater on Venus named after her," he said. "And yet, with all these mentions, there was no proof that she really existed. It soon became clear that there had been no ancient Egyptian woman physician called Merit Ptah."

Digging deep into the historical record, Kwiecinski discovered a case of mistaken identity that took on a life of its own, fueled by those eager for an inspirational story.

According to Kwiecinski, Merit Ptah the physician had her origins in the 1930s when Kate Campbell Hurd-Mead, a medical historian, doctor and activist, set out to write a complete history of medical women around the world. Her book was published in 1938.

She talked about the excavation of a tomb in the Valley of Kings where there was a "picture of a woman doctor named Merit Ptah, the mother of a high priest, who is calling her `the Chief Physician.'"

Kwiecinski said there was no record of such a person being a physician.

"Merit Ptah as a name existed in the Old Kingdom, but does not appear in any of the collated lists of ancient Egyptian healers - not even as one of the `legendary'; or `controversial cases," he said. "She is also absent from the list of Old Kingdom women administrators. No Old Kingdom tombs are present in the Valley of the Kings, where the story places Merit Ptah's son, and only a handful of such tombs exist in the larger area, the Theban Necropolis."

The Old Kingdom of Egypt lasted from 2575 to 2150 BC.

But there was another woman who bears a striking resemblance to Merit Ptah. In 1929-30, an excavation in Giza uncovered a tomb of Akhethetep, an Old Kingdom courtier. Inside, a false door depicted a woman called Peseshet, presumably the tomb owner's mother, described as the `Overseer of Healer Women.' Peseshet and Merit Ptah came from the same time periods and were both mentioned in the tombs of their sons who were high priestly officials.

This discovery was described in several books and one of them found its way into Hurd-Mead's private library. Kwiecinski believes Hurd-Mead confused Merit Ptah with Peseseth.

"Unfortunately, Hurd-Mead in her own book accidentally mixed up the name of the ancient healer, as well as the date when she lived, and the location of the tomb," he said. "And so, from a misunderstood case of an authentic Egyptian woman healer, Peseshet, a seemingly earlier Merit Ptah, `the first woman physician' was born."

The Merit Ptah story spread far and wide, driven by a variety of forces. Kwiecinski said one factor was the popular perception of ancient Egypt as an almost fairytale land "outside time and space" perfectly suited for the creation of legendary stories.

The story spread through amateur historian circles, creating a kind of echo chamber not unlike how fake news stories circulate today.

"Finally, it was associated with an extremely emotional, partisan - but also deeply personal - issue of equal rights," he said. "Altogether this created a perfect storm that propelled the story of Merit Ptah into being told over and over again."

Yet Kwiecinski said the most striking part of the story is not the mistake but the determination of generations of women historians to recover the forgotten history of female healers, proving that science and medicine have never been exclusively male.

"So even though Merit Ptah is not an authentic ancient Egyptian woman healer," he said. "She is a very real symbol of the 20th century feministic struggle to write women back into the history books, and to open medicine and STEM to women."

Article: *https://doi.org/10.1093/jhmas/jrz058*

http://bit.ly/36Y67Ma

New review study shows that egg-industry-funded research downplays danger of cholesterol

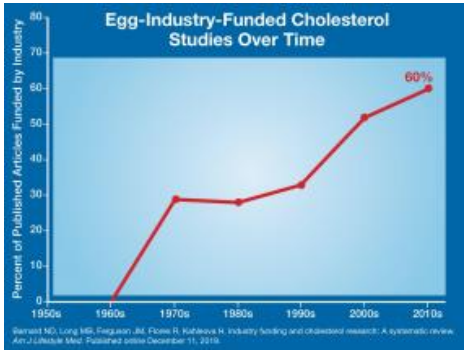
Researchers explain how faulty, industry-funded studies can harm public health

WASHINGTON--Controversial headlines claiming that eggs don't raise cholesterol levels could be the product of faulty industry-funded research, according to a new review published in the American Journal of Lifestyle Medicine.

Researchers with the Physicians Committee for Responsible Medicine examined all research studies published from 1950 to March of 2019 that evaluated the effect of eggs on blood cholesterol levels. The researchers examined funding sources and whether those sources influenced study findings.

The results show that prior to 1970, industry played no role in cholesterol research. The percentage of industry-funded studies increased over time, from 0 percent in the 1950s to 60 percent in 2010-2019.

"In decades past, the egg industry played little or no role in cholesterol research, and the studies' conclusions clearly showed that eggs raise cholesterol," says study author Neal Barnard, MD, president of the Physicians Committee for Responsible Medicine. "In recent years, the egg industry has sought to neutralize eggs' unhealthy image as a cholesterol-raising product by funding more studies and skewing the interpretation of the results."



The graph tracks the rise of egg-industry-funded cholesterol studies over time. **Physicians Committee for Responsible Medicine**

Overall, more than 85 percent of the studies--whether funded by industry or not--showed that eggs have unfavorable effects on blood cholesterol. Industry-funded studies, however, were more likely to downplay these findings. That is, although the study data showed cholesterol increases, study conclusions often reported that eggs had no effect at all. Approximately half (49 percent) of industry-funded intervention studies reported conclusions that were

discordant with actual study results, compared with 13 percent of non-industry-funded trials.

For example, in one 2014 study in college freshmen, the addition of two eggs at breakfast, five days a week over 14 weeks, was associated with a mean LDL cholesterol increase of 15 mg/dL. Despite this rise in cholesterol, investigators concluded that the "additional 400 mg/day of dietary cholesterol did not negatively impact blood lipids." The cholesterol change did not reach statistical significance, meaning that there was at least a 5 percent chance that the cholesterol rise could have been due to chance alone. "It would have been appropriate for the investigators to report that the cholesterol increases associated with eggs could have been due to chance. Instead, they wrote that the increases did not happen at all. Similar conclusions were reported in more than half of industry-funded studies," adds Dr. Barnard.

These studies have even influenced policymakers. In 2015, the U.S. Dietary Guidelines Advisory Committee reported that "available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol...." After reviewing the evidence, however, the government did not carry that statement forward in the final Guidelines, which called for eating "as little dietary cholesterol as possible."

"The egg industry has mounted an intense effort to try to show that eggs do not adversely affect blood cholesterol levels," adds Dr. Barnard. "For years, faulty studies on the effects of eggs on cholesterol have duped the press, public, and policymakers to serve industry interests."

Several meta-analyses have concluded that egg consumption does raise cholesterol levels. According to a 2019 meta-analysis, eating an egg each day raises low density lipoprotein (LDL, or "bad") cholesterol by about nine points. The study, published in the American Journal of Clinical Nutrition, combined the findings of 55 prior studies, finding that every 100 milligrams of added dietary cholesterol (approximately half an egg) raised LDL ("bad") cholesterol levels by about 4.5 mg/dL. A 2019 JAMA study of nearly 30,000 participants found that eating even small amounts of eggs daily significantly raised the risk for both cardiovascular disease and premature death from all causes.

Of 153 studies analyzed in the *American Journal of Lifestyle Medicine* report, 139 showed that eggs raise blood cholesterol (68 of these reached statistical significance, meaning the results were very unlikely to be due to chance). No studies reported significant net decreases in cholesterol concentrations. Non-significant net cholesterol decreases were reported by six non-industry-funded and eight industry-funded studies.

https://wb.md/2EMqve0

FCC Approves 988 as Suicide Hotline Number

The Federal Communications Commission (FCC) has approved using the 3-digit number 988 as a suicide prevention hotline number.

Valarie Basheda

Calls to the number will be directed to the National Suicide Prevention Lifeline, which includes 163 crisis centers. The lifeline is available by calling 800-273-TALK (800-273-8255) and through online chats. The center answered more than 2.2 million calls and 100,000 online chats in 2018.

The agency says that in studying the issue, it found that the 3-digit number "would likely make it easier for Americans in crisis to access potentially life-saving resources." Suicide rates increased in 49 of 50 states from 1999 to 2016, with an increase greater than 20% in more than half of those states, the FCC says. Rates are higher across several at-risk populations, including veterans and LGBT communities.

The agency is seeking public comment on the proposal, which could take up to 18 months to fully put into effect.

"Suicide and attendant mental health challenges have received far too little attention for far too long. That is now changing," FCC Commissioner Brendan Carr says in a statement. "Anything we can do to break down barriers, to make it easier for conversations about mental health and counseling to feel within reach, is something we should do."

The CDC says suicide is the 10th leading cause of death in the United States, with more 47,000 deaths in 2017. And millions of people think about it or attempt suicide. In 2017, 10.6 million American adults seriously thought about suicide, 3.2 million made a plan, and 1.4 million attempted it.

You can reach the National Suicide Prevention Lifeline at 800-273-TALK (800-273-8255) or by online chat.

http://bit.ly/38Xuv2e

Big step in producing carbon-neutral fuel: silver diphosphide

A new chemical process described in the journal Nature Communications does in the lab what trees do in nature—it converts carbon dioxide into usable chemicals or fuels.

by Alicia Roberts, Wake Forest University

This new, carbon-neutral process, created by researchers at Wake Forest University, uses silver diphosphide (AgP2) as a novel catalyst that takes carbon dioxide pollution from manufacturing plants and converts it to a material called syngas, from which the liquid fuel used in manufacturing is made.

The new catalyst allows the conversion of carbon dioxide into fuel with minimal energy loss compared to the current state-of-the-art process, according to the Wake Forest researchers.

"This catalyst makes the process much more efficient," said Scott Geyer, corresponding author of "Colloidal Silver Diphosphide Nanocrystals as Low Overpotential Catalysts for CO_2 Reduction to Tunable Syngas," published online Dec. 16 in *Nature Communications*. "Silver diphosphide is the key that makes all the other parts work. It reduces energy loss in the process by a factor of three."

Silver has been considered the best catalyst for this process to date. Adding phosphorous removes electron density from the silver, making the process more controllable and reducing energy waste.

In the future, Geyer sees being able to power this process with solar energy, directly converting sunlight into fuel. The more efficient the chemical conversion process becomes, the more likely solar energy—instead of coal or other non-renewable energy sources—can be used to make fuel.

"People make syngas out of coal all the time," Geyer said.

Geyer, whose lab focuses on understanding the role phosphorus plays in chemical reactions, is an assistant professor of chemistry at Wake Forest.

The team that produced this paper includes Hui Li, who led the work as a Ph.D. student in Geyer's lab, plus former Wake Forest undergraduate Zachary Hood; Ph.D. in chemistry student Shiba Adhikari; and Ph.D. student in physics student Chaochao Dun, who all have stayed connected with the program through their professional posts.

"The ability to collaborate with a network of outstanding Wake Forest University graduates who are now at top universities and national laboratories across the United States has been essential in preparing this work as it allows us to access one-of-a-kind instrumentation facilities at their current institutions," Geyer said.

More information: *Hui Li et al. Colloidal silver diphosphide (AgP2) nanocrystals as low overpotential catalysts for CO2 reduction to tunable syngas, Nature Communications (2019).* *DOI: 10.1038/s41467-019-13388-8*

https://go.nature.com/37bF1S3

Chinese institutes investigate pathogen outbreaks in lab workers

Students and staff at two research institutes have tested positive to the Brucella bacterium, which can lead to serious complications.

David Cyranoski

Two Chinese agriculture research institutions are investigating how more than 100 students and staff became infected with the bacterium *Brucella*, strains of which are typically found in farm animals but can also trigger potentially fatal complications in people.

The Lanzhou Veterinary Research Institute in central China confirmed on 7 December that 96 staff and students have tested positive for the infection. In a statement, the institute said most of the infected people are not experiencing signs of brucellosis, the illness caused by the bacterium, which can include fever and flu-like symptoms.

The institute says it has closed its labs following the outbreak. Although some mice have also tested positive to the infection, an investigation has yet to announce the strain of *Brucella* in the infected people, or the source of the outbreak.

On 10 December, the health commission for the province of Heilongjiang confirmed that 13 students at the Harbin Veterinary Research Institute, around 2,600 kilometres to the northeast of Lanzhou, also had the infection. The 13 students were among 49 students who had previously worked as interns at the Lanzhou institute. The Harbin institute says it is also investigating the outbreak.

Different types of *Brucella* occur in many mammals species, but infections are most commonly detected in farm animals such as goats, sheep, cattle and pigs. Human infections most commonly result from the ingestion of undercooked meat or raw milk — but the bacteria can also enter the body through the lungs or skin wounds. *Brucella* strains are not typically transmitted from person to person. If left untreated, the infection can travel to the heart or brain and, in rare cases, be fatal. It can also cause infertility in animals and humans.

The outbreak at the Lanzhou Veterinary Research Institute was first uncovered in November when some students in the institute‘s foot and mouth disease research unit noticed that large numbers of their lab mice were infertile, according to *The Beijing News*. The mice tested positive for *Brucella*, as did four students. The institute then tested 317 people, and found that 96 had been infected.

The Beijing News also reported that students at the institute often forgo wearing masks and taking other precautions.

The research institutes in Harbin and Lanzhou did not respond to *Nature*’s questions about how the outbreak occurred, or their lab‘s safety procedures.

Lab-acquired infection

The US Centers for Disease Control says brucellosis is the most commonly reported bacterial infection acquired in scientific laboratories. Several factors contribute to the risk of infection, such as working on the pathogen without bio-safety-level-3 conditions which recommend closed laboratory safety cabinets, masks, a positive-pressure ventilation system and other precautions. The bacterium is also easily transmitted in aerosols. In 2011, 28 students and staff at an agricultural university also in Heilongjiang province, were infected with *Brucella* from goats. They each received 61,000 yuan (US$8,740) in compensation.

Felipe Francisco Tuon, coordinator of the Laboratory of Emerging Infectious Diseases at the Pontifical Catholic University of Paraná in Curitiba, Brazil, says that outbreaks in laboratories are usually found to be linked to insufficient safety precautions.

doi: 10.1038/d41586-019-03863-z

https://wb.md/35OLiCx

Two Drugs Better Than One for Severe Influenza

Taking favipiravir and oseltamivir was more effective for treating severe influenza than taking oseltamivir alone

Ricki Lewis, PhD

Taking two antivirals — favipiravir and oseltamivir — was more effective for treating severe influenza than taking oseltamivir alone, according to a comparison of results from two clinical trials published online December 11 in the *Journal of Infectious Diseases*.

Preclinical studies suggest synergy between favipiravir (*Avigan*, Toyama Chemical) and oseltamivir (*Tamiflu*, Genentech) as combination therapy to treat severe influenza, but the effectiveness of the drug combination has not been evaluated in controlled clinical trials.

Each year, approximately 300,000 to 650,000 people die from seasonal influenza. The only drug in widespread use, the neuraminidase inhibitor (NAI) oseltamivir, is of limited use, and its efficacy for severe cases has not been adequately studied. Adding an antiviral that works by a different mechanism might boost effectiveness, especially for the most compromised patients.

Favipiravir works differently from oseltamivir, targeting a viral RNA polymerase rather than the neuraminidase. In vitro studies have shown favipiravir to work synergistically with oseltamivir against influenza A viruses, and the combination has been shown to be effective late in the disease course for a strain of mice with lethal influenza A (H5N1) infection.

Yeming Wang, from the Chinese Academy of Medical Sciences in Beijing, and colleagues compared findings from two prospective studies involving patients hospitalized for influenza: the "combination study" used both drugs, and the "monotherapy study" used only oseltamivir for patients who had community-acquired pneumonia and influenza.

For both studies, outcomes included the rate of clinical improvement (a decrease of two categories on a seven-category scale) and detection of viral RNA over time. Risks were compared by calculating the subhazard ratio (sHR).

The combination study assessed 40 patients from February 2018 through 2019 at tertiary critical care centers in China. Participants had a positive rapid influenza A or B test result, were in respiratory failure ($PaO_2/FiO_2 \leq 300$ mmHg or receiving mechanical ventilation) and had been ill for 10 or fewer days. They received oseltamivir 75 mg for 10 days and either of two regimens of favipiravir (1600 mg BID on day 1 and 600 mg BID on days 2 to 10, or 1800 mg BID on day 1 and 800 mg BID on days 2 to 10).

The 128 patients in the oseltamivir monotherapy group were part of a prospective multicenter observational study of community-acquired pneumonia and had laboratory-confirmed influenza. They were treated at a hospital in mainland China between October 2016 and February 2019.

To align the investigations, the researchers applied the three criteria of laboratory-confirmed diagnosis, respiratory failure, and symptoms for 10 or fewer days.

The primary clinical outcome was time to improvement after starting therapy, up to 28 days. That meant either hospital discharge or improvement on two of seven measures: not hospitalized with resumption of normal activities; not hospitalized but unable to resume normal activities; hospitalized but not requiring supplemental oxygen; hospitalized but requiring supplemental oxygen; hospitalized, with nasal high-flow oxygen therapy and/or noninvasive mechanical ventilation; hospitalized, with ECMO (extracorporeal membrane oxygenation) and/or invasive mechanical ventilation; and death.

The primary virologic endpoints were the proportion of patients whose nasopharyngeal swab test results were negative for influenza on days 2, 5, 7, and 10 after starting treatment.

On day 14, clinical improvement was greater among the patients who received both drugs (62.5% vs 42.2%; *P* = .0247), with adjusted sHR for combination therapy of 2.06. In addition, the proportion of patients with undetectable viral RNA at day 10 was higher in the combination group than in the monotherapy group (67.5% vs 21.9%; *P* < .01). Mortality did not differ.

"Our findings suggest that favipiravir and oseltamivir combination therapy may be associated with greater antiviral effects and faster clinical improvement in severe influenza" than monotherapy, the researchers conclude. They suggest that a double-blinded, randomized controlled clinical trial be conducted to confirm the finding.

The dual-drug approach could address "the relatively high frequency of emergence of oseltamivir-resistant [viral] variants in critically ill patients and their association with poor outcomes," the researchers write. In addition, results of the use of antibody-based therapies given with NAIs have been disappointing. Studies of other polymerase inhibitors (pimodivir and baloxavir) given with NAIs to treat severe influenza in hospitalized patients are underway. Study limitations include the retrospective design, small groups, and not analyzing coverage of influenza B strains.

The researchers have disclosed no relevant financial relationships.

J Inf Dis. Published online December 11, 2019. Abstract

https://wb.md/2Mn2oA1

Having Influenza May Keep the Common Cold Away

Interacting cold and influenza viruses can actually diminish the prevalence of the common cold thanks to adaptive immunity

Jennifer Garcia

Interaction between cold and influenza viruses can actually diminish the prevalence of the common cold during peak flu season thanks to adaptive immunity, according to a study published online today in the *Proceedings of the National Academy of Sciences*.

Sema Nickbakhsh, PhD, a postdoctoral research associate from the MRC-University of Glasgow Centre for Virus Research, United Kingdom, and colleagues analyzed data from 44,230 cases of respiratory illness between 2005 and 2013. They tested all cases for 11 respiratory virus groups and included in their analysis alternative drivers of infection frequency, including age, sex, and disease severity.

Using bespoke analysis and mathematical simulations to assess the propensity of a given virus to co-infect with another virus at both the population and individual host levels, the researchers confirmed a negative interaction between seasonal influenza A virus (IAV) and rhinovirus (RV), the virus which causes the common cold (odds ratio, 0.27; *P* < .001).

The study authors posit that "this negative interaction may be driven by virus competition for susceptible cells, for example as a consequence of influenza-induced destruction of cell surface receptors and/or cell death, or as a consequence of virus-induced innate immune responses, such as the secretion of interferon, which can cause noninfected neighboring cells to adopt a protective antiviral state."

The researchers go on to suggest this "transient immune-mediated cross-protection" may result in alterations in viral transmission such that recent infection with IAV would leave the host less susceptible to subsequent viral infection with RV.

They say their simulations show this "refractory period" could lead to a significant decline in common colds. As an example, they found that a refractory period of 2 days led to a 23% decrease in the

incidence of cold-like virus during peak influenza virus activity, whereas a 7-day refractory period resulted in a 61% decrease.

The researchers acknowledge virus–virus interactions are dependent on multiple host and environmental factors and that clinical symptoms of infection with IAV and RV can be quite variable at the population and individual host levels.

"Our findings imply that the incidence of influenza infections is interlinked with the incidence of noninfluenza viral infections with implications for the improved design of disease forecasting models and the evaluation of disease control interventions," the authors conclude.

The authors have disclosed no relevant financial relationships.

Proc Natl Acad Sci USA. Published online December 16, 2019. Full text

http://bit.ly/2sVhSUK

Ancient 'chewing gum' yields insights into people and bacteria of the past

Success in extracting a complete human genome from a thousands-of-years old "chewing gum"

Researchers from the University of Copenhagen have succeeded in extracting a complete human genome from a thousands-of-years old "chewing gum". According to the researchers, it is a new untapped source of ancient DNA.

During excavations on Lolland, Denmark, archaeologists have found a 5,700-year-old birch pitch. Researchers from the University of Copenhagen have succeeded in extracting a complete ancient human genome from the pitch seen in the photo. **Photo: Theis Jensen.**

During excavations on Lolland, archaeologists have found a 5,700-year-old type of "chewing gum" made from birch pitch. In a new study, researchers from the University of Copenhagen succeeded in extracting a complete ancient human genome from the pitch.

It is the first time that an entire ancient human genome has been extracted from anything other than human bones. The new research results have been published in the scientific journal *Nature Communications*.

'It is amazing to have gotten a complete ancient human genome from anything other than bone," says Associate Professor Hannes Schroeder from the Globe Institute, University of Copenhagen, who led the research.

'What is more, we also retrieved DNA from oral microbes and several important human pathogens, which makes this a very valuable source of ancient DNA, especially for time periods where we have no human remains,' Hannes Schroeder adds.

Based on the ancient human genome, the researchers could tell that the birch pitch was chewed by a female. She was genetically more closely related to hunter-gatherers from the mainland Europe than to those who lived in central Scandinavia at the time. They also found that she probably had dark skin, dark hair and blue eyes.

Sealed in mud

The birch pitch was found during archaeological excavations at Sylthom, east of Rødbyhavn in southern Denmark. The excavations are being carried out by the Museum Lolland-Falster in connection with the construction of the Fehmarn tunnel.

'Sylthom is completely unique. Almost everything is sealed in mud, which means that the preservation of organic remains is absolutely phenomenal,' says Theis Jensen, Postdoc at the Globe Institute, who worked on the study for his PhD and also participated in the excavations at Sylthom.

'It is the biggest Stone Age site in Denmark and the archaeological finds suggest that the people who occupied the site were heavily exploiting wild resources well into the Neolithic, which is the period when farming and domesticated animals were first introduced into southern Scandinavia,' Theis Jensen adds.

This is reflected in the DNA results, as the researchers also identified traces of plant and animal DNA in the pitch - specifically hazelnuts and duck - which may have been part of the individual's diet.

Bacterial evolution

In addition, the researchers succeeded in extracting DNA from several oral microbiota from the pitch, including many commensal species and opportunistic pathogens.

'The preservation is incredibly good, and we managed to extract many different bacterial species that are characteristic of an oral microbiome. Our ancestors lived in a different environment and had a different lifestyle and diet, and it is therefore interesting to find out how this is reflected in their microbiome,' says Hannes Schroeder.

The researchers also found DNA that could be assigned to Epstein-Barr Virus, which is known to cause infectious mononucleosis or glandular fever. According to Hannes Schroeder, ancient "chewing gums" bear great potential in researching the composition of our ancestral microbiome and the evolution of important human pathogens.

'It can help us understand how pathogens have evolved and spread over time, and what makes them particularly virulent in a given environment. At the same time, it may help predict how a pathogen will behave in the future, and how it might be contained or eradicated,' says Hannes Schroeder.

Chewing gum, all-purpose glue or medicine?

- ***Birch pitch is a black-brown substance that is produced by heating birch bark. It was commonly used in prehistory for hafting stone tools as an all-purpose glue. The earliest known use of birch pitch dates back to the Palaeolithic.***
- ***Pieces of birch pitch are often found with tooth imprints suggesting that they were chewed. As the pitch solidifies on cooling, it has been suggested that it was chewed to make it malleable again before using it for hafting etc.***
- ***Other uses for birch pitch have also been suggested. For example, one theory suggests that birch pitch could have been used to relieve toothache or other ailments as it is mildly antiseptic. Other theories suggest, people may have used it as a kind of prehistoric tooth brush, to suppress hunger, or just for fun as a chewing gum.***

http://bit.ly/390KjBz

Filtered coffee helps prevent type 2 diabetes, show biomarkers in blood samples

Coffee can help reduce the risk of developing type 2 diabetes - but only filtered coffee, rather than boiled coffee.

New research from Chalmers University of Technology and Umeå University, both in Sweden, show that the choice of preparation method influences the health effects of coffee.

Many previous studies have shown a connection between high coffee intake and a reduced risk of developing type 2 diabetes. Now, a study from Chalmers University of Technology and Umeå University, offers new insight into this connection, using a novel method to help differentiate between the effects of filtered coffee and boiled coffee.

"We have identified specific molecules - 'biomarkers' - in the blood of those taking part in the study, which indicate the intake of different sorts of coffee. These biomarkers are then used for analysis when calculating type 2 diabetes risk. Our results now clearly show that filtered coffee has a positive effect in terms of reducing the risk of developing type 2 diabetes. But boiled coffee does not have this effect," says Rikard Landberg, Professor in Food Science at Chalmers, and Affiliated Professor at the Department of Public Health and Clinical Medicine at Umeå University.

With the use of these biomarkers, the researchers were able to show that people who drank two to three cups of filtered coffee a day had

a 60% lower risk of developing type 2 diabetes than people who drank less than one cup of filtered coffee a day. Consumption of boiled coffee had no effect on the diabetes risk in the study.

Filtered coffee is the most common method of preparation in many places, including the US and Scandinavia. Boiled coffee in this case refers to an alternative method of coffee preparation sometimes used in Sweden and some other countries, in which coarse ground coffee is simply added directly to boiling water and left to brew for a few minutes. All the data used in the research came from a group of Swedish subjects and was collected in the early 1990s.

According to Rikard Landberg, many people wrongly believe that coffee has only negative effects on health. This could be because previous studies have shown that boiled coffee increases the risk of heart and vascular diseases, due to the presence of diterpenes, a type of molecule found in boiled coffee.

"But it has been shown that when you filter coffee, the diterpenes are captured in the filter. As a result, you get the health benefits of the many other molecules present, such as different phenolic substances. In moderate amounts, caffeine also has positive health effects," he says.

The question is whether diterpenes also negatively influence sugar metabolism and are therefore the cause of why boiled coffee does not help lower the risk of diabetes, in the way that filter coffee does. The researchers still cannot say the exact nature of the link.

Many other types of coffee preparation were not specifically investigated in the study, such as instant, espresso, cafetière, and percolator coffee. These types of coffee were not common among the Swedish study population when the data was collected.

But given that espresso coffee, from classic espresso machines or the now popular coffee-pods, is also brewed without filters, Rikard Landberg believes the health effects could therefore be similar to boiled coffee, in terms of the risk of type 2 diabetes. Coffee made in a cafetière, or French press, is prepared in a similar way to boiled coffee, so it may also not have the positive effect of reducing type 2 diabetes risk. It is unclear whether instant coffee, the most popular type in the UK, would be more similar to filtered or boiled coffee in this respect.

But the researchers are careful to note that no conclusions can be drawn yet regarding these other preparation methods. Rickard Landberg also stresses that the health impacts of coffee do not depend solely on if it is filtered or not. They also vary with how the coffee beans, and the drink in general, are managed.

To differentiate the diabetes risk for boiled and filtered coffee, a new technique called metabolomics was used, in combination with classic dietary questionnaires. Metabolomics makes it possible to identify the blood concentration of specific molecules from a given food or drink and use that as an objective measurement of intake - instead of simply relying on self-reported intakes from the questionnaires, which are prone to large errors.

"Metabolomics is a fantastic tool, not just for capturing the intake of specific foods and drinks, but also for studying the effects that that intake has on people's metabolism. We can derive important information on the mechanisms behind how certain foods influence disease risk," says Lin Shi, Postdoctoral researcher and the lead author of the study.

More about: Different types of coffee and geographic examples:

Filtered coffee refers to methods in which finely ground coffee beans are placed in a filter, and then water passes through, either in a machine or manually. Boiled coffee is made with coarsely ground coffee beans which are then added directly to the water. This method also includes Turkish and Greek coffee.

Sweden is one of the countries with the highest filtered coffee intake worldwide, also with a high consumption of boiled coffee, especially in the large, rural areas of northern Sweden.

In the USA, filtered coffee is the most common variety, while instant coffee dominates in the UK. Espresso-based drinks are most common in Southern Europe. Turkish coffee is popular in the Middle East and Eastern Europe.

More about the study:

The study was a case-control study nested in a prospective cohort in the Västerbotten region of northern Sweden between 1991 and 2005. Participants answered questionnaires about eating habits and lifestyle. They also left blood samples which were stored frozen. From those who took part, a total of 421 people were identified who, after around 7 years, had developed type 2 diabetes. They were compared with 421 healthy control subjects. The original blood samples were then analysed. In addition, blood samples that had been provided ten years after the first blood samples were analysed for 149 of the case-control pairs. Read the paper "Plasma metabolite biomarkers of boiled and filtered coffeeintake and their association with type 2 diabetes risk": https://onlinelibrary.wiley.com/doi/pdf/10.1111/joim.13009

https://wb.md/2ZqozNh

Fecal Transplants: 5 Things to Know

Here are five things to know about the evidence and recent controversy surrounding FMT.

Victoria Stern, MA

Although fecal microbiota transplantation (FMT) has not yet received approval from the US Food and Drug Administration (FDA), more than 10,000 patients receive FMT in the United States each year to treat *Clostridium difficile* infection, and hundreds of clinical trials are currently underway to explore whether FMT can treat a range of other conditions, such as ulcerative colitis, irritable bowel syndrome, and obesity. A recent FMT-related fatality, however, has led some experts to question its safety and widespread use. Here are five things to know about the evidence and recent controversy surrounding FMT.

1. Fecal transplantation cuts bloodstream infection risk.

A growing body of evidence shows that FMT is a safe and effective approach for treating both adults and children with *C difficile* infections. Now a recent study suggests that its benefits may extend beyond simply eliminating the infection—FMT may also curb *C difficile* infection-related complications and improve a patient's overall survival odds.

Investigators reported that patients with recurrent *C difficile* infection had a lower incidence of bloodstream infections following FMT compared with antibiotics. Less than 5% of patients receiving FMT (5 of 109) had a bloodstream infection after 90 days compared with 22% of those who received antibiotics (40 of 181). The difference in the incidence of bloodstream infections was even more pronounced when comparing propensity score–matched patients: 4% of FMT-treated patients (2 of 57) vs 26% of antibiotic-treated patients (15 of 57).

Almost three times more patients in the FMT group had a sustained cure rate (97% vs 38% in the antibiotic group). The FMT recipients also spent fewer days in the hospital and, perhaps most notably, had better overall survival at 90 days.

2. Early research hints at FMT as a treatment for obesity.

Although the most convincing evidence of efficacy with FMT is in its ability to eliminate *C difficile* infection, gastroenterologists are also exploring its usefulness to treat obesity. The limited findings to date suggest that gut microbiota can influence a person's metabolism and, more specifically, that the gut hormone glucagon-like peptide 1 (GLP-1) may play an important role in facilitating weight gain or loss.

FMT is potentially promising in this indication because it can alter the gut microbiome in a specific and durable way, possibly aiding in dropping excess pounds. A 2017 study found that FMT from lean donors improved insulin sensitivity and altered intestinal microbiota in overweight and obese recipients 6 weeks after treatment, though the changes in microbiota were not sustained at 18 weeks. More recently, a randomized controlled trial found that obese individuals who received FMT capsules from lean donors

over 12 weeks showed stool engraftment of the donor's microbiota throughout the 3-month study period. The treatment, however, did not lead to weight loss or notable differences in GLP-1 levels in the FMT and placebo groups. Although it is still early days for this research, some experts suggest that FMT could make a bigger mark on weight loss when paired with dietary modifications.

3. FMT may improve the effectiveness of cancer immunotherapy.

Recent evidence suggests that the gut microbiome could influence a person's response to cancer immunotherapy. A 2018 study found that patients who took antibiotics shortly before or after starting anti-programmed cell death ligand-1 (PD-1) immunotherapy to treat advanced lung and kidney cancers had a worse response to the immune checkpoint inhibitor. The patients who received antibiotics did not maintain the same levels of microbiota diversity as their peers who did not take antibiotics, and this antibiotic-related microbial imbalance (or dysbiosis) might limit the effectiveness of an inhibitor, according to the investigators.

But could altering the gut microbiome potentially enhance the efficacy of immunotherapy? Some early data indicate that this is indeed a possibility. A 2018 study found that mice who received FMT from patients with lung and kidney cancer who responded to anti–PD-1 therapy had significantly smaller tumors than mice who underwent FMT from patients who did not respond to therapy.

A recent phase 1 trial also provides initial evidence that the gut microbiome affects drug efficacy. In the trial, three patients with metastatic melanoma who did not respond to initial treatment with a PD-1 inhibitor received FMT from donors who had achieved a durable complete response on anti-PD-1 therapy. The investigators reported that, following FMT, the gut microbiome of the recipients appeared to resemble those of the donors, and two recipients "demonstrated clinical and radiological benefit from treatment."

4. A patient died after receiving FMT.

After two patients became infected with extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* following FMT, some experts are now questioning the safety of FMT and pushing for greater regulation of the practice.

Details of the fatality were first published in *The New England Journal of Medicine* in November 2019. The report described how two patients participating in different clinical trials ended up receiving contaminated FMT capsules from the same donor. One patient died from the infection, which presented 5 days after the transplant and led to sepsis. The second patient was more fortunate; when he didn't respond to treatment, his clinicians took a blood culture that revealed the ESBL-producing *E coli* and switched him to an antibiotic that eliminated the infection.

5. Following the patient death, the FDA has issued caution about FMT safety.

Since news of the fatality, some experts have called for more rigorous donor screening to prevent the transmission of serious infections, as well as for in-depth evaluations of the risks and benefits of FMT for different indications.

The FDA has expressed its concern as well. In June 2019, the agency issued a national safety alert, warning patients and providers about the risk for serious infection from FMT. But the FDA did not stop with a safety communication; it also suspended an unidentified number of FMT clinical trials and issued a second notice detailing protections providers should consider when using FMT. Specifically, they recommended carefully screening FMT donors and donor stool for multi-drug-resistant organisms, quarantining all stored FMT products that have not been screened, and discussing the risk for infection with patients during the informed-consent process.

http://bit.ly/2ELeQoR

Ancient human species made 'last stand' 100,000 years ago on Indonesian island

When seafaring modern humans ventured onto the island of Java some 40,000 years ago, they weren't the first humans to call the island home

By Michael Price

When seafaring modern humans ventured onto the island of Java some 40,000 years ago, they found a rainforest-covered land teeming with life—but they weren't the first humans to call the island home. Their distant ancestor, *Homo erectus*, had traveled to Java when it was connected to the mainland via land bridges and lived there for approximately 1.5 million years. These people made their last stand on the island about 100,000 years ago, long after they had gone extinct elsewhere in the world, according a new study assigning reliable dates to previously found *H. erectus* fossils. The finding suggests a trace of *H. erectus* DNA could live on in modern Southeast Asian populations, thanks to complex intermingling among the diverse humans who have lived in the region.

The newly dated fossils also bookend the existence of a remarkably long-lived human species, says Patrick Roberts, an archaeologist at the Max Planck Institute for the Science of Human History in Jena, Germany, who wasn't involved with the study. "With this date, the duration of *Homo erectus* occupation in Southeast Asia is nearly three times as long as our [own] species has been on the planet," he says. "There is no doubt it was successful."

H. erectus arose in Africa about 1.9 million years ago. These toolmakers with relatively large brains migrated out of Africa and across Asia, crossing into Java by land bridges about 1.6 million years ago, when savannalike open woodland covered much of the land. Later, sea levels rose, isolating these ancient Javans on an island. Meanwhile, in Africa and mainland Asia, *H. erectus* disappeared by about 500,000 years ago.

In the 1930s, a team of Dutch explorers excavated a site by Java's Solo River, near the village of Ngandong. They unearthed a rare trove of fossils: tens of thousands of animal bones—and 12 partial skulls and two leg bones identified as *H. erectus*. But the Dutch team couldn't date the bones with any certainty. Later scientists also struggled, despite more sophisticated dating methods, because these require material from the same sediment layers as the fossils—and nobody knew exactly where the original excavation took place.

"[The fossils] had been an enigma," says the new study's lead author, paleoanthropologist Russell Ciochon of the University of Iowa in Iowa City. "Many people had tried to date them, but there was no way to accurately do so."

O. Frank Huffman, an archaeologist at the University of Texas in Austin and a study co-author, spent 5 years poring over the Dutch explorers' photos and notes; he even met with their grandchildren. He and colleagues deduced that the 1930s excavation was located near what is now a sugarcane field abutting a dirt road. In 2008 and 2010, Ciochon's team re-excavated the site, turning up 867 new fossils belonging to deer, wild cattle, and an extinct, elephantlike animal called a stegodon. Based on photographs and documents from the original excavation, they established that some of the newly found animal fossils came from the same rich bone bed as the *H. erectus* fossils. The researchers applied five types of radiometric dating, including a new method that provides both minimum and maximum dates, to those animal fossils and the sediments around them. The team concluded that the bones were buried between 117,000 and 108,000 years ago, the researchers report today in *Nature*.

It's doubtful *H. erectus* lived on much longer, Ciochon says. A warmer, wetter climate turned Java's open woodlands into dense rainforests about 100,000 years ago, and Ciochon suggests *H. erectus* would have struggled to survive in such a transformed landscape. When modern humans arrived on Java, apparently about 40,000 years ago, *H. erectus* was probably long extinct, he adds.

Aida Gómez-Robles, an anthropologist at University College London who wasn't involved with the study, says the authors did great detective work in finding the original excavation sites, and that they have laid out a likely scenario. "We can never be certain that we have found the first or the last representative of any species," she says, "[but] a last appearance date of approximately 100,000 years ago for *H. erectus* looks reasonable."

H. erectus left an impressive legacy. Many researchers think it splintered into at least two additional species as it traveled throughout Southeast Asia—*H. floresiensis*, found on the Indonesian island of Flores, and *H. luzonensis*, found on the island of Luzon in the Philippines—and may have interbred at some point with the Denisovans, extinct close cousins to Neanderthals. In turn, Denisovans may have mated with modern humans in Indonesia and New Guinea, perhaps as recently as 30,000 years ago. Those pairings, the authors argue, could have introduced a smidgen of *H. erectus* DNA into the genomes of some modern Southeast Asians, whose DNA contains a trace—about 1%—of genetic material that doesn't appear to come from modern humans, Neanderthals, or Denisovans.

"[The new study's] date certainly adds support to this scenario," by suggesting *H. erectus* was still around in Java when Denisovans may also have been moving through the region, Roberts says, but, he adds, there's far too little evidence to confirm it. "Either way, Southeast Asia is clearly now one of the most exciting places to be working in human origins."

http://bit.ly/2QbkndH

Are herpes virus infections linked to Alzheimer's disease?

Evidence that refutes the link between increased levels of herpes virus and Alzheimer's disease

Researchers at Baylor College of Medicine report today in the journal *Neuron* evidence that refutes the link between increased levels of herpes virus and Alzheimer's disease. In addition, the researchers provide a new statistical and computational framework for the analysis of large-scale sequencing data.

About 50 million people worldwide are affected by Alzheimer's disease, a type of progressive dementia that results in the loss of memory, cognitive abilities and verbal skills, and the numbers are growing rapidly. Currently available medications temporarily ease the symptoms or slow the rate of decline, which maximizes the time patients can live and function independently. However, there are no treatments to halt progression of Alzheimer's disease.

"Like all types of dementia, Alzheimer's disease is characterized by massive death of brain cells, the neurons. Identifying the reason why neurons begin and continue to die in the brains of Alzheimer's disease patients is an active area of research," said corresponding author Dr. Zhandong Liu, associate professor of pediatrics at Baylor and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital.

One theory that has gained traction in the past year is that certain microbial infections, such as those caused by viruses, can trigger Alzheimer's disease. A 2018 study reported increased levels of human herpesvirus 6A (HHV-6A) and human herpesvirus 7 (HHV-7) in the postmortem brain tissues of more than 1,000 patients with Alzheimer's disease when compared to the brain tissues of healthy-

aging subjects or those suffering from a different neurodegenerative condition.

Presence of elevated levels of genetic material of herpes viruses indicated active infections, which were linked to Alzheimer's disease. In less than a year, this study generated a flurry of excitement and led to the initiation of several studies to better understand the link between viral infections and Alzheimer's disease.

Surprisingly, when co-author Dr. Hyun-Hwan Jeong, a postdoctoral fellow in Dr. Liu's group and others, reanalyzed the data sets from the 2018 study using the identical statistical methods with rigorous filtering, as well as four commonly used statistical tools, they were unable to produce the same results.

The team was motivated to reanalyze the data from the previous study because they observed that while the p-values (a statistical parameter that predicts the probability of obtaining the observed results of a test, assuming that other conditions are correct) were highly significant, they were being ascribed to data in which the differences were not visually appreciable.

Moreover, the p-values did not fit with simple logistic regression - a statistical analysis that predicts the outcome of the data as one of two defined states. In fact, after several types of rigorous statistical tests, they found no link between the abundance of herpes viral DNA or RNA and likelihood of Alzheimer's disease in this cohort.

"As high-throughput 'omics' technologies, which include those for genomics, proteomics, metabolomics and others, become affordable and easily available, there is a rising trend toward 'big data' in basic biomedical research. In these situations, given the massive amounts of data that have to be mined and extracted in a short time, researchers may be tempted to rely solely on p-values to interpret results and arrive at conclusions," Liu said.

"Our study highlights one of the potential pitfalls of over-reliance on p-values. While p-values are a very valuable statistical parameter, they cannot be used as a stand-alone measure of statistical correlation - data sets from high-throughput procedures still need to be carefully plotted to visualize the spread of the data," Jeong said. "Data sets also have to be used in conjunction with accurately calculated p-values to make gene-disease associations that are statistically correct and biologically meaningful."

"Our goal in pursuing and publishing this study was to generate tools and guidelines for big data analysis, so the scientific community can identify treatment strategies that will likely benefit patients," Liu said.

This study was funded by the Huffington Foundation.

http://bit.ly/397r3SC

Saccharin derivatives give cancer cells a not-so-sweet surprise

Recent studies indicate that saccharin can actually kill human cancer cells

Saccharin received a bad rap after studies in the 1970s linked consumption of large amounts of the artificial sweetener to bladder cancer in laboratory rats. Later, research revealed that these findings were not relevant to people. And in a complete turnabout, recent studies indicate that saccharin can actually kill human cancer cells. Now, researchers reporting in ACS' *Journal of Medicinal Chemistry* have made artificial sweetener derivatives that show improved activity against two tumor-associated enzymes.

Saccharin, the oldest artificial sweetener, is 450 times sweeter than sugar. Recently, scientists showed that the substance binds to and inhibits an enzyme called carbonic anhydrase (CA) IX, which helps cancer cells survive in the acidic, oxygen-poor microenvironments of many tumors. In contrast, healthy cells make different -- but very similar -- versions of this enzyme called CA I and II. Saccharine

and another artificial sweetener called acesulfame K can selectively bind to CA IX over CA I and II, making them possible anti-cancer drugs with minimal side effects. Alessio Nocentini, Claudiu Supuran and colleagues wondered whether they could make versions of the artificial sweeteners that show even more potent and selective inhibition of CA IX and another tumor-associated enzyme, CA XII.

The team designed and synthesized a series of 20 compounds that combined the structures of saccharin and acesulfame K and also added various chemical groups at specific locations. Some of these compounds showed greater potency and selectivity toward CA IX and XII than the original sweeteners. In addition, some killed lung, prostate or colon cancer cells grown in the lab but were not harmful to normal cells. These findings indicate that the widely used artificial sweeteners could be promising leads for the development of new anticancer drugs, the researchers say.

The authors acknowledge funding from the Ministry of Education, University and Research (Italy) and King Saud University.

The abstract that accompanies this paper can be found here.

http://bit.ly/2EM9eL2

New Oral Polio Vaccine to Bypass Key Clinical Trials

Health officials are rushing a genetically engineered product into the field to counter uncontained outbreaks of vaccine-derived polio.

Robert Fortner

To stem a growing polio crisis, health officials are accelerating the development of a new oral vaccine with plans for emergency approval and deployment in regions with active polio transmission as early as June 2020. The new vaccine, called nOPV2, might conclusively end the outbreaks, caused by the live virus in the vaccine reverting to a virulent form. But expedited approval means skipping the real-world testing of large clinical trials. Instead, key questions about the vaccine's effectiveness will be answered in the field.

"The nOPV strains have been tested in a small number of volunteers and we do not see reversion to neurovirulence," says Vincent Racaniello, a virologist at Columbia University, "but when they are used for mass immunization of millions of individuals, rare events can become evident."

Because of the compressed approval and deployment timeline, nOPV2 may be used in millions of kids beginning in mid-2020.

Oral polio vaccine strains, originally developed by Albert Sabin in the 1950s, can in rare instances revert to virulence, spread, and paralyze children just like polio itself, a phenomenon first recognized in 2000. Because the Sabin vaccine had successfully eradicated wild type 2 poliovirus in 2015, health officials across the world quit administering it the following year. However, herd immunity had not been achieved before the cessation of the type 2 vaccine, which gave an opportunity for un-immunized people to later become infected by the virus that had begun reverting to virulence in people who had gotten the vaccine. With successive transmission through the unvaccinated, the vaccine strain can regain the virulence of wild polio.

Nowadays, cases of polio caused by vaccine-derived strains outnumber those caused by the wild virus–and they continue to spread unchecked, most recently from the Phillipines to Malaysia. Vaccine-derived polio threatens as many as 210 million children globally, according to the World Health Organization. Using the reversion-prone Sabin type 2 vaccine to fight outbreaks caused more new outbreaks than it stopped, a virologist at the Centers for Disease Control and Prevention (CDC) told *Science* earlier this year.

Locking the gates to polio reversion

nOPV2, the new type 2 oral polio vaccine, has been genetically engineered to avoid the pitfalls of Sabin's vaccine. The project is

funded by the Gates Foundation and coordinated by PATH, a nonprofit developer of public health innovations, with scientific work taking place at the National Institute for Biological Standards and Control (NIBSC) in the UK, the University of California, San Francisco, the CDC, and the Food and Drug Administration.

Poliovirus "evolves readily to any situation it finds," says Andrew Macadam, a principal scientist at NIBSC and a designer of nOPV2. As RNA viruses, polio and polio vaccine strains evolve using mutation and recombination. Polio "has a polymerase that is not very accurate," says Macadam, so mutations occur frequently during replication. More importantly for rapid adaptation, recombination allows the virus to incorporate RNA strands from other C type enteroviruses in human hosts that enable gains in virulence. These partners include all the Sabin strains and Coxsackievirus, for example.

Two recombination events would be required to overcome nOPV2's genetically engineered safeguards, making reversion to virulence less likely to occur.

nOPV2 obstructs some key genetic routes to pathogenicity, believed to be controlled by "gatekeeper" mutations. In particular, a single point mutation at nucleotide 481 increases neurovirulence and actually occurs in most people soon after immunization. The pivotal change at 481 makes a return to virulence possible, according to Macadam. "The gatekeeper idea," he explains, "is that it needs to revert at 481 before it can do anything else and then you can incorporate these other mutations" that cause the vaccine to become pathogenic.

So nOPV2 developers modified 18 nucleotides near 481 in the poliovirus genome so that the well-known single substitution no longer opens the gate to virulence. This safeguard in turn is protected from wholesale replacement via recombination by relocating a gene necessary for replication to another part of the genome so that if the modifications near 481 are lost through recombination, the gene needed for replication will also be lost. As a result, reversion "requires two recombination events instead of one," according to Macadam, one being the acquisition of a second copy of the replication gene and the other being the loss of the 481-related modifications. "Therefore, it's less likely," says Macadam.

In addition, Macadam's team outfitted nOPV2 with a higher-fidelity polymerase that introduces fewer errors during replication while another gene received alterations to decrease the virus' propensity for recombination.

The risk of polio recombination

Testing so far validates the new design. A small, Phase 1 clinical trial in Belgium of 30 adults found nOPV2 completely stable against the main gatekeeper mutation about three weeks after vaccination. Ordinarily, 481 mutates within six days. Macadam and colleagues have also carried out as-yet unpublished studies in cell culture that demonstrate genetic stability.

Macadam nevertheless says it's "debatable" how much nOPV2's design will reduce recombination. Specifically, he is concerned about the recombination risks posed by the Sabin 1 and 3 strains. Before administration of the type 2 vaccine strain was halted in 2016, all three strains were co-administered in a single drop. Macadam cautions against co-administration of nOPV2 with Sabin 1 and 3. "I just wouldn't see the logic in doing that," he says. Recombination with the Sabin strains could set nOPV2 on the path to virulence. Co-administration could "jeopardize the safety of what you're trying to do," says Macadam.

However, delivering vaccines in separate campaigns creates a significant operational constraint. "This conundrum is real, and is already being seen," says WHO spokesperson, Oliver Rosenbauer. In parts of Nigeria and the Lake Chad region, some vaccination campaigns are conducted with Sabin 1 and 3, others with solely

with Sabin 2. “So that needs to be logistically managed appropriately.”

Also, the continually broadening scope of type 2 vaccine-derived outbreaks might necessitate co-administration at continent scale. Rather than tightly circumscribed use of nOPV2 in response to isolated outbreaks, says Temitope Faleye, there needs to “one, very well-coordinated immunization campaign that cuts across the whole of sub-Saharan Africa.” Faleye is a researcher at the Nigerian Institute of Medical Research. “You immunize as many children as possible to ensure that you don’t have pockets of people” who can start vaccine viruses back on the path to renewed virulence, which happened before and led to the current outbreaks.

Even if nOPV2 is kept away from Sabin 1 and 3, they are not the only available recombination partners. “The real concern out here is these species C [enteroviruses] that are circulating,” according to Faleye. “By default,” he says, “most of the children have enteroviruses in them” in Nigeria and across sub-Saharan Africa, where most of the world’s outbreaks of vaccine-derived polio are occurring. They are known to fuel reversion of the Sabin vaccine strains. Faleye’s research has found instances of vaccine-derived poliovirus arising from two independent recombination events with enteroviruses. “[I]t is a phenomenon that has been documented.”

Faleye says he still expects nOPV2 to revert less frequently than the Sabin 2 strain.

He describes nOPV2 as “beautiful, plausible, and theoretically based on solid science.” But, he says, “anybody in the field knows that with the current design, you don’t have control of viral recombination.”

The real of test of nOPV2

Racaniello, who wasn’t involved in the development of the vaccine, agrees that nOPV2 is “probably going to be better,” but with a caveat. “There is nothing like the selection force of millions of human guts.” Increased fitness and virulence overlap, so adaptations for surviving the brutish competition in the gut also increase virulence in the spinal cord, where polio causes damage. And because of the compressed approval and deployment timeline, nOPV2 may be used in millions of kids beginning in mid-2020, before a Phase 2 trial in Bangladesh, which will pit the vaccine against real-world conditions such as co-infections with other enteroviruses, could finish.

A completed Phase 2 trial in Panama sheds little light on recombination with enteroviruses. “Species C enterovirus prevalence was not an endpoint” in the Panama trial, says PATH’s John Konz, who leads the nOPV2 project. “We might get some sense of levels from next generation sequencing of virus in stool samples, but those results are not yet available.” In addition, according to Macadam, “the actual analysis pipeline won’t be as extensive as it might be, if we had unlimited resources.”

Racaniello commends nOPV2, which “was made using all the fundamental results that we and others have developed over the years.” But he questions how airtight nOPV2’s architecture is against reversion. The gatekeepers are essential for efficient replication, according to Racaniello, “but there are likely many others” beyond the few that have been identified. nOPV2 defends against just one of those.

Another question looms over nOPV2’s deployment: will the vaccine actually protect against polio? Clinical trials so far have measured the type 2-specific serum neutralizing antibodies elicited by nOPV2. Protection is believed to result when titres reach certain thresholds. “Can we measure antibody responses in animal models and in limited clinical tests and say, ‘This should be OK in people?’” asks Racaniello. “I think that’s what WHO, CDC, and [the] Gates [Foundation], and everyone else is hoping,” he says, naming some of the key partners in the Global Polio Eradication

Initiative, which decides and implements the vaccine strategy for polio eradication. “That should be enough . . . but there’s nothing like putting it in people to really find out.”

At PATH, “we don’t see any unique risks for nOPV2 over the current vaccine,” says Konz. The relative paucity of clinical data is offset by the knowledge from decades of using the Sabin 2 strain from which nOPV2 is derived. “In the end,” he says, “it’s a relative benefit-risk decision that the WHO, policymakers, and national authorities will have to make.”

While the polio eradication effort is betting nOPV2 will be a silver bullet, “nothing is off the table,” according to WHO’s Rosenbauer, “and everything is being explored,” including even a possible return to the old vaccine with the three original Sabin strains.

https://bbc.in/2EJjx2x

Motor neurone disease 'linked to cholesterol'

Scientists say they have discovered a possible underlying cause of the neurological disorder, motor neurone disease (MND).

The University of Exeter team says it has found evidence that MND is linked to an imbalance of cholesterol and other fats in cells.

It says the research could lead to more accurate diagnosis and new treatments. MND affects around 5,000 people in the UK and causes more than 2,000 deaths a year.

What is MND?

Motor neurone disease is a group of diseases that affect the nerve cells in the brain and spinal cord that tell your muscles what to do.

Also known as ALS, it causes muscle weakness and stiffness.

Eventually people with the disease are unable to move, talk, swallow and finally, breathe. There is no cure and the exact causes are unclear - it's been variously linked to genes, exposure to heavy metals and agricultural pollution.

What did the researchers find?

Scientists at the University of Exeter say they had a "eureka moment" when they realised that 13 genes - which, if altered, can cause the condition - were directly involved in processing cholesterol. They say their theory could help predict the course and severity of the disease in patients and monitor the effect of potential new drugs. The theory is outlined in a paper, published in Brain: A Journal of Neurology.

Lead author Prof Andrew Crosby said: "For years, we have known that a large number of genes are involved in motor neurone disease, but so far it hasn't been clear if there's a common underlying pathway that connects them." The finding particularly relates to what is known as the "spastic paraplegias", where the malfunction is in the upper part of the spinal cord.

Dr Emma Baple, also from the University of Exeter Medical School, said: "Currently, there are no treatments available that can reverse or prevent progression of this group of disorders. Patients who are at high risk of motor neurone disease really want to know how their disease may progress and the age at which symptoms may develop, but that's very difficult to predict."

Dr Brian Dickie, director of research at the MND Association, said the work raises some interesting ideas. "At the moment, it is unclear whether the imbalance observed is a cause of MND or a consequence of the disease. We look forward to seeing the outcome of further research in this area."

http://bit.ly/2Mle71W

Paper-based test could diagnose Lyme disease at early stages

Much more sensitive than existing tests, the assay requires 15 minutes to complete and costs only 42 cents per test

After a day hiking in the forest, the last thing a person wants to discover is a tick burrowing into their skin. Days after plucking off the bloodsucking insect, the hiker might develop a rash resembling

a bull's-eye, a tell-tale sign of Lyme disease. Yet not everybody who contracts Lyme disease gets the rash. Now, researchers reporting in *ACS Nano* have devised a blood test that quickly and sensitively diagnoses the disease at early stages.

About 300,000 cases of Lyme disease, which is caused by the tick-borne bacteria *Borrelia burgdorferi*, are diagnosed in the U.S. each year, according to the U.S. Centers for Disease Control and Prevention. Early symptoms of the disease include the characteristic skin rash, along with fever, headache, chills and muscle aches. If not treated promptly with antibiotics, more severe symptoms, such as facial palsy, nerve pain, heart palpitations and arthritis, can occur. However, 10-20% of infected people do not develop the rash, and existing diagnostic blood tests are slow, costly or insensitive at early stages, when treatment is most effective. Aydogan Ozcan and colleagues wanted to develop a fast, easy-to-use and inexpensive blood test to diagnose Lyme disease soon after infection.

The researchers built a handheld, paper-based device to detect antibodies against the *B. burgdorferi* bacteria in serum samples. The device included a sensing membrane that contained several spots covering seven bacterial antigens and a synthetic peptide. Antibodies from serum samples that attached to the spots were detected with a solution that changed color, depending on the amount of antibody captured. The researchers took pictures of the color changes on a smart phone, then analyzed all of the spots with a neural network they developed that could determine whether the sample was positive or negative for Lyme disease. When tested on 50 blood samples from people with or without early-stage Lyme disease, the assay had a specificity of 96.3% and a sensitivity of 85.7%. In addition to being much more sensitive than existing tests, the assay requires 15 minutes to complete and costs only 42 cents per test.

More information: *"Point-of-Care Serodiagnostic Test for Early-Stage Lyme Disease Using a Multiplexed Paper-Based Immunoassay and Machine Learning" ACS Nano (2019). pubs.acs.org/doi/abs/10.1021/acsnano.9b08151*

http://bit.ly/2QbNbCT

Study suggests early-life exposure to dogs may lessen risk of developing schizophrenia

Findings do not link similar contact with cats to either schizophrenia or bipolar disorder

Ever since humans domesticated the dog, the faithful, obedient and protective animal has provided its owner with companionship and emotional well-being. Now, a study from Johns Hopkins Medicine suggests that being around "man's best friend" from an early age may have a health benefit as well -- lessening the chance of developing schizophrenia as an adult.

And while Fido may help prevent that condition, the jury is still out on whether or not there's any link, positive or negative, between being raised with Fluffy the cat and later developing either schizophrenia or bipolar disorder.

"Serious psychiatric disorders have been associated with alterations in the immune system linked to environmental exposures in early life, and since household pets are often among the first things with which children have close contact, it was logical for us to explore the possibilities of a connection between the two," says Robert Yolken, M.D., chair of the Stanley Division of Pediatric Neurovirology and professor of neurovirology in pediatrics at the Johns Hopkins Children's Center, and lead author of a research paper recently posted online in the journal PLOS One.

In the study, Yolken and colleagues at Sheppard Pratt Health System in Baltimore investigated the relationship between exposure to a household pet cat or dog during the first 12 years of life and a later diagnosis of schizophrenia or bipolar disorder. For schizophrenia, the researchers were surprised to see a statistically

significant decrease in the risk of a person developing the disorder if exposed to a dog early in life. Across the entire age range studied, there was no significant link between dogs and bipolar disorder, or between cats and either psychiatric disorder.

The researchers caution that more studies are needed to confirm these findings, to search for the factors behind any strongly supported links, and to more precisely define the actual risks of developing psychiatric disorders from exposing infants and children under age 13 to pet cats and dogs.

According to the American Pet Products Association's most recent National Pet Owners Survey, there are 94 million pet cats and 90 million pet dogs in the United States. Previous studies have identified early life exposures to pet cats and dogs as environmental factors that may alter the immune system through various means, including allergic responses, contact with zoonotic (animal) bacteria and viruses, changes in a home's microbiome, and pet-induced stress reduction effects on human brain chemistry.

Some investigators, Yolken notes, suspect that this "immune modulation" may alter the risk of developing psychiatric disorders to which a person is genetically or otherwise predisposed.

In their current study, Yolken and colleagues looked at a population of 1,371 men and women between the ages of 18 and 65 that consisted of 396 people with schizophrenia, 381 with bipolar disorder and 594 controls. Information documented about each person included age, gender, race/ethnicity, place of birth and highest level of parental education (as a measure of socioeconomic status). Patients with schizophrenia and bipolar disorder were recruited from inpatient, day hospital and rehabilitation programs of Sheppard Pratt Health System. Control group members were recruited from the Baltimore area and were screened to rule out any current or past psychiatric disorders.

All study participants were asked if they had a household pet cat or dog or both during their first 12 years of life. Those who reported that a pet cat or dog was in their house when they were born were considered to be exposed to that animal since birth.

The relationship between the age of first household pet exposure and psychiatric diagnosis was defined using a statistical model that produces a hazard ratio -- a measure over time of how often specific events (in this case, exposure to a household pet and development of a psychiatric disorder) happen in a study group compared to their frequency in a control group. A hazard ratio of 1 suggests no difference between groups, while a ratio greater than 1 indicates an increased likelihood of developing schizophrenia or bipolar disorder. Likewise, a ratio less than 1 shows a decreased chance.

Analyses were conducted for four age ranges: birth to 3, 4 to 5, 6 to 8 and 9 to 12.

Surprisingly, Yolken says, the findings suggests that people who are exposed to a pet dog before their 13th birthday are significantly less likely -- as much as 24% -- to be diagnosed later with schizophrenia.

"The largest apparent protective effect was found for children who had a household pet dog at birth or were first exposed after birth but before age 3," he says.

Yolken adds that if it is assumed that the hazard ratio is an accurate reflection of relative risk, then some 840,000 cases of schizophrenia (24% of the 3.5 million people diagnosed with the disorder in the United States) might be prevented by pet dog exposure or other factors associated with pet dog exposure.

"There are several plausible explanations for this possible 'protective' effect from contact with dogs -- perhaps something in the canine microbiome that gets passed to humans and bolsters the immune system against or subdues a genetic predisposition to schizophrenia," Yolken says.

For bipolar disorder, the study results suggest there is no risk association, either positive or negative, with being around dogs as an infant or young child.

Overall for all ages examined, early exposure to pet cats was neutral as the study could not link felines with either an increased or decreased risk of developing schizophrenia or bipolar disorder.

"However, we did find a slightly increased risk of developing both disorders for those who were first in contact with cats between the ages of 9 and 12," Yolken says. "This indicates that the time of exposure may be critical to whether or not it alters the risk."

One example of a suspected pet-borne trigger for schizophrenia is the disease toxoplasmosis, a condition in which cats are the primary hosts of a parasite transmitted to humans via the animals' feces. Pregnant women have been advised for years not to change cat litter boxes to eliminate the risk of the illness passing through the placenta to their fetuses and causing a miscarriage, stillbirth, or potentially, psychiatric disorders in a child born with the infection.

In a 2003 review paper, Yolken and colleague E. Fuller Torrey, M.D., associate director of research at the Stanley Medical Research Institute in Bethesda, Maryland, provided evidence from multiple epidemiological studies conducted since 1953 that showed there also is a statistical connection between a person exposed to the parasite that causes toxoplasmosis and an increased risk of developing schizophrenia. The researchers found that a large number of people in those studies who were diagnosed with serious psychiatric disorders, including schizophrenia, also had high levels of antibodies to the toxoplasmosis parasite.

Because of this finding and others like it, most research has focused on investigating a potential link between early exposure to cats and psychiatric disorder development. Yolken says the most recent study is among the first to consider contact with dogs as well.

"A better understanding of the mechanisms underlying the associations between pet exposure and psychiatric disorders would allow us to develop appropriate prevention and treatment strategies," Yolken says.

Working with Yolken on the research team are the following members from Sheppard Pratt Health System: Cassie Stallings, Andrea Origoni, Emily Katsafanas, Kevin Sweeney, Amalia Squire, and Faith Dickerson, Ph.D., M.P.H.

The study was largely supported by grants from the Stanley Medical Research Institute.

http://bit.ly/2ZicuaH

Scientists have discovered the world's oldest forest—and its radical impact on life

Roots helped pull CO_2 from the air and lock it away, radically shifting the planet's climate and leading to our atmosphere

By Colin Barras

Scientists have discovered the world's oldest forest in an abandoned quarry near Cairo, New York. The 385-million-year-old rocks contain the fossilized woody roots of dozens of ancient trees. The find marks a turning point in Earth's history. When trees evolved these roots, they helped pull carbon dioxide (CO_2) from the air and lock it away, radically shifting the planet's climate and leading to the atmosphere we know today.

***Researchers analyzing one of the radial* Archaeopteris *tree root systems at the Cairo, New York, site* Charles Ver Straeten**

"The Cairo site is very special," says team member Christopher Berry, a paleobotanist at Cardiff University in the United Kingdom. The quarry floor, about half the size of a U.S. football field, represents a horizontal slice through the soil just below the surface of the ancient forest. "You are walking through the roots of ancient trees," Berry says. "Standing on the quarry surface we can reconstruct the living forest around us in our imagination."

Berry and colleagues first discovered the site in 2009 and are still analyzing the fossils it contains. Some of the fossilized roots there are 15 centimeters in diameter and form 11-meter-wide horizontal radial patterns spreading out from where the vertical tree trunks once stood. They seem to belong to *Archaeopteris*, a type of tree with large woody roots and woody branches with leaves that is related in some way to modern trees, the team reports today in *Current Biology*. Previously, the oldest *Archaeopteris* fossils were no more than 365 million years old, Berry says, and exactly when the tree evolved its modern-looking features has been unclear.

The Cairo site suggests *Archaeopteris* did so 20 million years earlier, says Patricia Gensel, a paleobotanist at the University of North Carolina in Chapel Hill who was not involved with the work. "The size of those root systems—it's really changing the picture," she says, adding that, even 20 years ago, researchers assumed trees with such large and complex root systems did not evolve so early in geological time.

Trees like those at Cairo had a big effect on the ancient climate, says Kevin Boyce, a geoscientist at Stanford University in Palo Alto, California. Deep roots penetrate and break up the rocks within and below the soil. Geologists call this processing "weathering," and it triggers chemical reactions that pull CO_2 from the atmosphere and turn it into carbonate ions in groundwater. This ultimately runs off into the sea and is locked away as limestone.

Partly because of weathering and its knock-on effects, atmospheric CO_2 levels dropped to modern levels soon after the appearance of woody forests. A few tens of millions of years earlier they had been 10 to 15 times higher than today. Some research suggests the removal of so much atmospheric CO_2 led directly to a sustained rise in oxygen levels, with the atmosphere containing about 35% oxygen by 300 million years ago. This, in turn, may have led to the evolution of gigantic insects at that time, some with wing spans of 70 centimeters, which may have lived in the ancient forests.

The trees that grew a few tens of millions of years after the Cairo forest have also had an indirect impact on the modern climate. Berry has previously written about how the fossilized remains of these forests formed the coal that fueled the Industrial Revolution in Europe and North America.

Close-up of an* Archaeopteris *tree root system, viewed from above **William Stein & Christopher Berry**

This is not the first time Berry and his colleagues have explored a primitive forest. In the 19th century, researchers discovered a fossil forest in Gilboa, New York, about 40 kilometers from the Cairo site, containing 382-million-year-old specimens. Since 2010, Berry and his colleagues have been examining a quarry at Gilboa that also preserves ancient tree roots. But the Gilboa roots belong to more primitive trees that may be related to ferns and horsetails. They didn't produce deep, woody roots with much potential for weathering.

This means the trees that grew at the Cairo site were the innovators, Berry says. "Woody trees with leaves that can produce shade—and a big rooting system—is something fundamentally modern that wasn't there before."

http://bit.ly/2MoeAAp

Overspill of fat shown to cause Type 2 Diabetes

For the first time, scientists have been able to observe people developing Type 2 diabetes - and confirmed that fat over-spills from the liver into the pancreas, triggering the chronic condition.

The research, led by Professor Roy Taylor at Newcastle University, UK, is published in the academic journal, *Cell Metabolism*.

The study involved a group of people from Tyneside who previously had Type 2 diabetes but had lost weight and successfully reversed the condition as part of the DiRECT trial, which was funded by Diabetes UK and led by Professors Roy Taylor and Mike Lean (Glasgow University).

The majority remained non-diabetic for the rest of the two year study, however, a small group went on to re-gain the weight and re-developed Type 2 diabetes.

Professor Roy Taylor, from the Newcastle University Institute of Translational and Clinical Research, explained what the advanced scanning techniques and blood monitoring revealed.

He said: "We saw that when a person accumulates too much fat, which should be stored under the skin, then it has to go elsewhere in the body. The amount that can be stored under the skin varies from person to person, indicating a 'personal fat threshold' above which fat can cause mischief.

"When fat cannot be safely stored under the skin, it is then stored inside the liver, and over-spills to the rest of the body including the pancreas. This 'clogs up' the pancreas, switching off the genes which direct how insulin should effectively be produced, and this causes Type 2 diabetes."

This research by Professor Taylor confirms his Twin Cycle Hypothesis - that Type 2 diabetes is caused by excess fat actually within both the liver and pancreas, and especially that this process is reversible.

Body of research

This latest paper builds on previous Newcastle studies supported by Diabetes UK showing exactly why Type 2 diabetes can be reversed back to normal glucose control. Those studies led to the large DiRECT trial which showed that Primary Care staff can achieve remission of Type 2 diabetes by using a low calorie diet with support to maintain the weight loss.

A quarter of participants achieved a staggering 15 kg or more weight loss, and of these, almost nine out of 10 people put their Type 2 diabetes into remission. After two years, more than one third of the group had been free of diabetes and off all diabetes medication for at least two years.

In 2020, this approach to management of short duration Type 2 diabetes is to be piloted in the NHS in up to 5,000 people across England, and a similar programme is being rolled out in Scotland.

Professor Taylor adds: "This means we can now see Type 2 diabetes as a simple condition where the individual has accumulated more fat than they can cope with.

"Importantly this means that through diet and persistence, patients are able to lose the fat and potentially reverse their diabetes. The sooner this is done after diagnosis, the more likely it is that remission can be achieved."

The team are continuing work to establish what may affect an individual's personal threshold and are supporting the roll out of the NHS Initiatives in both England and Scotland. 'Life Without Diabetes - The definitive guide to understanding and reversing your Type 2 diabetes' by Professor Roy Taylor will be published by Short Books on 26th December 2019.

Reference: Hepatic Lipoprotein Export and Remission of Human Type 2 Diabetes after Weight Loss. Cell Metabolism. *https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30662-X*

NOTES TO EDITORS: *https://www.england.nhs.uk/2018/11/very-low-calorie-diets-part-of-nhs-action-to-tackle-growing-obesity-and-type-2-diabetes-epidemic/*

http://bit.ly/2Zomcs4

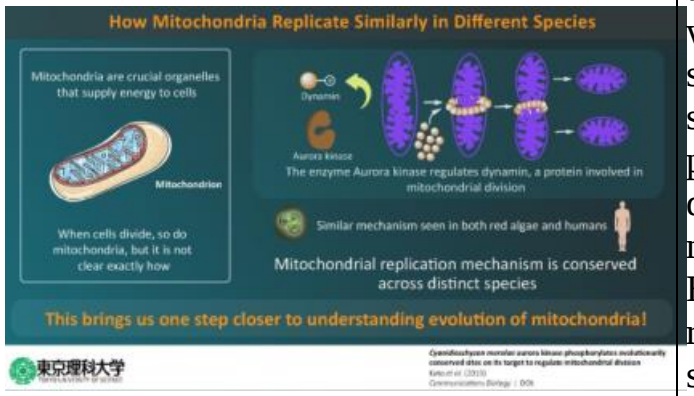
A step closer to understanding evolution -- mitochondrial division conserved across species

New study shows exactly how the manner in which mitochondria divide has remained the same since evolution began

Cellular origin is well explained by the "endosymbiotic theory," which famously states that higher organisms called "eukaryotes"

have evolved from more primitive single-celled organisms called "prokaryotes." This theory also explains that mitochondria--energy-producing factories of the cell--are actually derived from prokaryotic bacteria, as part of a process called "endosymbiosis." Biologists believe that their common ancestry is why the structure of mitochondria is "conserved" in eukaryotes, meaning that it is very similar across different species--from the simplest to most complex organisms. Now, it is known that as cells divide, so do mitochondria, but exactly how mitochondrial division takes place remains a mystery. Is it possible that mitochondria across different multicellular organisms--owing to their shared ancestry--divide in an identical manner? Considering that mitochondria are involved in some of the most crucial processes in the cell, including the maintenance of cellular metabolism, finding the answer to exactly how they replicate could spur further advancements in cell biology research.

In a new study published in *Communications Biology*, a group of scientists at Tokyo University of Science, led by Prof Sachihiro Matsunaga, wanted to find answers related to the origin of mitochondrial division.



This exciting new research describes how mitochondrial replication is similar in the simplest to most complex organisms, shedding light on its origin. **Tokyo University of Science**

For their research, Prof Matsunaga and his team chose to study a type of red alga--the simplest form of a eukaryote, containing only one mitochondrion. Specifically, they wanted to observe whether the machinery involved in mitochondrial replication is conserved across different species and, if so, why. Talking about the motivation for this study, Prof Matsunaga says, "Mitochondria are important to cellular processes, as they supply energy for vital activities. It is established that cell division is accompanied by mitochondrial division; however, many points regarding its molecular mechanism are unclear."

The scientists first focused on an enzyme called Aurora kinase, which is known to activate several proteins involved in cell division by "phosphorylating" them (a well-known process in which phosphate groups are added to proteins to regulate their functions). By using techniques such as immunoblotting and kinase assays, they showed that the Aurora kinase in red algae phosphorylates a protein called dynamin, which is involved in mitochondrial division. Excited about these findings, Prof Matsunaga and his team wanted to take their research to the next level by identifying the exact sites where Aurora kinase phosphorylates dynamin, and using mass spectrometric experiments, they succeeded in identifying four such sites. Prof Matsunaga says, "When we looked for proteins phosphorylated by Aurora kinase, we were surprised to find dynamin, a protein that constricts mitochondria and promotes mitochondrial division."

Having gained a little more insight into how mitochondria divide in red algae, the scientists then wondered if the process could be similar in more evolved eukaryotes, such as humans. Prof Matsunaga and his team then used a human version of Aurora kinase to see if it phosphorylates human dynamin--and just as they predicted, it did. This led them to conclude that the process by which mitochondria replicate is very similar in different eukaryotic organisms. Prof Matsunaga elaborates on the findings by saying, "Using biochemical in vitro assays, we showed that Aurora kinase

phosphorylates dynamin in human cells. In other words, it was found that the mechanism by which Aurora kinase phosphorylates dynamin in the mitochondrion is preserved from primitive algae to humans."

Scientists have long pondered over the idea of mitochondrial division being conserved in eukaryotes. This study is the first to show not only the role of a new enzyme in mitochondrial replication but also that this process is similar in both algae and humans, hinting towards the fact that their common ancestry might have something to do with this. Prof Matsunaga concludes by talking about the potential implications of this study, "Since the mitochondrial fission system found in primitive algae may be preserved in all living organisms including humans, the development of this method can make it easier to manipulate cellular activities of various organisms, as and when required."

As it turns out, we have much more in common with other species than we thought, and part of the evidence lies in our mitochondria!

This study was supported by MEXT/JSPS KAKENHI grants (15H05955 and 15H05962).

http://bit.ly/2ZdJNvs

One-off genetic score can detect stroke risk from birth

Genetic data from a single sample can be used to identify individuals at a 3-fold increased risk of developing ischaemic stroke

A group of investigators from Australia, Germany, and the UK have shown that genetic data obtained from a single blood draw or saliva sample can be used to identify individuals at a 3-fold increased risk of developing ischaemic stroke, a devastating condition and one of the leading causes of disability and death world-wide. The scientists developed a genetic risk score that is similarly or more predictive than commonly known risk factors for stroke. Their work further suggests that individuals with high genetic risk may require more intensive preventive measures to mitigate stroke risk than is recommended by current guidelines.

Genomic risk prediction, based on an individual's unique DNA sequence, has distinct advantages over established risk factors as it could be used to infer risk of disease from birth. It may thus allow initiation of preventive strategies before individuals develop conventional risk factors for stroke such as hypertension or hyperlipidemia, said Martin Dichgans, Professor of Neurology and Director at the Institute for Stroke and Dementia Research (ISD), University Hospital, Ludwig-Maximilians-University (LMU) Munich, and one of the leaders of the current study.

The results of this study were published online in the journal, Nature Communications. The study utilised large-scale genetic data from research groups worldwide and applied their results to data on 420.000 individuals from the UK Biobank.

The study was led by investigators from the Baker Heart and Diabetes Institute (Australia), University of Cambridge (UK), and Ludwig-Maximilians-University, Munich (Germany).

"The sequencing of the human genome has revealed many insights. For common diseases, such as stroke, it is clear that genetics is not destiny; however, each person does have their own innate risk for any particular disease. The challenge is now how we best incorporate this risk information into clinical practice so that the public can live healthier and longer." said Dr Michael Inouye, of the Baker Heart and Diabetes Institute and University of Cambridge, and another leader of the current study.

Stroke is the second most common cause of both death and disability-adjusted life-years worldwide. About 80% of stroke cases are caused by occlusion of a brain supplying artery (so-called 'ischaemic stroke'). The risk of ischaemic stroke is determined by genetic and environmental factors, which act through modifiable risk factors such as hypertension and diabetes.

In the study, the researchers employed a machine learning approach to integrate stroke-related genetic data from various sources into a single genetic risk score for each individual. They then assessed the performance of this new genetic risk score in the UK Biobank and found that it both outperformed previous genetic scores and had similar predictive performance as other well-known risk factors for stroke, such as smoking status or body mass index.

Importantly, the new genetic risk score was significantly better than family history at predicting future ischaemic stroke, to the extent that it could detect the roughly 1 in 400 individuals at 3-fold increased risk.

Individuals at high genetic risk of ischaemic stroke are not without options however, and the researchers further showed that these individuals may still substantially reduce their stroke risk by minimizing their conventional risk factors. These include lowering blood pressure and body mass index, as well as ceasing smoking.

The study's analyses show that current clinical guidelines may be insufficient for individuals at high genetic risk of stroke, and that these individuals may need more intensive interventions.

With non-invasive, affordable DNA genotyping array technology together with a new genetic risk score for ischaemic stroke, the future looks bright for genomic medicine to enable effective early interventions for those at high risk of strokes and, indeed, other cardiovascular diseases.

https://wb.md/2ShoO9p

FDA Warns of 'Serious' Respiratory Problems With Gabapentin

Life-threatening breathing difficulties can occur in patients who use gabapentin or pregabalin with opioids

Megan Brooks

Life-threatening breathing difficulties can occur in patients who use gabapentin or pregabalin with opioids or other drugs that depress the central nervous system, as well as those with underlying respiratory impairment and the elderly, the US Food and Drug Administration (FDA) warned in a drug safety communication issued today.

"Reports of gabapentinoid abuse alone, and with opioids, have emerged and there are serious consequences of this co-use, including respiratory depression and increased risk of opioid overdose death," Douglas Throckmorton, MD, deputy director for Regulatory Programs at the FDA's Center for Drug Evaluation and Research, said in a statement.

"In response to these concerns, we are requiring updates to labeling of gabapentinoids to include new warnings of potential respiratory depressant effects. We are also requiring the drug manufacturers to conduct clinical trials to further evaluate the abuse potential of gabapentinoids, particularly in combination with opioids, with special attention being given to assessing the respiratory depressant effects," said Throckmorton.

Gabapentinoid products include gabapentin, marketed as *Neurontin* (Pfizer) and *Gralise* (Assertio Therapeutics), as well as generics; gabapentin enacarbil, a prodrug of gabapentin marketed as *Horizant* (Arbor Pharmaceuticals); and pregabalin, marketed as *Lyrica* and *Lyrica CR* (Pfizer), as well as generics.

Gabapentin and pregabalin are approved by the FDA for a variety of conditions, including seizures, nerve pain, and restless legs syndrome and may be prescribed for unapproved or off-label uses in patients with other types of pain as alternatives to opioids, the FDA notes.

Reports submitted to the FDA and data from the medical literature show that serious breathing difficulties can occur when gabapentinoids are taken by patients with pre-existing respiratory risk factors.

Among 49 case reports submitted to FDA from 2012 to 2017, 12 people died from respiratory depression with gabapentinoids. All of them had at least one risk factor. This number includes only reports submitted to FDA, so there may be additional cases, the FDA says.

The agency also reviewed data from two randomized, double-blind, placebo-controlled clinical trials in healthy people, three observational studies, and several studies in animals.

One trial showed that taking pregabalin alone and with an opioid pain reliever can depress breathing function. The other trial found gabapentin alone increased pauses in breathing during sleep.

The three observational studies from one academic medical center found a relationship between gabapentinoids given before surgery and respiratory depression occurring after different types of surgery. Several animal studies also found pregabalin alone and with opioids can depress respiratory function.

"Our goal in issuing today's new safety labeling change requirements is to ensure healthcare professionals and the public understand the risks associated with gabapentinoids when taken with central nervous system depressants like opioids or by patients with underlying respiratory impairment," Throckmorton said.

According to the FDA, drug utilization data indicate a growing number of prescriptions for gabapentinoids. Between 2012 and 2016, the estimated number of patients who filled a gabapentin prescription increased from 8.3 million to 13.1 million annually, and the number of patients who filled a pregabalin prescription increased from 1.9 million to 2.1 million annually.

In addition, data collected in 2016 from an office-based physician survey showed that an estimated 14% and 19% of patient encounters involving gabapentin and pregabalin, respectively, also involved opioids.

Healthcare professionals should report side effects associated with gabapentin, pregabalin, or other medicines to the FDA's MedWatch program.

https://wb.md/361B6GU

More Than Half of Doctors Get Industry Payments/Meals: Poll

More than half of physicians (57%) who responded to a recent Medscape poll said they accepted meals or payments from a drug or device maker last year.

Marcia Frellick

However, a substantial portion of physicians said meals and/or payments should never be acceptable, and they believe such actions always or often influence physician practice. The poll was posted on September 4. It received responses from 382 physicians.

Answers varied widely among physicians on what is acceptable. Responses show that 24% of physicians say they should never accept free meals from drug or device makers. When asked about payments instead of meals, 44% said such payments were never acceptable.

Answers varied greatly on what types of activities might warrant payment from industry.

	% Physician Agreement
Consulting	57
Speeches	54
Research	63
Education	55
Money from royalties/investments	23
None of the above	15

Table. In General, for Which Types of Activities Should Physicians Accept Payments From Industry?

Physicians early on in their career were most likely to say free meals from industry are acceptable. While 22% of those with 5 years or less of experience said they are acceptable, only 14% of those with more than 30 years' experience agreed.

Hospital policy also appears to be divided on the subject. Almost 1 in 5 physicians (18%) said they were unsure whether their hospital placed any restrictions on industry contributions, while 38% said there were hospital restrictions on meals and/or payments, and 44% said there were no restrictions on either.

Influence on Practice?

Physicians were also asked about the effect of free meals or industry payments on practice.

More than one third (37%) responded that they thought payments always or often influenced physician practice (6% said they never influence practice), and 27% said complimentary meals always or often did (12% said they never influence practice).

As *Medscape Medical News* has reported, studies have found associations between payments or meals from drug and device makers and changes in practice overall.

A study in *JAMA Internal Medicine* found that physicians who received even an industry-sponsored meal promoting a particular drug were more likely to prescribe the brand-name drug than a less expensive generic one.

Industry Payments to Physicians Over $9B in 2018

The poll followed a report from the Centers for Medicare & Medicaid Services (CMS) that found that pharmaceutical and medical device industry payments to physicians totalled $9.35 billion in 2018, $380 million more than in 2017 and $770 million more than in 2014, the first full year of payments listed on the CMS's Open Payments website.

The larger sums are going to fewer physicians. In total, 627,000 doctors were listed on the website for 2018, 11,000 fewer than in 2016.

A rheumatologist asked in the comments of the poll why industry influence is roundly considered negative.

He wrote, "Being influenced is not necessarily bad. Otherwise, what is the point of attending teaching conferences, reading journals, consulting colleagues, doing CME, etc? If you never change your mind at all, you are a rigid robot, not a human doctor, and a really outdated one at that."

Many responders to the poll say they used to accept payments but no longer do.

A family medicine physician in the United Kingdom wrote, "I have not received a meal from the pharmaceutical industry for over 20 years. I stopped as I decided it was immoral and might unduly influence my prescribing, even if it might only be subliminal."

Others say they continue to accept the offers. A surgeon in Cameroon said, "I accept the meals when I'm hungry and can't step out for lunch, but I don't let it influence my clinical decisions."

A US physician in addiction medicine considers it reimbursement. The physician wrote: "I used to go to dinner presentations and listen to lectures. I considered the dinner as a payment for my time. My wife was allowed to accompany me. Now spouses are not welcome. I am not willing to give up time from my family even if I am provided a meal for it."

An obstetrician-gynecologist in the United States said free meals, "which are frequently mediocre, to listen to discussions of new medications that may be beneficial to our patients are acceptable. You can also ignore everything they say and just eat an enjoyable meal with your peers."

https://wb.md/2Qf8Zxh

Prehospital Plasma for Trauma Saves Lives for Long Transport

Plasma transfusion during transport to a hospital is associated with greater survival if the transport takes more than 20 minutes

Ricki Lewis, PhD

For patients with severe injuries, plasma transfusion during transport to a hospital is associated with greater survival at 28 days if the transport takes more than 20 minutes, according to a comparison of two recent studies. The comparison was published online December 18 in *JAMA Surgery*.

Civilian and military clinical practice guidelines call for early transfusion of plasma in cases of severe trauma and hemorrhagic shock so as to achieve a plasma-to-red-blood-cell ratio of 1:1 to 1:2.

The seemingly contradictory findings of two recent randomized clinical trials prompted Anthony E. Pusateri, PhD, of the US Army Institute of Surgical Research, and colleagues to hypothesize that duration of prehospital plasma delivery affects 28-day mortality.

The Prehospital Air Medical Plasma (PAMPer) multicenter clinical trial followed 501 trauma patients who were transported via helicopter to a level I trauma center. Patients received either plasma and then standard care or only standard care. Prehospital administration of plasma resulted in a significantly lower 30-day mortality of 23.2%, vs 33.0% (P = .03) for patients who did not receive plasma en route to the hospital.

The second investigation, the single-center Control of Major Bleeding After Trauma (COMBAT) clinical trial, found that there was no survival advantage for 125 patients in an urban area who were driven to a nearby hospital and who had immediate access to blood components upon arrival. These patients received prehospital plasma and then standard care or standard care with crystalloid.

In both studies, 2 units of thawed plasma were delivered. Median time to the hospital was longer in the PAMPer helicopter study (41 min; range, 33 – 52 min) compared to COMBAT (18 min; range, 15 – 22 min). Perhaps the shorter time to the hospital of ground transport was insufficient for the plasma to have an effect.

The studies were developed with the aim of ad hoc comparison. The same design parameters and data elements were used, and samples and data were shared. For example, the investigations used the same inclusion and exclusion criteria, blood draw timings, adverse event monitoring, methods to assess transport time, and data collection.

"It was not possible to determine a time effect within either study independently, but analysis of the combined data from both studies offers the opportunity to examine this question," the researchers write.

The planners, from the Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC), which included researchers from the Department of Defense and the National Institutes of Health, intended for the studies to be compared. "This was proactive and smart, and it saved money that would have been requested for an additional clinical study to answer lingering questions after each of the COMBAT and PAMPer trials," write Todd E. Rasmussen, MD, and Laura R, Brosch, RN, PhD, of Edward Hébert School of Medicine at the Uniformed Services University, Bethesda, Maryland, in an invited commentary.

The post hoc analysis of 626 patients revealed "a significant overall survival benefit for plasma." The 28-day mortality was lower in the plasma group (61 of 297 patients; 20.5%) compared with the standard care group (94 of 329 patients; 28.6%; P = .02;), with a hazard ratio (HR) of 0.65 (P = .01) after adjustment for age, injury severity, and whether the patient was enrolled in PAMPer or COMBAT.

Combining the studies, patients in the standard care group had slightly more than double increased mortality risk when prehospital transport was longer than 20 minutes (HR, 2.12; P = .04), but this was not the case for the patients who received plasma on the ride to the hospital (HR, 0.78; P = .46).

Patients who received prehospital plasma were 47% less likely to arrive at the emergency department with coagulopathy than those

who had not received plasma (OR, 0.53; *P* = .002). This association held only for patients who were in transport for longer than 20 minutes.

The observation that for the standard care group, transport times longer than 20 minutes were associated with increased mortality "emphasizes the importance of minimizing time to definitive care," the researchers write, as well as the importance of rapid hemostasis. "The present findings have important implications for the treatment of patients with traumatic hemorrhage when surgical care and in-hospital transfusion may be delayed, such as in military settings, in rural and remote trauma, and in civilian disaster scenarios," the researchers conclude.

The commentators write that the coordinated studies approach validates registry-based studies, which have been criticized for nonrandomization, poor quality of data, and selection bias. "However, an often overlooked benefit of registry-based studies is their ability to improve the efficiency of subsequent prospective, controlled trials, such as in this sequence of studies," they write. They also applaud the collaboration of the Department of Defense and the National Institutes of Health, because the finding regarding the value of transfusing thawed plasma for more than 20 minutes is applicable to both combat and civilian settings for traumatic injuries with hemorrhagic shock. Limitations of the study are the different modes of transport in the two investigations and the lack of information on the time from injury to plasma transfusion.

The authors and commentators have disclosed no relevant financial relationships.

http://bit.ly/2MnHYXD

Woman had 524x the normal level of mercury in her blood from skin cream use

A new case report on the July poisoning highlights just how toxic organic mercury is.

Beth Mole

A 47-year-old woman in Sacramento, California, has been left severely impaired—unable to talk or care for herself and requiring a feeding tube—after using tainted face cream that contained highly toxic methylmercury.

Her poisoning, first reported in local media in September, is now the subject of a detailed case report published today in the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report (MMWR).

In it, health officials describe the progression of the woman's symptoms, which began in July with weakness in her upper extremities and abnormal, painful sensations (dysesthesia). Over the next two weeks, she developed slurred speech, blurry vision, and unsteadiness while walking. She was then admitted to the hospital where her condition went downhill quickly, resulting in a state of agitated delirium.

Blood and urine screens in the hospital detected mercury. But the levels were so high, they exceeded what the screens could quantify. At that point, the state's health department and poison control center got involved. The poison control center recommended that she start a treatment of oral dimercaptosuccinic acid, a metal chelator. This binds to and removes heavy metals from the body, and it has been used to treat heavy metal poisoning since the 1950s.

The health department, meanwhile, tracked the source of the poison to a skin-lightening cream she obtained from Mexico. The woman's family told health investigators she had used such face creams twice a day, every day for the past seven years.

Further testing determined that she had 2,620 micrograms of mercury per liter of blood. According to the New York State Department of Health, usual amounts of mercury in blood—typically from dietary sources—are up to about 5 micrograms/liter.

Poisonous products

Adulterated skin-lightening creams are well-known to contain forms of mercury. But until now, they've typically been found to contain only inorganic mercury salts. According to the World Health Organization, mercury salts can inhibit the formation of melanin, resulting in a lighter skin tone. Inorganic mercury in creams and soap most often causes kidney damage, but it can also cause psychosis and nerve damage, WHO reports.

In the woman's case, health officials found the organic mercury compound methylmercury in her skin cream, which is more dangerous. While inorganic mercury has been found in creams at concentrations up to 200,000 parts-per-million, the woman's face cream contained methylmercury at just 12,000ppm.

The relatively lower concentration "underscores the far higher toxicity of organic mercury compounds," the health officials write in the MMWR report. They go on to note that the woman's progression is pretty typical of such poisonings. "Central nervous system toxicity, the hallmark of organic mercury, typically manifests after weeks to months of exposure, progresses rapidly after onset, worsens despite cessation of further exposure, persists even with chelation (although mercury excretion might increase), and leaves profound residual impairment," the officials write.

The woman's son told a local news outlet that his mother knew that the cream was adulterated somehow, but she used it anyway because it worked better than other creams.

The authors of the MMWR report note that this is the first time that methylmercury has shown up in skin-lightening creams. It's still unclear why it was added and where it came from. The state's public health department is testing additional creams and is warning consumers about the potential threat.

Beyond the skin cream, the most common source of methylmercury exposure is from eating fish, which essentially accumulate it from polluted food. Pregnant women are advised to restrict the types and amounts of fish they eat because methylmercury can cause brain damage in a developing fetus.

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